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INVESTIGATIVE REPORT

Expanding the Clinical and Genetic Spectrum of *KRT1*, *KRT2* and *KRT10* Mutations in Keratinopathic Ichthyosis

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Twenty-six families with keratinopathic ichthyoses (epidermolytic ichthyosis, superficial epidermolytic ichthyosis or congenital reticular ichthyosiform erythroderma) were studied. Epidermolytic ichthyosis is caused by mutations in the genes *KRT1* or *KRT10*, mutations in the gene *KRT2* lead to superficial epidermolytic ichthyosis, and congenital reticular ichthyosiform erythroderma is caused by frameshift mutations in the genes *KRT10* or *KRT1*, which lead to the phenomenon of revertant mosaicism. In this study mutations were found in *KRT1*, *KRT2* and *KRT10*, including 7 mutations that are novel pathogenic variants. Novel clinical features found in patients with congenital reticular ichthyosiform erythroderma are described, such as mental retardation, spasticity, facial dysmorphisms, symblepharon and malposition of the 4th toe. Key words: epidermolytic ichthyosis; congenital reticular ichthyosiform erythroderma; *KRT1*; *KRT2*; *KRT10*.

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Keratinopathic ichthyoses (KPI) are defined as inherited skin disorders caused by mutations in keratin genes. These genes encode keratin proteins, which form part of the cytoskeleton and are important for normal tissue structure and function. The KPI classification includes epidermolytic ichthyosis (EI, OMIM #113800), superficial epidermolytic ichthyosis (SEI, OMIM #146800) and congenital reticular ichthyosiform erythroderma (CRIE, OMIM #609165) (1).

EI, formerly known as epidermolytic hyperkeratosis or bullous congenital ichthyosiform erythroderma of Brocq (BCIE), is characterized by diffuse erythroderma

and blistering at birth. With increasing age, blistering and erythroderma improve and are replaced by progressive hyperkeratosis. EI is usually inherited in an autosomal dominant manner and is caused by heterozygous mutations in the keratin genes *KRT1* (OMIM *139350) or *KRT10* (OMIM *148080). Approximately 50% of cases of EI occur *de novo* due to spontaneous mutations (2). Mutations in *KRT1* usually lead to a phenotype with much more severe palmoplantar hyperkeratosis than those in *KRT10*. In rare cases EI is inherited in an autosomal recessive manner and has been described in consanguineous families with homozygous mutations in *KRT10* (3–8).

CRIE, also known as *ichthyosis en confetti*, can be caused by heterozygous mutations in *KRT10* (9) or, as has been shown recently, in *KRT1* (10). At birth it may be difficult to distinguish this phenotype from a severe congenital ichthyosiform erythroderma (CIE), because CRIE is not associated with blistering skin. Small confetti-like spots of almost normal skin appear in childhood and increase in size and number with time. They can be explained by mitotic recombination and a revertant mosaicism from clonal expansion of a corrected stem cell (9). These reversions seem to develop significantly later in life (at approximately 20 years of age) in CRIE associated with a *KRT1* mutation (10).

SEI, in the past known as ichthyosis bullosa of Siemens (IBS), is due to heterozygous mutations in *KRT2* (OMIM *600194). Clinical findings are similar to those of EI, but the phenotype is generally milder and can be quite variable in severity (11, 12). Patients with SEI show generalized erythroderma and blistering at birth. Symptoms usually improve with age. Later in life, erythroderma regresses almost completely and keratotic lichenification may concentrate on the joint areas of arms and legs typically showing the so-called “Mauserung phenomenon”.

The clinical and genetic features of a series of 26 families with KPI, including 7 novel mutations, are described here.

MATERIALS AND METHODS

Informed consent was obtained from all patients. Genomic DNA was isolated from peripheral blood leucocytes by standard methods. For mutation analysis, all coding exons and adjacent splice sites of the genes *KRT1*, *KRT2* and *KRT10* were amplified by polymerase chain reaction (PCR) using exon-specific primer pairs, which were established in our laboratory. These primers are listed in Table S1¹. Automated DNA sequencing analysis was performed on an ABI 3500 DNA Sequencer (Applied Biosystems, Foster City, CA, USA). In some patients next generation sequencing was performed and the detected mutations were validated using direct Sanger sequencing. A Nextera[®] Rapid Capture Enrichment kit (Illumina, San Diego, CA, USA) was used for enrichment of the sequences and performed sequencing analysis onto the Illumina MiSeq instrument (Illumina, San Diego, CA, USA).

