News Release

Title

Elucidation of Novel Genetic Pathogenesis based on Mendelian Inheritance: Revertant Mutation-Triggered Onset of Congenital Disease by Release of Confined Lethal Mutations

Key Points

○An estimated 11,000 individuals in Japanese population may have a potentially lethal dominant pathogenic mutation in *GJB2* gene, nonetheless protected from the disease because of a common coexisting tandem nonsense mutation that "confine" the effect of the pathogenic mutation.

○The present study report the first instance in the literature where the reversion of a "confining" nonsense mutation released the dominant pathogenic effect of a coexisting gain-of-function mutation, eliciting a lethal disease.

Summary

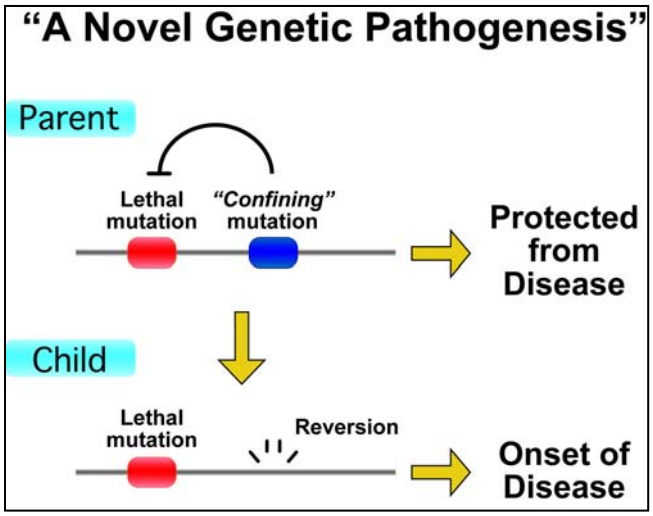
A Joint research team from Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.) led by Dr. Masashi Akiyama (Professor, Department of Dermatology) found and elucidated a novel pathogenic mechanism that leads to onset of genetic diseases. Other members included Dr. Yasushi Ogawa (Assistant Professor, Department of Dermatology), Dr. Nobuyuki Hamajima (Professor, Department of Healthcare Administration) and Dr. Toshimichi Yamamoto (Associate Professor, Department of Legal Medicine and Bioethics).

The research team reported the first instance in the literature where a reversion of a nonsense mutation elicited a lethal genetic disease by releasing the dominant pathogenic effect of another gain-of-function mutation coexisting in the same gene.

Their study also suggested that approximately 11,000 Japanese populations carry the same pathogenic mutation; nonetheless remain unaffected because they also carry the nonsense mutation in tandem that confines the effect of the pathogenic mutation.

The finding of the reversion-triggered onset of the genetic disease adds a novel insight in the classic Mendelian inheritance, and may provide relevant information to the Japanese populations who have the same mutations.

The result of their research was published in an article in *PLOS Genetics* on May 1 ,2014. .



Research Background

Genetic mutations may often cause genetic diseases. For instance, a missense mutation may change the function of the product of the affected gene and exert a dominant pathologic effect leading to disease manifestations.

On the other hand, a revertant mutation is a mutation that restores an existing mutation to the normal sequence. Revertant mutations may occur in mitosis or in meiosis via gene recombination mechanisms such as gene conversions or crossovers. Several cases of dermatological or hematological hereditary disorders are reported where reversion of existing mutations ameliorate genetic diseases.

While the loss of gene functions due to nonsense mutations is a typical pathogenic mechanism of hereditary diseases, they may, in certain genetic contexts, confine the effects of other dominant pathogenic mutations and suppress disease manifestations. Theoretically, in such cases, reversion of the "confining" mutation could release the toxic effect of the other mutation and may elicit disease, although actual cases of this revertant-triggered genetic pathogenesis have not been reported.

