Received: 27 September 2021 | Revised: 27 October 2021 | Accepted: 31 October 2021

DOI: 10.1002/ccr3.5082

CASE REPORT

Clinical Case Reports Open Access WILEY

Novel compound heterozygous mutations in the CYP4F22 gene in a patient with autosomal recessive congenital ichthyosis

Haiyan Tang[1,2] | **Xiaoliu Shi**[1] | **Guiying Zhang**[3]

[1]Department of Medical Genetics, The Second Xiangya Hospital, Central South University, Changsha, China

[2]Center for Medical Genetics, School of Life Sciences, Central South University, Changsha, China

[3]Department of Dermatology, The Second Xiangya Hospital, Central South University, Changsha, China

Correspondence
Xiaoliu Shi, Department of Medical Genetics, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China.
Email: Shixl6@csu.edu.cn

Guiying Zhang, Department of Dermatology, The Second Xiangya Hospital, Central South University, Renmin Road 139, Changsha 410083, Hunan, China.
Email: lindazgy@csu.edu.cn

Funding information
No funding was applicable

Abstract

Autosomal recessive congenital ichthyosis (ARCI) is a rare form of keratinization disorder of the skin, which can be caused by mutations in 14 ARCI genes. We present a rare case of ARCI that carried a novel null mutation and a novel splice site mutation in the CYP4F22 gene.

KEYWORDS

case report, congenital ichthyosis, CYP4F22, null mutation, splice site mutation

1 | INTRODUCTION

Autosomal recessive congenital ichthyoses (ARCIs) are rare, clinically heterogeneous keratinization disorders of the skin.[1,2] The estimated incidence is one in 200,000–300,000 individuals in the United States.[3] Classically, ARCI is divided into two clinical subtypes, lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE). The patients with LI have big, dark, plate-like scales with no severe erythroderma, while those with CIE show variable erythroderma and generalized fine scaling[2,4]). To date, thirteen different genes, ABCA12 (OMIM #601277), ALOX12B (OMIM #242100), ALOXE3 (OMIM #606545), CASP14 (OMIM #617320), CERS3 (OMIM #615023), CYP4F22 (OMIM #604777), LIPN (OMIM #613943), NIPAL4 (OMIM #612281), PNPLA1 (OMIM #615024), SDR9C7 (OMIM #617574), ST14 (OMIM #602400), SULT2B1 (OMIM #604125), and TGM1 (OMIM #242300), have been known to be associated with ARCI. Due to its high heterogeneity, the clinical presentation of ARCIs is variable, and the molecular diagnosis is very challenging,[5].

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2021 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.

Next-generation sequencing is valuable in the molecular diagnosis of ARCI, with complex correlation of genotype and phenotype.

2 | CASE PRESENTATION

The patient was a 3-year-old girl of Chinese origin. She was from non-consanguineous Chinese parents and born full term to a G1P1 mother. The patient was ichthyotic at birth. After birth, she presented clinical aspects of generalized LI with brown, plate-like scale, which was more pronounced in the periumbilical region (Figure 1A), on the lower part of the body, and on the buttocks. Hyperlinearity of palms and soles was observed in the patient (Figure 1B, C), similar to that found in ichthyosis vulgaris. Her parents had no history of skin disorders. The patient had no other disorders. Skin biopsies of the proband's trunk was for H&E histology and examined by transmission electron microscopy.

The proband was phenotyped as part of her clinical evaluation in a standard medical genetics clinic after obtaining the approval of the Ethics Committee of the Second Xiangya Hospital, Central South University (Changsha, China). All experiments were carried out in accordance with the approved protocol. Written informed consent was obtained from all subjects who participated in this study or from their legal guardians for minors.

Venous blood was collected from the patient and her parents. All genomic DNA samples were extracted from peripheral blood leukocytes using a blood DNA extraction kit according to the protocol provided by the manufacturer (TianGen). Whole exome sequencing was performed on DNA sample of the proband by using an Agilent SureSelect Human All Exon V6 kit. The captured libraries were sequenced using Illumina HiSeq 2000 Sequencer. The mapping reference sequence version was hg19. The sanger sequencing was used to validate the mutation detected by next-generation sequencing and confirm that the two detected mutations were on different alleles of CYP4F22. Specific primers (fwd:5′-cagttagccgagattgtgcc-3′ and rev: 5′-aagtggcttgtctgaggtca-3′) were used to amplify the candidate variation and validate the c.1084C>T, and primers (fwd:5′-gcccctgagagagagagaga-3′ and rev: 5′-agagctatcccatctgcagg-3′) were used to for the c.1137-2delA.