Reference sequences NM_006121.3 for *KRT1*, NM_000423.2 for *KRT2* and NM_000421.3 for *KRT10* were used. All novel mutations detected are not referenced as single nucleotide polymorphisms (SNPs) and were not found in the HGMD Professional Database (www.hgmd.cf.ac.uk), 1000 Genomes Database (<http://www.1000genomes.org>) or in the Exome Aggregation Consortium (<http://exac.broadinstitute.org>). They are predicted to be disease-causing in Mutation Taster (<http://www.mutationtaster.org/>) and Poly-Phen 2 (<http://genetics.bwh.harvard.edu/pph2/>). For splice variants splice prediction tools, such as Human Splicing Finder (<http://www.umd.be/HSF/>), were used.

Formalin-fixed paraffin-embedded skin biopsies were used for immunofluorescence staining. Deparaffinized 5 µm-thick sections were blocked with phosphate-buffered saline (PBS) containing 5% normal goat serum and incubated with the mouse monoclonal anti-human K10 primary antibody (LH2, Santa Cruz Biotechnology, Dallas, TX, USA) diluted 1:800 for 1 h at 37°C. After incubation with the secondary antibody Alexa-Fluor[®]-488-conjugated goat anti-mouse IgG (Life Technologies, Paisley, UK) diluted 1:1000, nuclei were stained with 4'-6'-diamidino-2-phenylindole (DAPI; Sigma-Aldrich, St Louis, MO, USA). The slides were mounted with Mowiol 4-88 (Merck Millipore, Darmstadt, Germany) and images were obtained using a Nikon Eclipse 80i microscope equipped with a Nikon DXM 1200C digital camera and NIS image analysis software.

RESULTS

Twenty-six families were studied: 4 with SEI, 16 with EI and 6 with CRIE, in whom heterozygous mutations were found in *KRT2*, *KRT1* or *KRT10*, respectively. Seven mutations are novel pathogenic sequence variants. The patients, their clinical and histological findings and the mutations identified are summarized in Table SII¹.

Superficial epidermolytic ichthyosis

Heterozygous mutations were identified in the *KRT2* gene in 7 patients from 4 families with SEI (Table

¹<http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2299>

²The mutations c.558C>A, p.Asn186Lys (patient P1) and c.1459G>A, p.Glu487Lys (family 3 (patients P3-1, P3-2 and P3-3) and patient P4) have been described previously (12, 13).

SII)². A novel mutation, c.1438T>C, p.Tyr480His, was identified. This mutation has not been described previously, is located in a highly conserved region and is therefore predicted to be disease causing. The mutation was found in a 9-year-old boy (patient P2-2) and in his father (patient P2-1). The boy presented mild hyperkeratosis, and bullous lesions appeared only in the warm season (Fig. 1A–C). The father presented the same mild hyperkeratosis; his bullous phenotype disappeared at puberty.

Epidermolytic ichthyosis

The phenotypes of the patients with EI in this study confirm the observation that mutations in *KRT1* usually lead to more severe palmoplantar hyperkeratosis than *KRT10* mutations (Table SII)³. For example patient P5 developed severe palmoplantar keratoderma (PPK) and generalized ichthyosis that was pronounced at the extensor side of the joints (Fig. 2A–D).

In patient P10 the novel *KRT1* mutation c.1752dupT, p.Gly585Trpfs69* was discovered. The patient was born with ichthyosis and developed moderate PPK and generalized ichthyosis that was pronounced at the extensor side of the joints (Fig. 2E–H). The mutation leads to an elongated protein (Fig. S1¹).

An additional 9 families with EI and without PPK show mutations in exon 1 of the *KRT10* gene [Table SII)⁴.

One patient with EI (patient P20) carried the novel mutation c.1345T>C, p.Tyr449His in exon 6 of the *KRT1* gene. Many other mutations in this 2B domain of the K10 protein have been reported. Patient P20 showed typical EI, no special features were observed. Similar mutations at this residue with other amino acid changes have been described (7, 23).

