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Case Report
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A *De novo* Mutation in *KRT10* Gene in an Infant with Epidermolytic Hyperkeratotic

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Abstract

Epidermolytic Hyperkeratosis (EHK) is a rare autosomal dominant genodermatosis and caused by mutations in *KRT1* gen or *KRT10* gene. The clinical features of EHK are erythroderma, scales, and formation of epidermal blisters at birth, and later the blistering and redness will be replaced by progressive hyperkeratosis in the stratum corneum mainly involving the flexion skin of the extremities, and with thick grayish brown scales. Besides the more than 120 mutations of *KRT1* and *KRT10* genes have been identified in EHK in Human Gene Mutation Database. It is a novel heterozygous missense variation (c.494G>C, p.R165P) in exon 1 of the *KRT10* gene. Our finding will be benefit for early diagnosis of EHK and might lead to better treatment.

Keywords: Epidermolytic hyperkeratosis; Infant; *KRT10* mutation

Introduction

Epidermolytic Hyperkeratosis (EHK; OMIM#113800), earlier termed as Bullous Congenital Ichthyosiform Erythroderma (BCIE), has been reported to affect 1 in 200,000 to 300,000 infants and caused by mutations in *KRT1* gen or *KRT10* gene [1,2]. The clinical symptoms of EHK seriously affect the quality of life of the infant [3] and illustrate the pathogenesis of the disease is essential to the prevention and treatment of the disease.

Case Presentation

In our study, we identified a de novo mutation in *KRT10* gene in a newborn girl with EHK. A 2-days-old female infant first presented to our hospital with severely rashes on her face. It rapidly develops to the flaky desquamation of her fingers, buttocks, and armpits. On the day of admission, it appeared scattered bullous rashes on the buttocks and arms, with local damage accompanied by yellow clear liquid exudation. There were flushing of local skin and obvious tenderness. No bleeding point has been found. Gram's staining of blister fluid showed negative. The couple was healthy and had a non-consanguineous marriage. There is no history of family genetic disease, no drug exposure, chemical substances, or radiation exposure during pregnancy.

Laboratory evaluation showed elevated in White Blood Cell (WBC 17.8×10^9/L), while percentage of neutrophil and CRP are normal. There were also slightly increased in several biochemistry examinations [Aspartate Aminotransferase (AST) 56 IU/L, Total Bilirubin (TBIL) 100.3 μmol/L, Direct Bilirubin (DBIL) 5.4 μmol/L, Creatine Kinase (CK) 636 μmol/L]. Blood gas analysis showed pH was 7.293, carbon dioxide partial pressure (PCO_2) was 44.4 mmHg, Oxygen Partial Pressure (PO_2) was 58.4 mmHg, Oxygen Saturation (SpO_2) was 93.7%, Lactate (Lac) was 4.7 mmol/L. Syphilis specific antibodies showed positive, while hepatitis B, HIV and HCV showed negative. The results showed that the titer of RPR was 1:1 negative in early pregnancy and negative in late pregnancy.

Blood DNA was extracted from whole blood of the patient and her parents at the same day with Blood & Cell Culture DNA Midi Kit (Qiagen, 13343). The patient and her parents were screened for causal variants using Whole-Exome Sequencing (WES) and a customized panel targeting 442 genes that potentially associated with EHK and other skin diseases. Base calling and sequence read quality assessment were performed using Illumina HCS 2.2.58 software (Illumina, Inc., San Diego, CA). The reads were mapped to the reference human genome (Human GRCh38.p13; SNP139) using NextGENe software (SoftGenetics LLC, State College, PA). The following variants were initially excluded: the common variants with the minor allele frequency greater than 1% in the control databases, including 1000 Genomes Project, ESP6500 (NHLBI Exome Sequencing Project), EXAC (The Exome Aggregation Consortium) and EXAC-EAS. The PolyPhen-2 (Cambridge, MA) and SIFT software was used to predict the potential effects of mutations.