Histopathology of the proband revealed orthohyperkeratosis and keratotic plugging of follicular orifices on the light microscopic level (Figure 2), which was compatible with ARCI.

Mutation analysis of the patient identified a heterozygous nonsense mutation (chr19:15655038, NM_173483: c.1084C > T) in exon 10th and a heterozygous donor splicing mutation (chr19:15658917, NM_173483: c.1137-2delA) around exon 11th in the CYP4F22 gene. Sanger sequencing was also performed on the patient's parents (Figure 1D). Sequencing analysis showed that the father

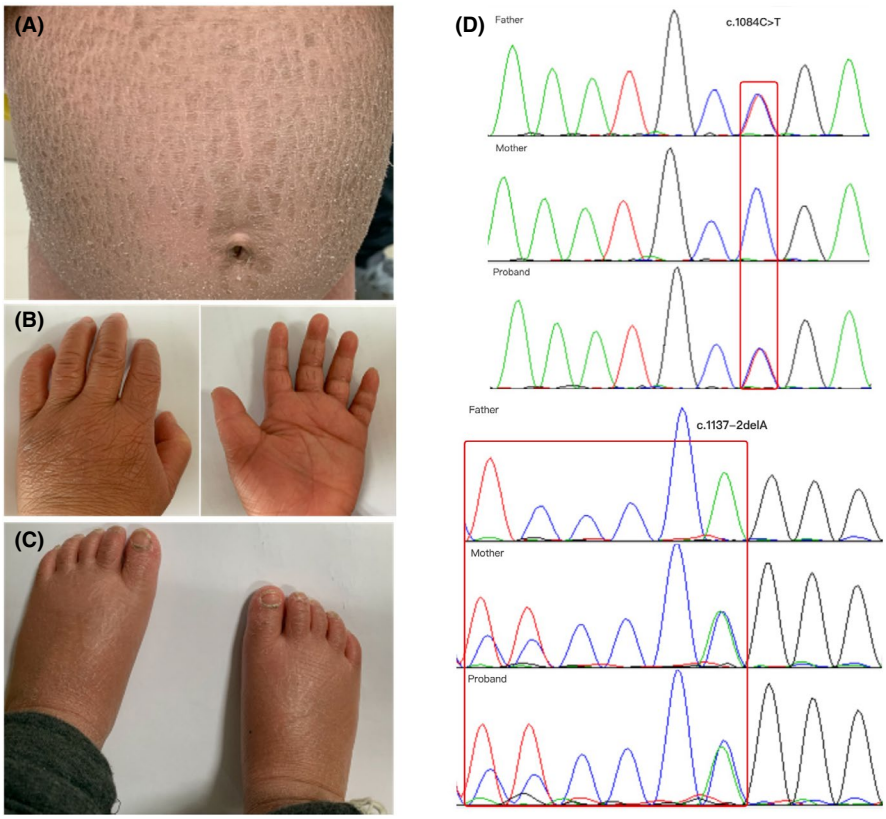

FIGURE 1 (A) Lamellar ichthyosis in the peri-umbilical region. (B and C) Hyperlinearity of the palms and soles. (D) Sequences of the mutation sites are shown for the proband and her parents

carried the heterozygous nonsense mutation(NM_173483: c.1084C > T). Her mother was heterozygous for the splicing mutation(NM_173483: c.1137-2delA). The heterozygous nonsense mutation and the heterozygous donor splicing were compound heterozygous in the proband. These two variations have not been detected in 1000 Genome Project and ExAC. For the nonsense mutation (NM_173483: c.1084C > T) identified in this pedigree, a premature termination codon was predicted to generate in the 362 amino acid. The 362 amino acid is in the most evolutionarily conserved domain of the CYP4F22 enzyme. The length of the protein would change from 532 to 362. The c.1137-2delA mutation of CYP4F22 was in the classical acceptor splice site. Splice site mutations represent a significant proportion of gene alterations leading to Mendelian disorders. Based on the interpretation of sequence variants criteria of the American College of Medical Genetics and Genomics (ACMG) guidelines, both mutations were calculated as likely pathogenic. Also, these two mutations were in trans, so it is highly likely that the two novel variations of CYP4F22 identified herein were responsible for the pathogenesis of ARCI in this pedigree. No extra potential pathogenic variants were identified in other congenital ichthyosis-related genes.