Congenital reticular ichthyosiform erythroderma

Six patients were affected with CRIE, 5 of them exhibited novel mutations in *KRT10* (Table SII)¹. In patient P23 the splice site mutation c.1374-1G>C,

³The mutations c.698C>T, p.Ser233Leu (14) in patient P6, c.1436T>C, p.Ile479Thr (15) in family 8 (P8-1, P8-2), c.1434G>T, p.Glu478Asp (16–18) in patient P7, c.1468G>A, p.Glu490Lys (7) in patient P9 and c.563A>G, p.Asn188Ser (19) in patient P5 have been described previously.

⁴Six patients have the mutation c.467G>T, p.Arg156His (20) and 1 patient has the mutation c.467G>T, p.Arg156Leu (21). This suggests that codon 156 is a hotspot for mutations in EI. The mutation c.482T>C, p.Leu161Ser in patients P18 and P19 has been previously reported in Bygum et al. (22), who described 2 patients with this mutation. In family 12, the mother (P12-2) of the affected boy (P12-1) carries the mutation p.Arg156His in a mosaic state; approximately 22% of the leucocytes are affected. This resulted in a relatively mild phenotype in the mother. She had bullous ichthyosiform erythroderma at birth, but fewer blisters than her son. At present she shows blistering and hyperkeratosis only after mechanical stress. Epidermolytic naevi have not been observed in the mother.

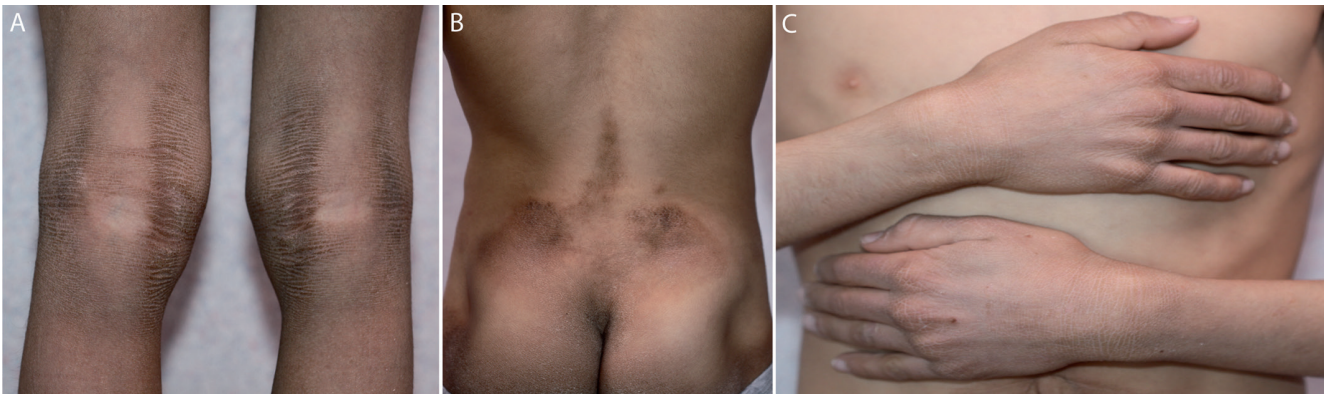


Fig. 1. (A–C) Clinical example of 9-year-old patient P2-2 with superficial epidermolytic ichthyosis (SEI). The patient carries the novel mutation c.1438T>C, p.Tyr480His in *KRT2*.

p.Ser458Argfs*120 was identified in *KRT10*, which has been described previously in 2 cases with CRIE (24, 25)⁵. This patient shows CRIE with PPK and ectropion as well as several additional extracutaneous features such as severe mental retardation, malposition of the 4th toe, short stature, facial dysmorphism, spasticity, agenesis of nipples, thick hair and onychodystrophy (Fig. 3A). Slight mental retardation has also been found in patient P25 with CRIE and PPK, who carries the novel mutation c.1544dupG in *KRT10*. This patient shows

similar features to patient P23, such as malposition of the 4th toe, short stature and facial dysmorphism (Fig. 3B–E). The same mutation was detected in P26, who shows CRIE and hypertrichosis, but no other extracutaneous malformations.

Immunofluorescence labelling for K10 in ichthyotic skin from patient P23 showed a weak and irregular cytoplasmic staining with a bright nuclear staining, consistent with the characteristic K10 mislocalization previously described in CRIE (9, 24, 26). In contrast, this nuclear staining, as well as vacuolization in the suprabasal epidermis layers is no longer visible in the confetti-like spots on the skin, consistent with the revertant phenotype (Fig. 3F–H).