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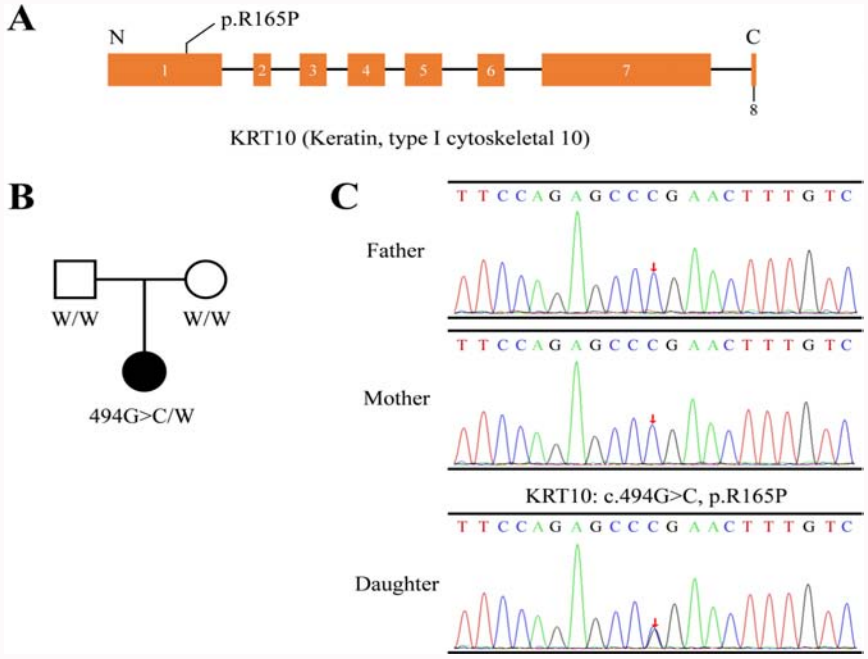

Figure 1: A *de novo* mutation was identified in the *KRT10* gene. (A) The schematic diagram of the mutant amino acids site in KRT10 protein; (B) the family tree; (C) sequences showed a heterozygous nonsense mutation (c.494G>C, p.R165P in exon 1) in the patient, and the parents were normal. Red arrows in daughter's sequences, mutant bases. R: Arginine; P: Proline

Discussion

Finally, a novel heterozygous missense variation (c.494G>C, p.R165P) in exon 1 of the *KRT10* gene was identified in the affected individual. Sanger sequencing was used to examine the proband and parents in order to further confirm the WES results and to assess whether the identified variation was present in either of the parents. The Sanger sequencing results confirmed the presence of the *KRT10* gene variant in the patient and showed that the parents were normal, indicating that the variant was de novo (Figure 1).

In a mother and son with EHK, Rothnagel et al. [4] firstly identified heterozygosity for 2 missense mutations in the *KRT10* gene, L15S and R10H [4]. Letai et al. [5] reported that clinical severity of EHK is related to the location of point mutations within the keratin polypeptides and the degree to which these mutations perturb keratin IF structure [5]. The arginine at position 156 of the *KRT10* protein is a hot spot mutation. Genetic studies found that mutations from arginine to cystine, histidine, serine or proline are associated with EHK [6]. To data, more than 120 mutations of *KRT1* and *KRT10* genes have been identified in EHK in Human Gene Mutation Database. Functional study suggested that arg156 of *KRT10* plays a special role in maintaining keratin network integrity.

Conclusion

In conclusion, we described an individual with EHK harboring a de novo mutation, c.494G>C, p.R165P. Our results expanded the database of *KRT10* gene mutations. However, further molecular studies to confirm relations between the variation and EHK are needed. Our finding will be benefit for early diagnosis of EHK and might lead to better treatment.

Author Contributions

Y.Y. designed and organized the study. L.G. did all the nursing work and analyzed the data. X.H. and R.M. acquired the clinical data. L.G. wrote the manuscript which was then edited by Y.Y. All authors contributed to and approved the manuscript.

Ethics Statement

This study was approved by the research board of the Ethics Committee of the Capital Institute of Pediatrics, Beijing, China. The patient information was anonymized; informed consent was not needed for this study, as per the guidelines of the Ethics Committee of the Capital Institute of Pediatrics.

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