3 | DISCUSSION AND CONCLUSION

The patient was diagnosed as congenital ichthyosis based on detection of brown, plate-like scale over the entire body. No family history was mentioned. The proband's exome sequencing indicated a compound heterozygous nonsense mutation (NM_173483: c.1084C>T) and an acceptor splicing mutation (NM_173483: c.1137-2delA) in the CYP4F22 gene. Sanger sequencing confirmed that the parents were heterozygous carriers. No extra potential pathogenic variants were identified in other congenital ichthyosis-related genes. Although no RNA was available from family members for analysis, the introduction of a nonsense mutation in exon 10 of CYP4F22 is likely to result in nonsense-mediated mRNA decay. The mutation in the classical splice site (NM_173483: c.1137-2delA) is predicted to result in complete skipping of 11th exons. As 11th exon contains 130 base pairs, frame shift will be produced,[6,7]. Taken together, it is highly likely that the two novel variations of CYP4F22 identified herein are responsible for the pathogenesis of ARCI in this pedigree.

CYP4F22 deficiency is an autosomal recessive inherited genetic defect. Since the first mutation in the human CYP4F22 gene reported by Caroline,[8] 57 CYP4F22 pathogenic mutations have been identified among ARCI patients in Human Gene Mutation Database to date. We further analyzed the 27 CYP4F22 mutations in 44 patients with available ethnicity information and found that all the patients were from Asia, Europe, and Africa (Figure 3). Fifteen mutations were detected in 16 patients from Asia. Nine mutations were unique to the Asians and three mutations were hot spots (c.59dup, c.728G>A, and c.1303C > T). In 2013, Sugiura et al.[9] reported the first Japanese ARCI patient with c.728G > A mutation compound heterozygous with the first novel c.1138del mutation.[9] In 2017, two CYP4F22 mutations (c.466 > T and c.844C > T) were reported in China,[10] which were separately reported by Israell and Buckova in Jewish and Czech populations.[11,12] The present study reported the first ARCI patient with two novel mutations in the CYP4F22 gene in Asia.

In conclusion, this study expands the mutation spectrum of CYP4F22 resulting in ARCIs in Chinese, which could provide insights into the molecular diagnosis and genetic counseling of families.

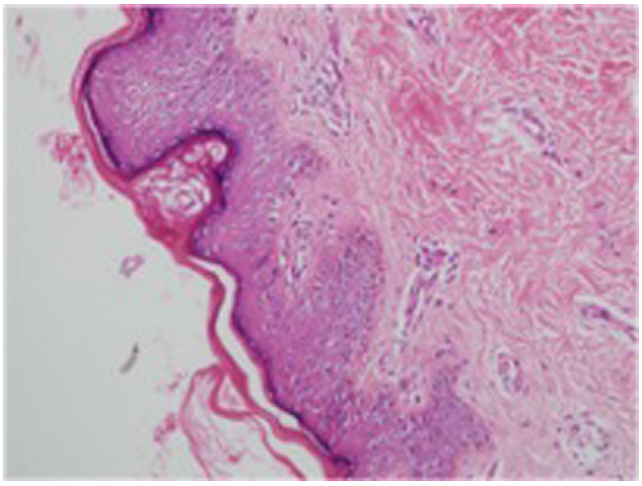

FIGURE 2 Orthohyperkeratosis, prominent granular layer, and lack of dermal inflammation, demonstrated by H&E staining. Indicated magnification =200×

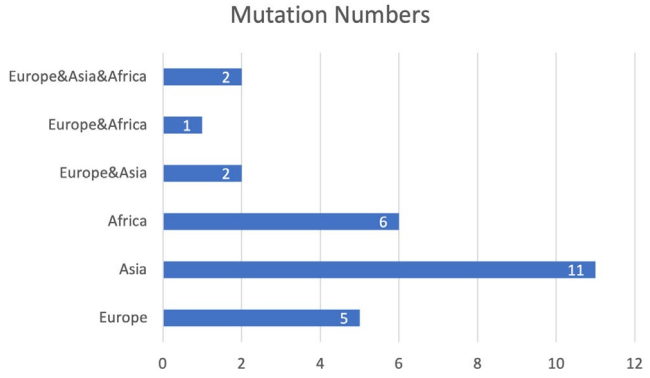

FIGURE 3 CYP4F22 mutations found in patients with autosomal recessive congenital ichthyosis with available ethnicity information to date

ACKNOWLEDGEMENTS

We thank our patient and her family for their cooperation and participation in our study.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

HYT was involved in DNA isolation, genetic analysis of data, and manuscript drafting. GYZ carried out family recruitment, blood sampling, and clinical analysis. XLS supervised the whole study, helped in data analysis, edited, and refined the manuscript. All authors have read and approved the refined manuscript.