Additional splice site mutations in the same splice site region described above, the mutations c.1374-1G>A,

⁵The patient described by Diociaiuti et al. (24) exhibited CRIE with PPK, mild ectropion, pruritus, hypertrichosis, ear deformity and growth retardation, but no mental retardation. The patient reported by Spoerri et al. (25) exhibited a similar phenotype with CRIE and hypertrichosis, hyperpigmentation of healthy spots, hypoplasia of mammillae, ear deformity, ectropion and strabismus.



Fig. 2. Clinical examples of patients with epidermolytic ichthyosis (EI) and mutations in *KRT1*: patient P5 shows EI with (A–C) severe palmoplantar keratoderma (PPK) and (D) hyperkeratosis on the elbows. (E–H) A milder phenotype is presented in patient P10 with moderate PPK. The patient has the novel mutation c.1752dupT, p.Gly585Trpfs69*.

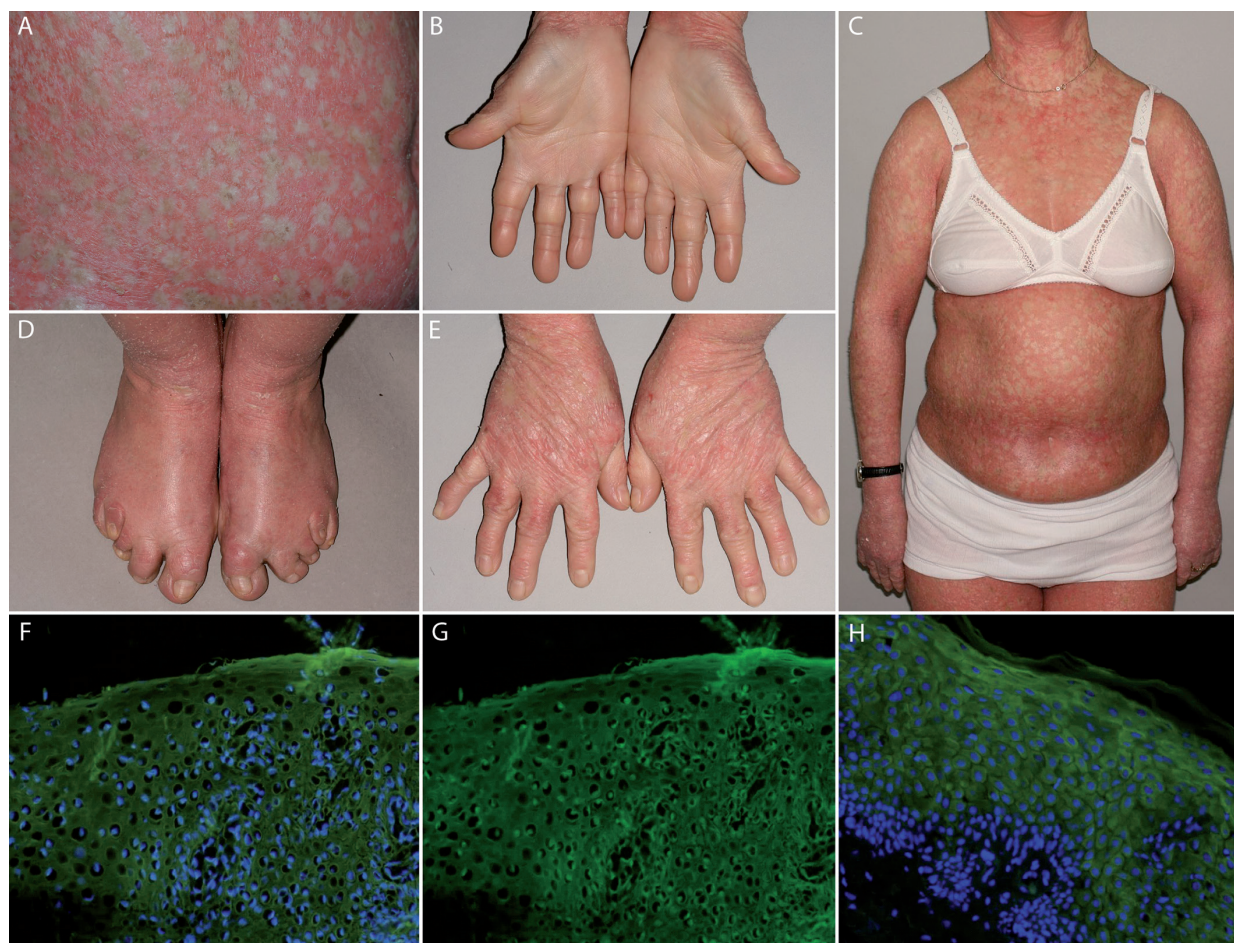


Fig. 3. Clinical examples of patients with congenital reticular ichthyosiform erythroderma (CRIE) who carries mutations in *KRT10*: (A) confetti-like spots in patient P23. Patient P25 carries the novel mutation c.1544dupG, p.Gly516Argfs*65 and shows (C) confetti-like spots, (B, D, E) shortened fingers and toes and malposition of the 4th toe and (D) syndactyly of the 2nd and 3rd toes. (F, G) Immunofluorescence labelling for K10 (green) in patient P23 shows a weak heterogeneous cytoplasmic staining and a bright nuclear staining in lesional skin contrasting with (H) the near normal staining in confetti-like spot non-lesional skin. In (F) and (H), nuclei are counterstained with 4',6-diamidino-2-phenylindole (DAPI) (blue).

c.1374-2A>G and c.1374-2delA, have been described by Choate et al. (9) in patients with CRIE⁶.

Furthermore, 1 novel insertion mutation was discovered in *KRT10*, c.1411_1412insA in patient P24. The phenotype of patient P24 is more severe than of patient P26⁷; P24 was born with a collodion membrane and developed a highly inflammatory ichthyosis including alopecia totalis. She has severe growth retardation and

partially blocked joints due to constrictive skin. The first spot was noted at the age of 2 years.

DISCUSSION

In this study, 26 families with SEI, EI and CRIE who carry mutations in *KRT1*, *KRT2* or *KRT10* were analysed, thereby expanding the genotypic and phenotypic spectrum of these diseases.

