

News Release

Title

A child with epidermolytic ichthyosis from a parent with epidermolytic nevus: risk evaluation of transmission from mosaic to germline

Key Points

- Epidermolytic nevus (EN), which is a rare subgroup of epidermal nevi, produced epidermolytic ichthyosis (EI), which is a keratinopathic ichthyosis, in the next generation.
- We rigorously measured mutant allele frequency in cells of the father's lesional skin, father's blood and semen by next-generation sequencing.
- We established the method to evaluate the risk of disease transmission as EI from the father having EN and to provide significant information at genetic counseling.

Summary

A research team from Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, M.D., Ph.D.) including Prof. Masashi Akiyama (Professor, Department of Dermatology) and Dr. Michihiro Kono (Associate professor, Department of Dermatology) proved that the phenomenon of epidermolytic nevus (EN), which is a rare subgroup of epidermal nevi, produced epidermolytic ichthyosis (EI), which is the systemic form of the identical skin lesion, in the next generation through germline mutation directly. In addition, the team succeeded in the risk evaluation of transmission from EN to EI by next generation sequencing. This work has been carried out as a collaboration study with Professor Yasushi Suga (Department of Dermatology, Juntendo University Urayasu Hospital).

There are various kinds of birthmarks. During we grow as an embryo, we get mutations in several genes in some cells of our bodies. It is thought that certain gene mutations in the cells of the skin could cause birthmarks. In many cases, birthmarks do not inherit because genes in sperm and eggs are rarely mutated, but in exceptional cases, it may be inherited to the next generation. In such cases, children develop the systemic form of skin symptoms identical to the birthmark.

EN, the subject of the present study, was a unique type of birthmarks due to mosaicism of *KRT1* or *KRT10* mutations. We encountered a family including a father with EN and his daughter with EI. We diagnosed daughter's disease by detection of heterozygous *KRT10* mutation in her. Then, we investigated gDNA extracted from a skin sample from an EN lesion of her father and detected the identical mutation. Considering the risk of EI in their future children, the parents wanted to know what percentage of the father's gametes had the mutation. Thus, we investigated the percentage of sperm with the pathogenic *KRT10* mutation in a semen sample from the

father by next-generation sequencing (NGS). We evaluated that approximately 3.9% of his sperm had the causative mutation.

In the present study, we investigated the precise prevalence of cells carrying the causative *KRT10* mutation in the skin lesions, white blood cells in the peripheral blood, and the gametes of the EN patient by NGS. In cases of EN, genetic diagnosis of the skin lesion and proper genetic counseling on the risk of disease transmission to the next generation would be beneficial to patients who wish to bear children.

Research Background

Epidermolytic nevus (EN) is a rare subgroup of epidermal nevi, caused by somatic mutations in *KRT1* or *KRT10*. Epidermolytic ichthyosis (EI) is caused by autosomal dominant germline mutations in *KRT1* or *KRT10*. Rarely, EN can produce EI in the next generation. In those cases, somatic mutations causative of EI in a parent involve germline cells and are transmitted to children.

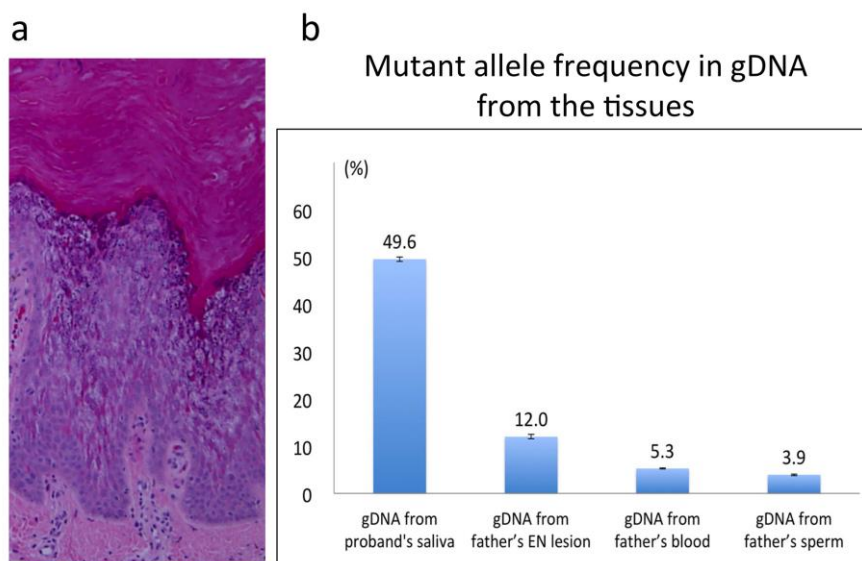
Research Results

A young Japanese girl, the proband, showed diffuse erythema, multiple blisters and erosions on the whole body at birth. With growth, she showed scales and hyperkeratosis on the entire body surface. She was clinically and histopathologically diagnosed with EI. Her father presented hyperkeratotic lesions on the upper limb and the lumbar regions. The affected skin accounted for 0.5% of his whole body surface. First, mutation analysis identified a heterozygous mutation in *KRT10* of genomic DNA (gDNA) from the proband. Then, we investigated gDNA extracted from the skin sample of the EN lesion of her father and detected the identical mutation. In considering future children, the parents wanted to know what percentage of the father's gametes had the mutation. Thus, we investigated the percentage of sperm with the pathogenic *KRT10* mutation in semen from the proband's father by next-generation sequencing (NGS). We evaluated that approximately 3.9% of his semen had the causative mutation and that the mutant allele frequency in his peripheral blood was 5.3%, although we were unable to detect the mutation in either of the samples by Sanger sequencing. These results clearly indicate the limited ability of Sanger sequencing to find low-level mosaicism. The mutant allele frequency in his lesional skin, including in the dermis, was 12.0%.

Research Summary and Future Perspective

We investigated the level of mosaicism in some tissues, including semen, by next-generation sequencing (NGS). From the mutant rates in sperm, we evaluated the risk of disease transmission from a father with EN to a child at future pregnancies. In cases of EN, genetic diagnosis of the skin lesion and proper genetic counseling on the risk of disease transmission to the next generation would be beneficial to patients who

wish to bear children.



a. Histological examination of the scaly lesion on the paraumbilical abdomen of the proband's father reveals thick orthokeratotic hyperkeratosis and granular degeneration in the epidermis. b. The mutant allele frequency in gDNA samples from the saliva of the proband and from the EN lesion, blood and sperm of the proband's father was determined by amplicon sequencing. Approximately 3.9% of the father's sperm has the causative mutation (mutant allele frequency) and the mutant allele frequency in his peripheral blood cells is 5.3 %, as obtained by deep sequencing. The mutant allele frequency in his EN lesion, including the dermis, as determined by deep sequencing is 12.0 %. The mutant allele frequency in the proband's saliva is 49.6 % as determined by deep sequencing.

Publication

Michihiro Kono, Yasushi Suga, Tomohiro Akashi, Yasutomo Ito, Takuya Takeichi, Yoshinao Muro and Masashi Akiyama. A child with epidermolytic ichthyosis from a parent with epidermolytic nevus: risk evaluation of transmission from mosaic to germline. *Journal of Investigative Dermatology*, published (online) on May 19, 2017.

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https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Investigative_Dermatology_20170522.pdf