ETHICAL APPROVAL

This study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University (Changsha, China). The reference number was S046 in 2014.

CONSENT

Written informed consent was obtained from the patient's parents for publication. A copy of the written consent is available for review by the Editor of this journal. The authors know and consent for publication.

DATA AVAILABILITY STATEMENT

The data generated or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

Haiyan Tang https://orcid.org/0000-0002-9029-8431

REFERENCES

1. Richard G. Autosomal recessive congenital ichthyosis. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, eds. *GeneReviews((R))*. University of Washington; 1993.
2. Williams ML, Elias PM. Heterogeneity in autosomal recessive ichthyosis. Clinical and biochemical differentiation of lamellar ichthyosis and nonbullous congenital ichthyosiform erythroderma. *Arch Dermatol*. 1985;121(4):477–488. 10.1001/archderm.121.4.477
3. Rodriguez-Pazos L, Ginarte M, Fachal L, Toribio J, Carracedo A, Vega A. Analysis of TGM1, ALOX12B, ALOXE3, NIPAL4 and CYP4F22 in autosomal recessive congenital ichthyosis from Galicia (NW Spain): evidence of founder effects. *Br J Dermatol*. 2011;165(4):906–911. 10.1111/j.1365-2133.2011.10454.x
4. Oji V, Tadini G, Akiyama M, et al. Revised nomenclature and classification of inherited ichthyoses: results of the first ichthyosis consensus conference in Soreze 2009. *J Am Acad Dermatol*. 2010;63(4):607–641. 10.1016/j.jaad.2009.11.020
5. Rodriguez-Pazos L, Ginarte M, Vega A, Toribio J. Autosomal recessive congenital ichthyosis. *Actas Dermosifiliogr*. 2013;104(4):270–284. 10.1016/j.adengl.2011.11.021
6. Berget SM. Exon recognition in vertebrate splicing. *J Biol Chem*. 1995;270(6):2411-2414. 10.1074/jbc.270.6.2411
7. Roca X, Sachidanandam R, Krainer AR. Intrinsic differences between authentic and cryptic 5′ splice sites. *Nucleic Acids Res*. 2003;31(21):6321–6333. 10.1093/nar/gkg830
8. Lefèvre C, Bouadjar B, Ferrand V, et al. Mutations in a new cytochrome P450 gene in lamellar ichthyosis type 3. *Hum Mol Genet*. 2006;15(5):767–776. 10.1093/hmg/ddi491
9. Sugiura Kazumitsu, Takeichi Takuya, Tanahashi Kana, et al. Lamellar ichthyosis in a collodion baby caused by CYP4F22 mutations in a non-consanguineous family outside the Mediterranean. *J Dermatol Sci*. 2013;72(2):193–195. 10.1016/j.jdermsci.2013.06.008
10. Feng C, Wang H, Lee M, Zhao J, Lin Z, Yang Y. Two missense mutations in CYP4F22 in autosomal recessive congenital ichthyosis. *Clin Exp Dermatol*. 2017;42(1):98–100. 10.1111/ced.12988
11. Bučková H, Nosková H, Borská R, et al. Autosomal recessive congenital ichthyoses in the Czech Republic. *Br J Dermatol*. 2016;174(2):405–407. 10.1111/bjd.13918
12. Israeli S, Goldberg I, Fuchs-Telem D, et al. Non-syndromic autosomal recessive congenital ichthyosis in the Israeli population. *Clin Exp Dermatol*. 2013;38(8):911–916. 10.1111/ced.12148

How to cite this article: Tang H, Shi X, Zhang G. Novel compound heterozygous mutations in the CYP4F22 gene in a patient with autosomal recessive congenital ichthyosis. *Clin Case Rep*. 2021;9:e05082. doi:10.1002/ccr3.5082