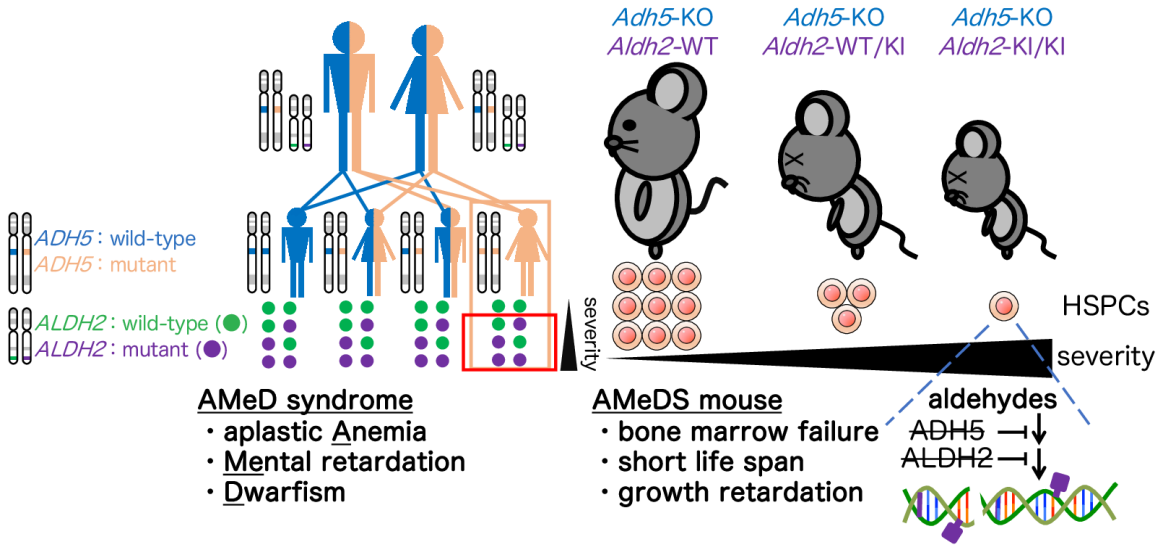
News Release

Title

Malfunctions in the formaldehyde clearance processes cause a previously uncharacterized "AMeD syndrome."

Key Points

- Identification of the defective allele of *ALDH2* gene in combination with mutations in *ADH5* causes "AMeD" (aplastic anemia, mental retardation, and dwarfism) syndrome from undiagnosed patients with inherited bone marrow failure syndromes.
- The number of the defective allele of *ALDH2* gene determines the severity of clinical features of "AMeD syndrome."



Summary

The research group led by Dr. Yasuyoshi Oka and Prof. Tomoo Ogi (Department of Genetics, Research Institute of Environmental Medicine, Nagoya University) in collaboration with Dr. Motoharu Hamada, Prof. Yoshiyuki Takahashi and Prof. Emer. Seiji Kojima (Department of Pediatrics, Nagoya University Graduate School of Medicine) identified digenic mutations in *ALDH2* and *ADH5* cause "AMeD syndrome" which is characterized by aplastic anemia, mental retardation, and dwarfism. Based on the clinical findings and the analysis of the animal model of AMeD syndrome, a functional single nucleotide polymorphism (SNP) in the *ALDH2* gene determines the severity of clinical features. The study has been published in *Science Advances* on December 18, 2020 (EST).

Research Background

Inherited bone marrow failure syndromes (IBMFS) are extremely rare diseases, occurring in one in tens or hundreds of thousands of people, in which hematopoietic cells are unable to produce blood due to abnormal cell differentiation and proliferation. IBMFS have been known to include Fanconi anemia (FA), dyskeratosis congenita (DC), and Diamond-Blackfan anemia (DBA); FA is caused by a defect in the mechanism of DNA interstrand crosslink repair, DC is caused by a disruption in the mechanism of telomere length maintenance, and DBA is caused by abnormalities in the maturation of ribosomal proteins. However, some patients with IBMFS have been undiagnosed due to the complicated and unclassified molecular pathology.

Research Results

We identified biallelic mutations in the *ADH5* gene, an enzyme related to aldehyde metabolism, in all of the AMeD syndrome cases (ten cases in eight unrelated families) which are extracted from the Rare/Intractable Disease (nanbyo) Project of Japan and the central review system of the Japanese Society of Pediatric Hematology and Oncology.

However, because previous studies showed that *Adh5*-null mice did not show any devastating phenotype that causes a survival disadvantage, we evaluated the pathogenicity of the ADH5 deficiency in humans. We searched for Japanese individuals with biallelic *ADH5* rare variants in genotype-available databases including ToMMo (Tohoku Medical Megabank), HGVD (Human Genetic Variation Database, Kyoto University), BBJ (Bio Bank Japan, Tokyo University), and Nagahama Study (Nagahama Prospective Cohort for Comprehensive Human Bioscience, Kyoto University) datasets. Furthermore, we genotyped the *ADH5* pathogenic variant alleles in Japanese individuals (Hospital-based Epidemiologic Research Program at Aichi Cancer Center, HERPACC, Aichi Cancer Center). From these screenings and cellular experiments, we found a healthy subject (female, age 55, no pre-existing conditions) with a homozygous hypomorphic mutation in the *ADH5* gene, indicating that the *ADH5*-monogenic deficiency is not sufficient to cause AMeD syndrome.

