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Research Article | Journal of Dermatology and Pigmentation Research | Open Access

Genetic Investigation Confirms Acral Peeling Skin Syndrome in a Hungarian Family Clinically Diagnosed with Localized Epidermolysis Bullosa Simplex

Katalin Farkas[1], Adrienn Sulak[2], Lajos Kemeny[1,3], Marta Szell[1,2] and Nikoletta Nagy[1,2,3]*

[1]MTA-SZTE Dermatological Research Group, University of Szeged, Szeged, Hungary
[2]Department of Medical Genetics, University of Szeged, Szeged, Hungary
[3]Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary

Received Date: June 20, 2017, **Accepted Date:** July 28, 2017, **Published Date:** August 03, 2017.

***Corresponding author:** Nikoletta Nagy, Department of Medical Genetics, University of Szeged, 4 Somogyi utca, 6720 Szeged, Hungary, Tel: +36-625-451-34, E-mail: nikoletta.nagy@gmail.com*

Abstract

Introduction: Localized Epidermolysis Bullosa Simplex (EBS, localized form, OMIM 131800) is a rare monogenic skin disease characterized by the development of blisters on the hands and feet. Acral peeling skin syndrome (APSS, OMIM 609796) is a monogenic condition characterized by superficial painless peeling of the skin predominantly on the dorsal aspects of hands and feet. In this study, we investigated a Hungarian patient, whose clinical symptoms suggested the localized form of EBS.

Methods: After genomic DNA was isolated from peripheral blood of the patients, mutation analysis of the *keratin 5 (KRT5), keratin 14 (KRT14), β4* and *α6integrin (ITGB4* and *ITGA6)* and *transglutaminase 5 (TGM5)* genes was performed to identify the causative genetic abnormality responsible for the development of the skin symptoms. *In silico* tools were applied to identify the functional impact of the newly detected mutations.

Results: Direct sequencing of the *KRT5, KRT14, ITGB4* and *ITGA6* genes detected only wild type sequences. Since the clinical symptoms of localized EBS and APSS overlap, mutation screening of the *TGM5* gene was also performed. Two missense mutations of the *TGM5* gene were detected in heterozygous form: one novel (c.427T > C, p.Trp143Arg) and one recurrent (c.337G > T, p.Gly113Cys). *In silico* tools suggested that the newly identified variant is a disease causing mutation. Family screening demonstrated that the novel mutation had a paternal origin, and the recurrent mutation a maternal origin.

Conclusions: A patient with EBS clinical symptoms carried *TGM5* mutations and, in fact, suffered from APSS. Our study provides further insight into the underlying genetic background of patients diagnosed with localized EBS for which the disease-causing mutation could not be identified by the screening the classic EBS genes.

Keywords: Epidermolysis bullosa simplex; Peeling skin syndrome; *TGM5* gene; Novel mutation; Recurrent mutation

Abbreviations

EBS: Epidermolysis Bullosa Simplex; APSS: Acral Peeling Skin Syndrome; KRT5: Keratin 5; KRT14: Keratin 14; ITGB4: β4 Integrin; ITGA6: α6 Integrin; TGM5: Transglutaminase 5

Introduction

Epidermolysis Bullosa Simplex (EBS) is a clinically and genetically heterogeneous skin disorder characterized by blistering of the skin following minor physical trauma as a result of cytolysis within the basal epidermal cells [1]. Most forms of EBS show autosomal dominant inheritance. The localized form (EBS, localized form; OMIM 131800) is characterized by localized blistering primarily on the hands and feet [1]. EBS is aggravated by heat, humidity, pressure and exposure to water. The localized form of EBS has been identified in approximately 2000–3000 individuals and is usually the consequence of mutations in the *KRT5, KRT14, ITGB4,* and *ITGA6* genes [2].

EBS is the most frequent form of epidermolysis bullosa, its prevalence is 1/35,000 to 1/150,000 worldwide [3]. The syndrome is usually the consequence of mutations in the *KRT5, KRT14, ITGB4,* and *ITGA6* genes [2].