It is notable that previously reported *KRT10* mutations in patients with autosomal dominant EI are substitutions of a single base in exons 1 or 6, whereas mutations in *KRT10*, which lead to CRIE, are deletions or duplications in exon 7 or splice site mutations at

⁶All of these splice site mutations lead to an 8-base deletion in the cDNA with frameshift leading to an arginine-rich reading frame (9, 24). Both novel splice site mutations c.1373+2T>C in patient P22 and c.1373+1G>C in the 3 patients of family 21 change the donor splice site and are expected to lead to a loss of the generally used splice site. Choate et al. (9) described a mutation at the same position c.1373+1, but switching a G to an A. In patient P22, the initial diagnosis of autosomal recessive congenital ichthyosis (ARCI) was revised to CRIE at the age of 4 years, when the first revertant skin spots developed. In patient P21-1, the development of white spots escaped attention up to the age of 57 years, when diagnosis was made by an experienced dermatologist. Interestingly, this patient not only shows white spots, but has also developed patchy hyperpigmentation. Two of her children are also affected; like their mother, expression of CRIE is mild and resembles a mild to moderate type of congenital ichthyosiform erythroderma.

⁷Both insertion mutations lead to an arginine-rich reading frame and a truncated protein, which is shortened by 4 amino acids compared with the wild-type protein (Fig. S1¹). The variable severity of the phenotypes could be explained by the position of the mutation and the number of altered amino acids, which change protein function to different extents. However, other genetic or epigenetic factors may also influence the disease severity.

the acceptor splice site of exon 6 or the donor splice site of exon 7. It has been suggested that the dominant *KRT10* mutations in CRIE result in an arginine-rich C-terminal frameshift leading to a mislocalization of the protein to the nucleus, which would impair the normal function of the keratin network (9, 26). The novel mutations c.1411_1412insA and c.1544dupG also result in an arginine-rich reading frame and a premature stop codon. Our results support previous assumptions that an arginine-rich C-terminal peptide is required for the development of the CRIE phenotype.

