Title: A Novel Missense Mutation of ABCA1 in Transmembrane α-Helix in a Japanese Patient with Tangier Disease

Author: Maekawa, M., Kikuchi, J., Kotani, K., Nagao, K., Odgerel, T., Ueda, K., Kawano, M., Yusuke Furukawa, Y., and Sakurabayashi, I.


Abstract: Tangier disease (TD) is a hereditary disorder characterized by the severe deficiency or absence of high-density lipoprotein cholesterol (HDL-C). TD is caused by mutations in the ATP-binding cassette transporter A1 (ABCA1) gene, most of which are located in the extracellular loops and nucleotide-binding domains. Here we describe the first case of TD carrying a missense mutation in a transmembrane-helix of ABCA1. A 31-year-old Japanese woman had an extremely low level of HDL-C (1 mg/dl) and yellowish tonsillar swelling, leading to the diagnosis of TD. The proband was homozygous for a point mutation of T4978C in exon 37, which results in the substitution of cysteine-1660 to arginine (C1660R) in the 8th transmembrane segment of ABCA1. Her parents, grandmother, and brother were found to be heterozygous for the same mutation. Both peripheral blood leukocytes from the patient and HEK293 cells transfected with T4978C-mutated ABCA1 normally expressed ABCA1 on the plasma membrane and had normal apolipoprotein A1-binding ability. However, apolipoprotein A1-mediated efflux of cholesterol and phospholipids was reduced to approximately 10% and 25% of the control, respectively, in HEK293 cells transfected with T4978C-mutated ABCA1. These results suggest that this mutant is normally translated and exists as a stable product with normal localization, yet is functionally defective. Cysteine-1660 appears to be a critical residue for cholesterol transport of ABCA1.