Acral peeling skin syndrome (APSS; OMIM 609796) is an autosomal recessive monogenic skin disease characterized by superficial painless peeling and blisters of the skin predominantly on the dorsal surface of the hands and feet [4,5]. During blistering, cleavage occurs in the upper layers of the epidermis, between the stratum granulosum and the stratum corneum [6,7]. The condition is also aggravated by heat, humidity, and exposure to water. APSS has been reported in approximately 75 patients worldwide to date [8]. The disease is caused by homozygous or compound heterozygous mutations in the *TGM5* gene [4,9].

In this study, we reported a Hungarian patient, whose clinical symptoms suggested the localized form of EBS. However, genetic analysis did not identify abnormality in the genes classically associated with localized EBS (*KRT5, KRT14, ITGB4* and *ITGA6*). Subsequently, mutation screening of the *TGM5* gene identified causative mutations and suggested correction of the clinical diagnosis from EBS to APSS.

Patients and Methods

Patient

A 11 years old Hungarian boy was referred to our out-patient clinic with the common phenotype associated with the EBS localized form. The patient presented with recurrent superficial blisters and erosions on his hands and feet (Figure 1a). These skin symptoms were recurrent since the birth. Based on the clinical findings, the diagnosis of localized EBS was established. The patient (II/1) is the only affected family member in this Hungarian pedigree; his parents (I/1 and I/2) and sister (II/2) are clinically unaffected (Figure 1b).

Genetic Investigation

Blood samples were drawn from the patient and from his family members (n = 3), as well as from unrelated healthy controls (n = 50). Genomic DNA was isolated by a Bio Robot EZ1 DSP Workstation (QIAGEN, Hilden, Germany). The coding regions and the flanking introns of the *KRT5, KRT14, ITGB4, ITGA6* and *TGM5* genes were amplified and sequenced with a traditional capillary sequencer (ABI Prism 7000). Primer sequences were obtained from the UCSC Genome Browser. The investigation was approved

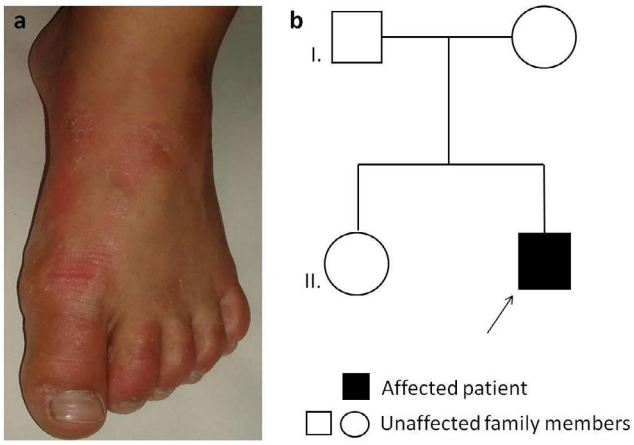

Figure 1: Clinical symptoms and pedigree of the investigated Hungarian patient. (a) Blister formation and peeling were present on the dorsal surface of the patient's left leg. (b) The patient (II/1) was the only clinically affected individual in his pedigree: his parents (I/1 and I/2) and his sister (II/2) was clinically unaffected.

