News Release

Title

Two totally different diseases to be caused by RNA editing abnormality ~we have tied a hereditary inflammatory neurologic disease and a genodermatosis to one~

Key Points

○We have tied hereditary inflammatory neurologic disease and genodermatosis to one.

○We have shown the possibility that the difference of skin manifestation of DSH was due to the different degrees of the skin pigmentation by a race.

○We showed the possibility that RNA editing efficiency was associated with onset of neurologic symptoms and the eruption.

Summary

A research team from Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.) including Dr. Masashi Akiyama (Professor, Department of Dermatology) and Dr. Michihiro Kono (Lecturer, Department of Dermatology) elucidated the association of skin and neurological symptom of two quite different diseases caused by an identical gene *ADAR1*, genetic skin disease dyschromatosis symmetrica hereditaria (DSH) and inflammatory neurologic disease Aicardi-Goutières syndrome (AGS6).

Dyschromatosis symmetrica hereditaria (DSH: MIM#127400) is an autosomal dominant skin disease and is characterized by a mixture of hyper- and hypo-pigmented small macules on the dorsal aspects of the extremities. Our laboratory elucidated that DSH caused by adenosine deaminase acting on RNA 1 gene (*ADAR1*, NM_001111.4).

AGS is a genetic inflammatory disorder that affects the nervous system, main symptoms are developmental delay and intracranial calcification. AGS is thought to be caused by inflammation that is caused by enhanced interferon-production. AGS have some subtypes including AGS6, which is caused by *ADAR1* mutations.

No AGS6 patient reported previously showed DSH skin symptom. The relationship between DSH and AGS6 have remained to be elucidated.

We found a case who showed skin manifestation of DSH and neurological symptom of AGS6 and who have bi-allelic mutations in *ADAR1*.

We paid our attention to there being a difference in the degree of the skin symptom of DSH by a race and proposed the race-specific genotype/phenotype correlations of DSH/AGS caused by ADAR1 mutations.

We showed the possibility that RNA editing efficiency was associated with the onset of neurologic symptoms and the cutis symptom by RNA editing assay.

By this study, it was elucidated that an inflammatory neurologic disease AGS6 and a hereditary pigmentary disorder DSH are a series of diseases due to *ADAR1* mutations.

It is expected that these results of our research will accelerate elucidation of pathogenesis and establishment of the therapy in the near future. Particularly, it is significant that our investigation of the development of a therapy for the skin disease DSH may contribute to the establishment of treatments for neurologic disease AGS6.

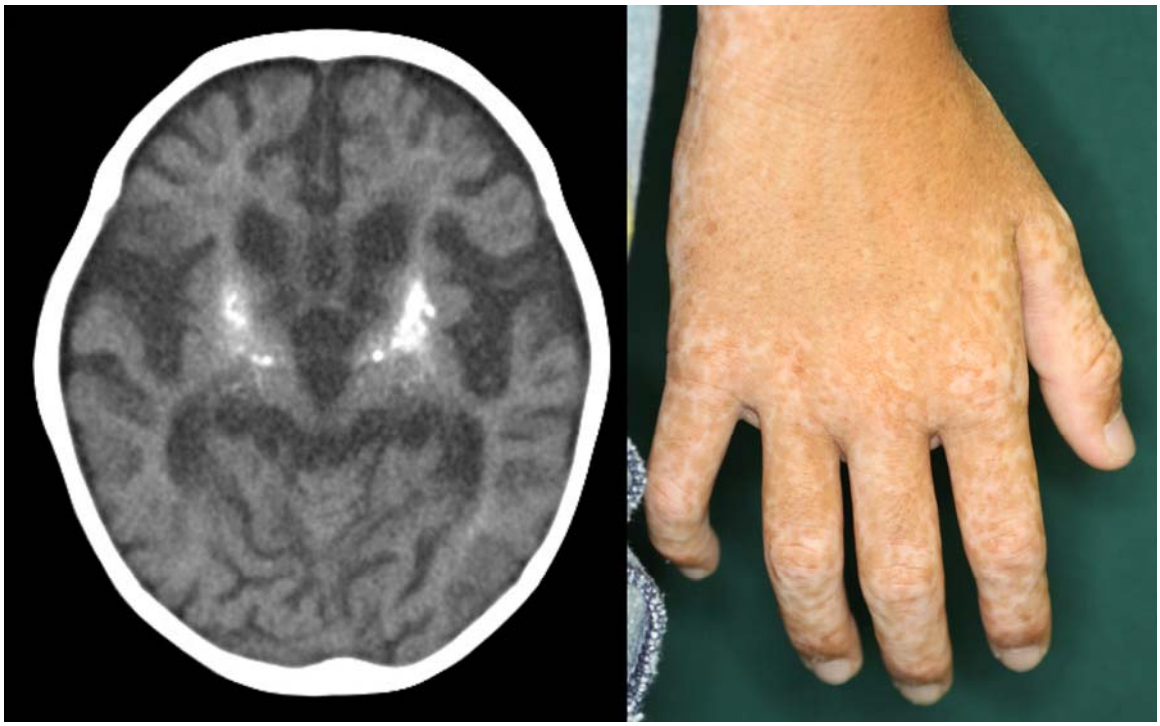
The result of their research was published online in an article in Journal of Investigative Dermatology on January 21, 2016.

