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**


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

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