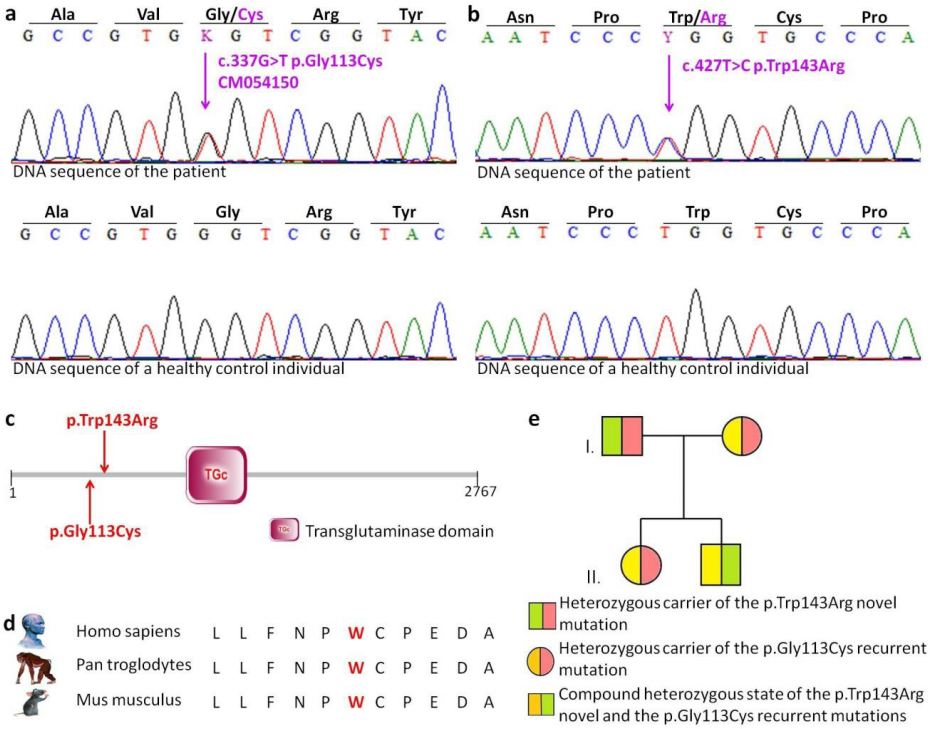

Figure 2: Identification of the disease-causing mutations in the *TGM5* gene. Direct sequencing revealed (a) a recurrent heterozygous missense mutation (c.337G > T, p.Gly113Cys) and (b) a novel heterozygous missense mutation (c.427T > C, p.Trp143Arg) in the third exon of the *TGM5* gene. Both mutations were present in the affected patient. Unrelated controls (n = 50) carried the wild type sequence. (c) The novel p.Trp143Arg mutation does not affect any known functional domain on the transglutaminase 5 enzyme. (d) The novel p.Trp143Arg mutation is located in a region highly conserved in mammals. (e) Family screening indicted that the novel mutation was of paternal origin, and the recurrent mutation was of maternal origin. In addition, the clinically unaffected sister carried the maternal recurrent mutation.

by the Internal Review Board of the University of Szeged. Written informed consent was obtained from all donors, and the study was conducted according to the principles of the Declaration of Helsinki.

Pathogenicity Predictions

In silico tools were applied to identify the functional impact of the newly detected missense mutation. Here we used PolyPhen 2.0 (Polymorphism Phenotyping), SIFT (Sorting Intolerant from Tolerant) and Mutation Taster tools.

Results

Based on the clinical diagnosis of EBS, mutation screening of the *KRT5, KRT14, ITGB4* and *ITGA6* genes was performed but any pathogenic mutations were not detected. As EBS and APSS have overlapping clinical symptoms, mutation screening of the *TGM5* gene was also performed, and two heterozygous missense mutations were identified in the third exon of the *TGM5* gene: one recurrent (c.337G > T, p.Gly113Cys) (Figure 2a) and one novel (c.427T > C, p.Trp143Arg) (Figure 2b). The affected patient carried

both mutations in heterozygous form. The novel p.Trp143Arg missense mutation does not affect any known functional domains of the *TGM5* gene (Figure 2c), but it is located in a highly conserved region of the protein (Figure 2d). Polyphen-2, SIFT and Mutation Taster analyses all suggested that the novel p.Trp143Arg missense mutation is pathogenic.

Genetic screening of family members indicated that the novel mutation is of paternal origin, whereas the recurrent mutation is of maternal origin (Figure 2e). The clinically unaffected sibling (II/2) carried the maternal missense mutation in heterozygous form, but did not carry the paternal mutation. All unrelated healthy controls (n = 50) carried the wild type sequence.

Discussion

Here, we reported a Hungarian patient with clinically suspected localized EBS that was not confirmed with mutation screening of the classic localized EBS genes, *KRT5, KRT14, ITGB4* and *ITGA6*. Based on the phenotypic similarity between EBS and APSS, we also investigated the *TGM5* gene. Using direct sequencing, two mutations were identified on the *TGM5* gene: a recurrent mutation (c.337G > T, p.Gly113Cys) and a novel mutation (c.427T > C, p.Trp143Arg). Genetic investigation, therefore, confirmed that the patient is suffering from APSS.