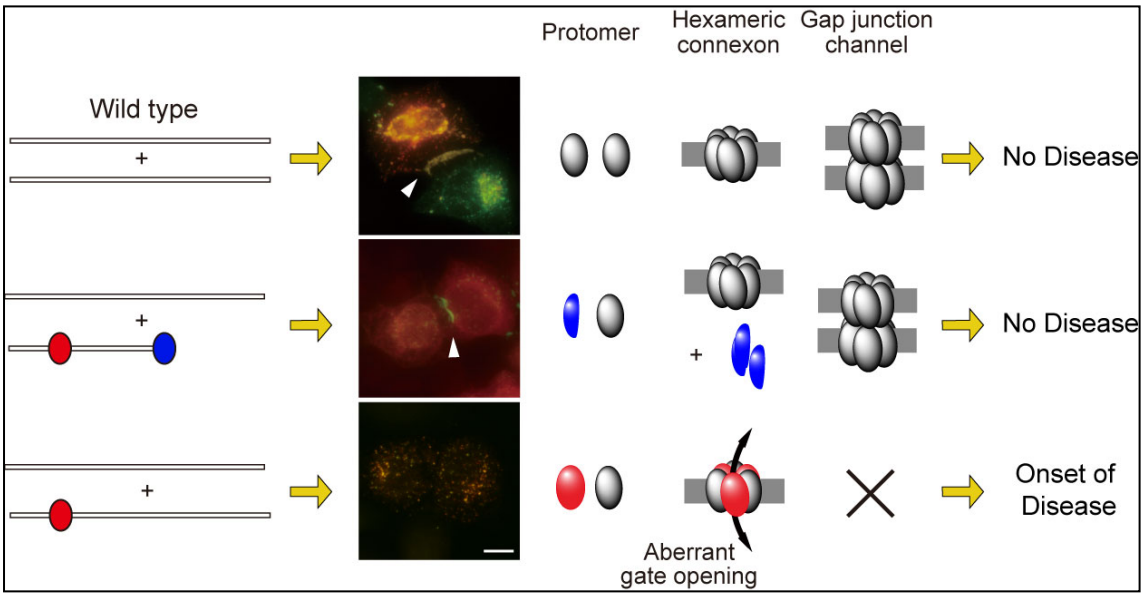
The present study reports the first instance in the literature where the reversion of a "confining" nonsense indeed elicited a lethal disease.

Research Results

The new genetic pathogenesis was found in a patient of keratitis-deafness-ichthyosis syndrome who had a dominant pathogenic p.Gly45Glu mutation in *GJB2* gene. One of the parent also had the same mutation, however, remained unaffected by the disease. Further investigation revealed that absence of the disease in the parent was due to another coexisiting p.Tyr136X nonsense mutation in the same allele of *GJB2* gene that confined the dominant pathogenic effect of the other mutation. From the results of a haplotype analysis using 40 SNPs spanning the >39 kbp region surrounding *GJB2* gene and an extended SNP microarray analysis spanning throughout chromosome 13, the p.Tyr136X mutation was considered to be reverted in the patient's allele during meiotic division of the gamete.

Previous reports and the result of our mutation screening support that the p.Gly45Glu is in complete linkage disequilibrium with the p.Tyr136X in the Japanese population. An epidemiologic estimation demonstrate that approximately 11,000 individuals in Japanese population may have the same lethal *GJB2* mutation, nonetheless protected from the manifestation of the syndrome because they also inherit the common p.Tyr136X mutation.

Studies using cultured cells elucidated the molecular pathogenesis of p.Gly45Glu and the mechanism that p.Tyr136X neutralizes the effect of p.Gly45Glu. Cx26, the product of *GJB2*, is a gap junction protein. Cx26 is a protomer of a hexameric connexon, and two connexons expressed on the membranes of neighboring cells connect to form a gap junction channel. We confirmed that cx26 carrying single p.Gly45Glu mutation formed the hexameric connexons mixed with normal cx26 protomers, but failed to form gap junctions. Furthermore, the protomers that contain p.Gly45Glu cx26 showed an aberrant channel activity. In contrast, cx26 that carry both p.Gly45Glu and p.Tyr136X mutations failed to be incorporated into the hexameric connexons that was formed solely by the wildtype cx26.



Research Summary and Future Perspective

The finding of the reversion-triggered onset of the genetic disease adds a novel insight in the classic Mendelian inheritance, and may provide relevant information to the Japanese populations who have the same mutations.

The concept of functional crosstalk of genetic mutations highlighted by the present study may provide a theoretical basis in development of new dermatological therapeutics that utilize gene manipulation or natural revertant mosaicism.

Ogawa Y, Takeichi T, Kono M, Hamajima N, Yamamoto T, Sugiura K, Akiyama M. *PLOS Genetics* 2014(To be published on May 1,2014)

Japanese ver.

http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material_/nu_medical/_res/topix/2014/gjb2_20140502jp.pdf