Research Background

Dyschromatosis symmetrica hereditaria (DSH: MIM#127400) is an autosomal dominant skin disease caused by a heterozygous mutation in adenosine deaminase acting on RNA 1 gene (*ADAR1*, NM_001111.4) (Miyamura *et al.*, 2003). DSH is characterized by a mixture of hyper- and hypo-pigmented small macules on the dorsal aspects of the extremities. Our laboratory elucidated that DSH caused by adenosine deaminase acting on RNA 1 gene.

AGS is a genetic inflammatory disorder that affects the nervous system, main symptoms are developmental delay and intracranial calcification. AGS is thought to be caused by inflammation that is caused by enhanced interferon-production. AGS have some subtype including AGS6, which is caused by *ADAR1* mutation (Rice *et al.*, 2012). AGS6 has an autosomal recessive inheritance trait.

It has been known that both of DSH and AGS6 are caused by mutations in *ADAR1*. Mono-allelic mutations of *ADAR1* cause DSH and bi-allelic mutations result in AGS6. However, no AGS6 patient reported previously showed the DSH skin symptoms. Thus, the relationship between DSH and AGS6 have remained to be elucidated.



Research Results

As a result of our reseach, we found a case who showed skin manifestations of DSH and neurological symptoms of AGS6 and who have bi-allelic mutations in *ADAR1*.

We paid our attention to there being a difference in the degree of the skin symptoms of DSH by a race and investigated genome data of 4300 European Americans using the NHLBI GO Exome Sequencing Project (ESP) Exome Variant Server. We found two mutations which reported previously as pathogenic mutations of DSH. These two Caucasians who have one mutation each must not show the distinct skin manifestation. This result indicated that eastern Asians could have more obvious skin lesion than Caucasian. We proposed the race-specific genotype/phenotype correlations of DSH/AGS caused by ADAR1 mutations.

We showed the possibility that RNA editing efficiency was associated with the onset of neurologic symptoms and the cutis symptom by RNA editing assay.

In this study, above-mentioned findings combined these two diseases as a disease to be caused by the abnormality of the ADAR1 gene. We conclude that inflammatory neurologic disease AGS6 and hereditary pigmentary disorder DSH are a series of diseases due to *ADAR1* mutations.

Table. Summary of race-specific genotype/phenotype correlations of DSH/AGS caused by ADAR1 mutations

State of ADAR1 mutations	Non-East Asian	East Asian
Homozygous or compound heterozygous	AGS	AGS + DSH
Heterozygous for p.G1007R	AGS or No apparent disorder	AGS + DSH or DSH only
Heterozygous for mutations other than p.G1007R	No apparent disorder	DSH

Research Summary and Future Perspective

In future, it is expected that elucidation of pathogenesis and establishment of the therapy will be accelerate by the results of our research. Particularly, it is significant that our investigation of the development of a therapy for the skin disease DSH may contribute to the establishment of treatments for neurologic disease AGS6.

Article

Kono M, Matsumoto F, Suzuki Y, Suganuma M, Saitsu H, Ito Y, Fujiwara S, Matsumoto K, Moriwaki S, Matsumoto N, Tomita Y, Sugiura K, Akiyama M. Dyschromatosis symmetrica hereditaria and Aicardi-Goutières syndrome 6 are phenotypic variants caused by ADAR1 mutations. Journal of Investigative Dermatology; Jan. 21, 2016.

Japanese ver.

http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material_/nu_medical/_res/topix/2015/AGS6_20160121jp.pdf