The recurrent p.Gly113Cys *TGM5* mutation has been previously reported in Finnish, Norwegian, Swedish, Scottish and German patients (n = 9) (Table 1) [4,5]. Eight of nine patients carried the p.Gly113Cys mutation in homozygous form; and one patient carried the heterozygous p.Gly113Cys mutation in combination with the Trp255Arg missense mutation [4,5]. Patients carrying the homozygous p.Gly113Cys mutation exhibited wide phenotypic heterogeneity: half of the patients presented erythema, blistering and peeling, whereas the other half presented blistering (n = 1) or erythema and blistering (n = 1) or blistering and peeling (n = 2). Seven of the eight patients with the homozygous p.Gly113Cys mutation developed recurrent blistering. The frequency of peeling was consistent, affecting seven patients, and erythema was present in only half of the patients. Our Hungarian patient, who carried the p.Gly113Cys mutation in heterozygous form, also presented blistering and peeling. From these observations, we conclude that blistering and peeling are frequently associated with the phenotype linked to the p.Gly113Cys mutation.

In silico analyses suggested that the novel p.Trp143Arg *TGM5* variant is a disease causing mutation. Since it does not affect any known functional domain of the encoded protein, further functional studies are required to explain how this mutation contributes to the development of APSS. To date, only 75 patients have been reported with APSS; within this group, approximately 35 *TGM5* mutations have been identified [8,10]. Therefore, our study contributes to the mutation information for *TGM5* and also adds detailed phenotypic description of the affected patient. These data provide a significant basis for future genotype–phenotype correlation studies.

Our study also gives further insight to the underlying genetic background for patients who have been diagnosed with localized EBS, but for whom EBS screening did not identify disease-causing mutation. This phenomenon is not unique in the literature, as other independent research groups have already patients initially diagnosed with EBS for whom molecular genetic data indicated APSS [11,12]. The result of our study and others in the literature have diagnostic significance, as they indicate the need for *TGM5* screening with localized EBS patients when screening of the classic EBS genes does not identify the underlying genetic abnormality.

Acknowledgements

TAMOP-4.2.1/B-09/1/KONV-2010-0005, TAMOP-4.2.2/B-10/1/KONV-2010-0012, TAMOP-4.2.2.A-11/1/KONV-2012-0035 and GINOP-2.3.2-15-2016-00039 grants.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Patient	Nationality	Symptoms	Mutation 1	Mutation 2	References
1	Hungarian	Blistering, peeling	p.Gly113Cys	p.Trp143Arg	This study
2	Swedish	Blistering, peeling,erythema	p.Gly113Cys	p.Trp255Arg	Kiritsi et al. 2010
3	German	Blistering, peeling	p.Gly113Cys	p.Gly113Cys	Kiritsi et al. 2010
4	Finnish	Blistering, peeling	p.Gly113Cys	p.Gly113Cys	Kiritsi et al. 2010
5	German	Blistering, peeling, erythema	p.Gly113Cys	p.Gly113Cys	Kiritsi et al. 2010
6	German	Blistering	p.Gly113Cys	p.Gly113Cys	Kiritsi et al. 2010
7	German	Blistering, peeling	p.Gly113Cys	p.Gly113Cys	Kiritsi et al. 2010
8	German	Blistering, peeling, erythema	p.Gly113Cys	p.Gly113Cys	Kiritsi et al. 2010
9	German	Blistering, peeling, erythema	p.Gly113Cys	p.Gly113Cys	Kiritsi et al. 2010
10	Scottish	Peeling, erythema	p.Gly113Cys	p.Gly113Cys	Cassidy et al. 2005

Table 1: Comparison of the clinical phenotype of patients carrying the p.Gly113Cys recurrent mutation.

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***Corresponding author:** Nikoletta Nagy, Department of Medical Genetics, University of Szeged, 4 Somogyi utca, 6720 Szeged, Hungary, Tel: +36-625-451-34, E-mail: nikoletta.nagy@gmail.com

Received Date: June 20, 2017, **Accepted Date:** July 28, 2017, **Published Date:** August 03, 2017.

Citation: Farkas K, Sulak A, Kemeny L, Szell M, Nagy N (2017) Genetic Investigation Confirms Acral Peeling Skin Syndrome in a Hungarian Family Clinically Diagnosed with Localized Epidermolysis Bullosa Simplex. J Derma Pigm Res 1(2): 106.