

News Release

Title

Biallelic mutations in *KDSR* disrupt ceramide synthesis and result in a spectrum of keratinization disorders associated with thrombocytopenia

Key Points

○ Using whole-exome sequencing in four probands with undiagnosed skin hyperkeratosis/ichthyosis complicated with thrombocytopenia, we identified compound heterozygosity for mutations in *KDSR*, encoding an enzyme in the *de novo* synthesis pathway of ceramides.

○ The mutations in *KDSR* were associated with reduced ceramide levels in skin and impaired platelet function.

○ Mutations in *KDSR* cause defective ceramide biosynthesis, underscoring the importance of ceramide and sphingosine synthesis pathways in skin and platelet biology.

Summary

Prof. Masashi Akiyama, Dr. Takuya Takeichi (first author) at Department of Dermatology, Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, MD, PhD), Prof. John A. McGrath (corresponding author) at St John's Institute of Dermatology, King's College London, Guy's Hospital, and Prof. Akio Kihara at Faculty of Pharmaceutical Sciences, Hokkaido University, discovered that biallelic mutations in *KDSR* disrupt ceramide synthesis and result in a spectrum of keratinization disorders associated with thrombocytopenia.

Mutations in ceramide biosynthesis pathways have been implicated in a few Mendelian disorders of keratinization although ceramides are known to have key roles in several biological processes in skin and other tissues. Using whole-exome sequencing in four probands with undiagnosed skin hyperkeratosis/ichthyosis, we identified compound heterozygosity for mutations in *KDSR*, encoding an enzyme in the *de novo* synthesis pathway of ceramides. Two individuals had hyperkeratosis confined to palms and soles as well as anogenital skin, whereas the other two had more severe, generalized harlequin ichthyosis-like skin. Of note, thrombocytopenia was present in all cases. The mutations in *KDSR* were associated with reduced ceramide levels in skin and impaired platelet function. *KDSR* enzymatic activity was variably reduced in all cases resulting in defective acylceramide synthesis. Our study demonstrates that biallelic mutations in *KDSR* are implicated in an extended spectrum of disorders of keratinization in which thrombocytopenia is also part of the phenotype. Mutations in *KDSR* cause defective ceramide biosynthesis, underscoring the importance of ceramide and sphingosine synthesis pathways in skin and platelet biology.

Research Background

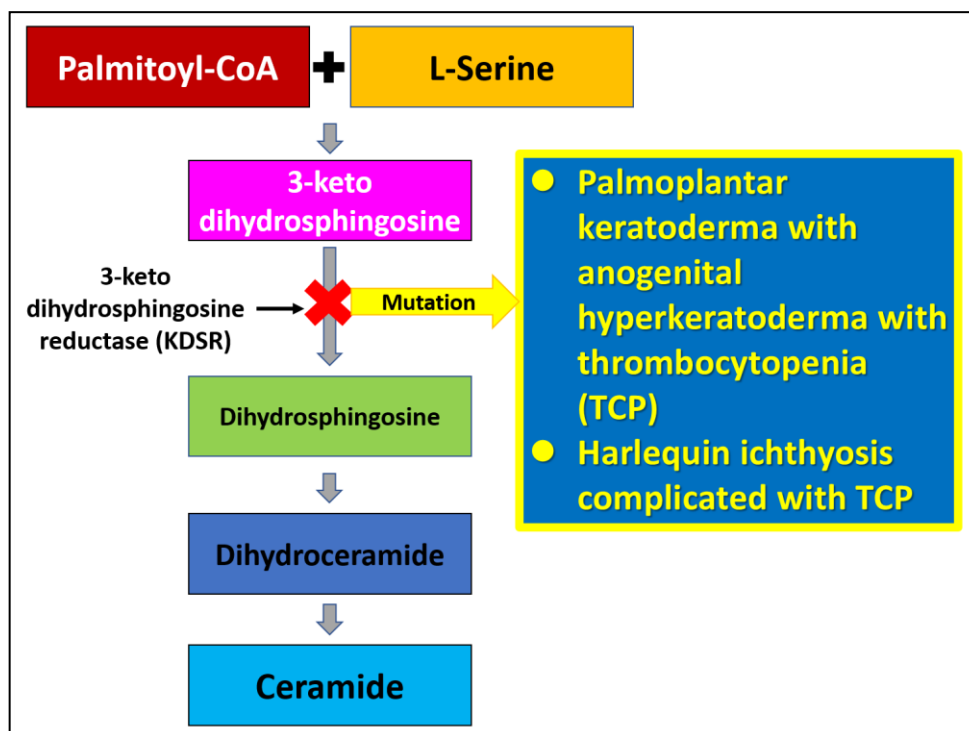
The hereditary palmoplantar keratodermas and ichthyoses comprise a heterogeneous collection of genodermatoses caused by mutations in >100 genes involved in a multitude of biologic pathways and processes. Despite major advances in discovering the underlying molecular genetic basis of many of these disorders, several cases remain unresolved, indicating the likely contribution of further gene pathology. In this study, we investigated four individuals from Spain, Japan and the United Kingdom who presented with inherited disorders of keratinization. Notably, two patients displayed a milder phenotype of palmoplantar and anogenital hyperkeratosis, whereas the other two cases had a more severe phenotype resembling harlequin ichthyosis. An additional finding, present in all our subjects was a reduction in the number of blood platelets (thrombocytopenia).

Research Results

Using whole-exome sequencing in four probands with undiagnosed skin hyperkeratosis/ichthyosis, we identified compound heterozygosity for mutations in *KDSR*. *KDSR* encodes 3-ketodihydrosphingosine reductase which catalyzes the reduction of 3-ketodihydrosphingosine to dihydrosphingosine, a key step in the *de novo* ceramide synthesis pathway. Of note, thrombocytopenia was present in all cases. The mutations in *KDSR* were associated with reduced ceramide levels in skin and impaired platelet function. *KDSR* enzymatic activity was variably reduced in all cases resulting in defective acylceramide synthesis.

Research Summary and Future Perspective

Our study demonstrates that biallelic mutations in *KDSR* are implicated in an extended spectrum of disorders of keratinization in which thrombocytopenia is also part of the phenotype. Mutations in *KDSR* cause defective ceramide biosynthesis, underscoring the importance of ceramide and sphingosine synthesis pathways in skin and platelet biology.



Publication

Takuya Takeichi, Antonio Torrelo, John Y. W. Lee, Yusuke Ohno, María Luisa Lozano, Akio Kihara, Lu Liu, Yuka Yasuda, Junko Ishikawa, Takatoshi Murase, Ana Belén Rodrigo, Pablo Fernández-Crehuet, Yoichiro Toi, Jemima Mellerio, José Rivera, Vicente Vicente, David P. Kelsell, Yutaka Nishimura, Yusuke Okuno, Daiei Kojima, Yasushi Ogawa, Kazumitsu Sugiura, Michael A. Simpson, W. H. Irwin McLean, Masashi Akiyama, John A. McGrath. Biallelic mutations in *KDSR* disrupt ceramide synthesis and result in a spectrum of keratinization disorders associated with thrombocytopenia. *The Journal of Investigative Dermatology*, Published online before print July 31, 2017.

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