Therefore, we considered a possibility of digenic/oligogenic inheritance. We focused on the *ALDH2* gene because ALDH2 is an enzyme involved in the metabolism of aldehydes, and approximately 40% of the East Asian population (equivalent to 8% of the world's population) carries a functional SNP which is well known associated with alcohol flushing. By examining the SNP genotype, we found that all ten AMeDS syndrome patients carry at least one copy of the defective allele. Most importantly, the healthy subject with the hypomorphic *ADH5* variant harbors the homozygous wild-type SNP alleles. Furthermore, all three cases homozygous for the *ALDH2* SNP defective alleles manifested more severe phenotypes, suggesting that the aldehyde detoxification activity determined by the *ALDH2* SNP genotype underlies the severity of AMeDS clinical features. Collectively, we conclude that the *ALDH2* SNP defective allele in combination with biallelic loss of function mutations in the *ADH5* gene is necessary and sufficient to cause a digenic disorder, AMeD syndrome.

To investigate the consequences of the *ADH5* and *ALDH2* digenic deficiency for the

development of multisystem abnormalities in AMeD syndrome, we generated gene-edited mice with mutations found in AMeD patients. The mice recapitulated key clinical features of AMeD syndrome, showing short life span, dwarfism, and haematopoietic failure.

Future Perspective

Our study demonstrates detailed clinical manifestations of AMeD syndrome cases, which enables us to distinguish AMeD syndrome from other IBMFS. As the exact molecular mechanisms underlying the various phenotypes of AMeD syndrome caused by impairment of aldehyde clearance remains enigmatic, further analysis will be necessary to address the question.

Publication

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Digenic mutations in *ALDH2* and *ADH5* impair formaldehyde clearance and cause a multisystem disorder, AMeD syndrome

Yasuyoshi Oka[1, 2], Motoharu Hamada[3], Yuka Nakazawa[1, 2], Hideki Muramatsu[3], Yusuke Okuno[3], Koichiro Higasa[4, 5], Mayuko Shimada[1, 2], Honoka Takeshima[1, 2, 6], Katsuhiro Hanada[7], Taichi Hirano[8], Toshiro Kawakita[8], Hirotoshi Sakaguchi[9], Takuya Ichimura[10], Shuichi Ozono[11], Kotaro Yuge[11], Yoriko Watanabe[11], Yuko Kotani[12, 13], Mutsumi Yamane[14], Yumiko Kasugai[15], Miyako Tanaka[16, 17], Takayoshi Suganami[16, 17], Shinichiro Nakada[18, 19], Norisato Mitsutake[20], Yuichiro Hara[1, 2], Kohji Kato[1, 2], Seiji Mizuno[21], Noriko Miyake[22], Yosuke Kawai[23, 24#], Katsushi Tokunaga[23#], Masao Nagasaki[24, 25], Seiji Kito[14], Keiichi Isoyama[26], Masafumi Onodera[27], Hideo Kaneko[28], Naomichi Matsumoto[22], Fumihiko Matsuda[5], Keitaro Matsuo[15, 29], Yoshiyuki Takahashi[3], Tomoji Mashimo[12, 13, 30], Seiji Kojima[3], Tomoo Ogi[1, 2]

[1]Department of Genetics, Research Institute of Environmental Medicine (RIeM), Nagoya University, Nagoya, Japan

[2]Department of Human Genetics and Molecular Biology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[3]Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan

[4]Department of Genome Analysis, Institute of Biomedical Science, Kansai Medical University, Osaka, Japan

[5]Center for Genomic Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[6]School of Medicine, Nagoya University, Nagoya, Japan

[7]Clinical Engineering Research Center, Faculty of Medicine, Oita University, Yufu, Japan

[8]Department of Hematology, National Hospital Organization, Kumamoto Medical Center, Kumamoto, Japan

[9]Department of Hematology and Oncology, Children Medical Center, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan

[10]Department of Pediatrics, Graduate School of Medicine, Yamaguchi University, Ube, Japan

[11]Department of Pediatrics and Child Health, School of Medicine, Kurume University, Kurume, Japan
[12]Institute of Experimental Animal Sciences, Graduate School of Medicine, Osaka University, Osaka, Japan
[13]Genome Editing Research and Development (R&D) Center, Graduate School of Medicine, Osaka University, Osaka, Japan
[14]Center for Animal Research and Education, Nagoya University, Nagoya, Japan
[15]Division of Cancer Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan
[16]Department of Molecular Medicine and Metabolism, Research Institute of Environmental Medicine (RIeM), Nagoya University, Nagoya, Japan
[17]Department of Immunometabolism, Nagoya University Graduate School of Medicine, Nagoya, Japan
[18]Department of Bioregulation and Cellular Response, Graduate School of Medicine, Osaka University, Osaka, Japan
[19]Institute for Advanced Co-Creation Studies, Osaka University, Osaka, Japan
[20]Department of Radiation Medical Sciences, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, Japan
[21]Department of Pediatrics, Aichi Developmental Disability Center, Kasugai, Japan
[22]Department of Human Genetics, Yokohama City University Graduate School of Medicine, Yokohama, Japan
[23]Department of Human Genetics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[24]Department of Integrative Genomics, Tohoku Medical Megabank Organization, Tohoku University, Sendai, Japan
[25]Human Biosciences Unit for the Top Global Course Center for the Promotion of Interdisciplinary Education and Research, Kyoto University, Kyoto, Japan
[26]Department of Pediatrics, Showa University Fujigaoka Hospital, Yokohama, Japan
[27]Division of Immunology, National Center for Child Health and Development, Tokyo, Japan
[28]Department of Clinical Research, National Hospital Organization, Nagara Medical Center, Gifu, Japan
[29]Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[30]Division of Animal Genetics, Laboratory Animal Research Center, Institute of Medical Science, The University of Tokyo, Tokyo, Japan

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