Recently, Choate et al. (10) described a patient with a CRIE-like phenotype in whom they found a frameshift mutation in *KRT1* (c.1866insG, p.Val622Cysfs*30). This patient's first confetti-like spots appeared at the age of 22 years with a maximum size of 4 mm. His skin showed no parakeratosis, milder perinuclear vacuolization and prominent coarse keratohyalin granules. This is in contrast to CRIE patients with *KRT10* mutations, whose confetti-like spots typically appear early in childhood and reach a size of up to 2 cm and whose skin reveals parakeratosis, pronounced perinuclear vacuolization and absent keratohyalin granules (9, 10). Milder forms of CRIE can also occur in patients with mutations in *KRT10*. In family 21, the mother (P21-1) was diagnosed with CRIE at age 57 years, and the diagnostic significance of her white spots escaped attention up to this age. Two children (P21-2, P21-3) from this family are also affected with a mild form of CRIE, resembling a mild to moderate type of congenital ichthyosiform erythroderma. The mutation c.1866insG leads to the same reading frame as in previously reported patients with mutations in *KRT1* showing mild ichthyosis hystrix Curth-Macklin (c.1861insT) (27) and mild EI without skin fragility (c.1757dupG) (28). Patient P10 with EI, who carries the mutation c.1752dupT in *KRT1*, shows the same reading frame (Fig. S1[†]). Frameshift mutations in *KRT1* can therefore lead to very different phenotypes.

The genotype-phenotype correlations in SEI, EI and CRIE are very complex. The differential diagnosis between these diseases can be difficult, since the phenotypes can vary in severity. In some of our patients who were first suspected to have EI and to carry mutations in *KRT1* or *KRT10*, we found mutations in *KRT2*. Conversely, patients with suspected SEI sometimes exhibited a mild EI phenotype and carried a mutation in *KRT1* or *KRT10*. Therefore, in patients with suspected SEI or EI, in which no mutation in the corresponding genes can be found, analysis of other keratin genes could be useful⁸.

The type and position of *KRT10* mutations can provide information regarding the correct clinical diagnosis EI or CRIE, since CRIE mutations are deletions, duplications or splice site mutations in exon 7 and flanking introns, whereas EI mutations are substitutions in exons 1 or 6. Immunofluorescence staining for keratin 10 is another possibility for early diagnosis of CRIE, since

nuclear staining for keratin 10 has been described only in CRIE and might be considered as a diagnostic hallmark (24).

Clinical features, which were consistently associated with CRIE, can be defined as major criteria, whereas features, which are not obligatory present in patients, can be defined as minor criteria (25, 26). Several previously described features in patients with CRIE are consistent with our findings, such as growth retardation (P23–P25), palmoplantar keratoderma (P23, P25), hypertrichosis (P26), ectropion (P23, P24), hypoplasia of mamillae (agenesia of nipples in P23), scalp hair loss (alopecia totalis in P24) malformations of the nails (onychodystrophy in P23), joint contractions (P24), hyperpigmentation (P21-1), decreased finger length (shortened fingers and toes in P25) (24, 25, 26). To our knowledge, some clinical findings that we have found in our cohort have not been described previously in patients with this disease. These include malposition of 4th toe (P23, P25), spasticity (P23), facial dysmorphisms (P23, P25), symblepharon (P25) and mental retardation (P23, P25). However, psychomotor retardation has been described in a 2-year-old patient with CRIE who carries the mutation c.1383_1414del32 in *KRT10* (24). These features can be added to the list of minor features in CRIE.

In conclusion, the findings of this study expand the clinical and mutational spectrum and genotype-phenotype correlation associated with SEI, EI and CRIE by describing 26 families and 7 novel pathogenic alterations.

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⁸This large variation in phenotype can even occur in patients with the same mutation. For example, the mutation c.1434G>T, p.Glu478Asp in *KRT1* has been reported previously in patients from Japan and Korea (16–18). Patients described in these publications showed a very mild phenotype and had similar clinicopathological features to SEI. The mutation p.Glu478Asp does not lead to a change in side-chain polarity, in contrast to the mutations p.Glu478Gln and p.Glu478Lys, which change polarity and lead to more severe phenotypes. Sung et al. (18) postulated that the polarity of the substituted amino acid can influence the phenotypic severity of EI. Indeed, patient P7, who carries the p.Glu478Asp mutation, showed a mild generalized ichthyosis. However, from the clinical point of view his adult phenotype could be classified as palmoplantar keratoderma with mild ichthyosis. The large variation in phenotypes in patients even with the same mutation suggests that other genetic or epigenetic factors, as well as environmental factors, may significantly influence the severity of the disease.

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