KSN 2017 Abstract

KSN-17-P283

A Novel Frameshift Mutation found in the Korean Family with Lecithin-Cholesterol AcylTransferase (LCAT) Deficiency

Hayne PARK[1,2], Hayne PARK[6], Yong woo KIM[3], Yongjin YI[1], Kye hyun KIM[1], Kichun KIM[1], Mimi KIM[4], Kyung chul MOON[4], *Hae-il CHEONG[2,5]

[1]Department of Internal Medicine, Armed Forces Capital Hospital, Korea,South, [2]Research Center for Rare Diseases, Seoul National University Hospital, Korea,South, [3]Department of Ophthalmology, Armed Forces Capital Hospital, Korea,South, [4]Department of Pathology, Seoul National University Hospital, Korea,South, [5]Department of Pediatrics and Adolescent, Seoul National University Children's Hospital, Korea,South, [6]Department of Internal Medicine, Armed Forces Capital Hospital, Korea,South

Case Study : Lecithin-cholesterol acyltransferase (LCAT) deficiency is an autosomal recessive (AR) disease resulting in dysregulated cholesterol metabolism. LCAT is a plasma enzyme essential for high-density lipoprotein (HDL) maturation, and the individuals with deleterious mutations on LCAT gene appear to have decreased HDL cholesterol level while increased free cholesterol level in blood. Homozygosity or compound heterozygosity for mutations in LCAT underlies familial LCAT deficiency (FLD). Currently, there are 94 causative mutations in LCAT described in Human Gene Mutation Database. Here, we report a novel frameshift mutation found in a family with FLD.
A 19-year-old soldier presented with a long history of microscopic hematuria and overt proteinuria. He has heard of presence of proteinuria since he was in the elementary school but did not receive precise medical exam since he did not have any symptoms. Two months ago, he has heard of increased amount of proteinuria when he visited outpatient clinic for a sore throat. Family history revealed that his father has a high blood pressure but was not on medical therapy and his elder sister recently visited ophthalmology clinic because of progressive loss of vision.
He showed normal blood pressure and renal function but increased amount of proteinuria (2.2 g/day). Plasma hemoglobin revealed 11.5 g/dL with schistocytes on peripheral blood smear suggesting hemolytic anemia. Lipid profile showed that low HDL cholesterol of 27 mg/dL and high triglycerides (TG) of 312 mg/dL. The contrast enhanced computed tomography (CT) exam showed splenomegaly about 16cm at maximum length. On slit lamp examination, his cornea was slightly hazy with remarkable peripheral arcus in both eyes. Her sister also had the similar findings. Renal biopsy showed glomerulomegaly with lipid deposits in glomerular capillaries and mesangium. Tubules also showed foamy changes with focal tubular atrophy, and interstitium

showed focal mild fibrotic changes.
To identify pathogenic mutations in the LCAT gene, genomic DNA was extracted from all family members – proband, father, mother and his elder sister. A sequence analysis revealed that the proband and his elder sister had two different mutations in exon 6. Aside from the previously reported frameshift mutation (c.794_810del8), a novel frameshift mutation was found on the complementary sequences (c.931delT) in exon 6. A deletion of T nucleotide after 931 nucleotides from the start codon in exon 6 of LCAT gene resulted in a frameshift following Phe310 and occurrence of a stop codon eventually. The father was heterozygous for the deletion of 8 nucleotides in exon 6 while the mother was heterozygous for the T deletion in the exon 6. Therefore, the proband and his elder sister demonstrated to be a compound heterozygote for both mutations.
In this case report, we demonstrated a novel frameshift mutation (c.931delT) in exon6 of LCAT gene through segregation analysis. It appears that this mutation alone does not result in clinical phenotype, but together with other pathogenic mutation in the complementary sequence it can cause reduced LCAT activity and clinically presents as FLD.

Keywords : Lecithin Cholesterol Acyltransferase Deficiency; Frameshift mutation; Heterozygote detection