ABCA1 transporter membrane proteins and coronary artery disease

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The ATP binding cassette transporter (ABC) genes represent the largest family of transmembrane proteins. These proteins bind ATP and use the energy to drive the transport of various molecules across all cell membranes. ABCA1 protein, the subgroup of ABC, is involved in disorders of cholesterol transport and high-density lipoproteins (HDL) biosynthesis. ABCA1 mutations can be responsible for some cases of familial high density lipoprotein (HDL) deficiency, characterized by impaired efflux of cholesterol and phospholipids from peripheral cells onto apolipoproteins such as apoA-1. Functional deficiency of ABCA1 could therefore induce an atherogenic decrease in HDL-C levels, incriminating the ABCA1 gene as a candidate for atherosclerotic complications. It still has been working on the effects of ABCA1 gene in development of coronary artery disease.

Key words: ATP binding cassette transporter genes, lipoproteins, coronary artery disease, reverse cholesterol transport


ATP binding cassette transporter (ABC) family is the most largest membrane transporters that function as ATP-dependent active transporters. The family members translocate a variety of substrates across extra and intra cellular membranes including lipids, drugs, sterols. Genetic mutations in these genes are the cause of some disorders like cystic fibrosis, cholesterol and bile transport defects, anemia, drug resistance.

ABC transporter family was divided seven subfamilies have 48 known members by phylogenetic analysis. ABC genes are highly conserved between species since the eucaryotic evolution. A typical ABC protein contains two nucleotide binding domains, two transmembrane domains. This form of the protein is called “Full Transporter. Nucleotide binding domain has characteristic conserved peptide motifs (Walker A and Walker B). The conserved sequence is located between Walker A and Walker B, called “ABC signature”. The signature: [LIVMFYC] - [SA] - [SAPLVFYKQH] - G - [DENQMW] - [KRQASPCCLIMFW] - [KRNGSTAVM] - [KRACLVM] - [LIVMFYPAN] - F[PHY] - [LIVMFYW] [SAGCLIVP] [FYWHP] - [KRHP] [LIVMFYWSTA]. This signature was coded by IUPAC one-letter codes for amino acids.4

Most ABC proteins are membrane transporters such as multidrug resistance proteins, the energy of ATP hydrolysis is utilized for transport by a mechanism which involves positive cooperatively between the two ABCs. This couple ensure the transmission of the conformational changes by substrate binding and by the hydrolysis of ATP to active transport.

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There has been studies about ABC genes because of their function on different illness.

Kajinami et.al showed that polymorphisms in ABCG8 and CYP7A1, both of which are functionally significant in the excretion of cholesterol from the liver into bile, interact in an allelic-cumulative manner on the response to atorvastatin treatment.3 Kotrych et.al demonstrated that no association between the MDR1 gene 3435CT polymorphism and tremor was revealed in renal transplant patients administered cyclosporine A as a principal immunosuppressive agent.4 Sulfonylureas promote insulin secretion, interact with the Sulfonylurea receptor of pancreatic ß cells. Mutations of Sulfonylurea receptor 1 (SUR 1, ABCC8) has been found to cause of some genetic disorders like diabetes mellitus. Reis et al showed that an significant relationship between type2 diabetes mellitus and exon 31 of the SUR1 gene.5 Dubin-Johnson syndrome is a hereditary disease transmitted as an autosomal recessive trait, characterized by conjugated hyperbilirubinemia. Wada et al found a few mutations of ABCC2 gene in patients with Dubin-Johnson syndrome.6 It has been suggested that ABCB4 mutations may cause of familial intrahepatic cholestasis.7

**ABC1 (ABCA1) Transporter Gene**

First member of the ABC family, the Mouse ABC1, was cloned by a PCR based techniques and human ABCA1 gene was identified by using sequence information of the mouse protein.8 Human and mouse ABC1 genes show 94% homology. ABC1 gene involved 2261 amino acids and 50 exons.9 ABC1 subgroup comprises 12 full transporters that are divided into two group based on phylogenetic analysis and intron structure. The first group includes seven genes dispersed on six different choromosomes (ABCA1, ABCA2, ABCA3, ABCA4, ABCA12, ABCA13) and the second group contains five genes (ABCA5, ABCA6, ABCA8, ABCA9, ABCA10).1 ABCA1 and ABCA4 proteins have been studied extensively. The tissue specific expression of human ABCA1 has been determined; the highest expression levels were detected in placenta, liver, lung, adrenal tissues and various fetal tissues.2

Different factors effect on expression of ABCA1 gene. Langmann et al demonstrated that sterol dependent regulation of hABC1 in human monocytes/macrophages, suggest a novel role for this transporter molecule in membran transport.10 It has been shown that oxysterol induced ABCA1 expression.11 Lawn et al suggested that ABC1 expression is induced by cholesterol loading and cAMP treatment and is reduced upon subsequent cholesterol removal by apolipoproteins.12 Chinetti et al identified a regulatory role for PPAR-alpha and PPAR-gamma in the first steps of the reverse-cholesterol-transport pathway through the activation of ABCA1-mediated cholesterol efflux in human macrophages.13 On the contrary, ABC1 expression is downregulated by cytokines such as IFN-γ.14

**ABC1 (ABCA1) Transporter Gene and Coronary Artery Disease**

Tangier disease is a rare autosomal recessive genetic disorder with less than 100 cases so far reported in the literature. In addition to large yellow-orange tonsils, presenting features of this disease include neuropathies, splenomegaly, hepatomegaly, hypocholesterolemia, and coronary artery disease. Homozygotes are characterized by a virtual absence of plasma HDL and apolipoprotein A-I and accumulation of cholesteryl esters in reticuloendothelial cells of tissues, including tonsils, thymus, bone marrow, spleen, liver, gall bladder, and intestinal mucosa. Tangier disease homozygotes over the age of 30 have a 6-fold higher incidence of coronary artery disease than do normolipidemic subjects.15

It has been found that similar but less severe defects in apolipoprotein-mediated lipid removal in fibroblasts from subjects with familial HDL deficiency (FHD), a disorder characterized by very low HDL levels (less than the fifth percentile) and reduced apo A-I (30-50% normal).16

Multiple and diverse mutations in ABCA1 are linked to Tangier disease and FHD. These mutations encompass most of the protein, near or within the ATP binding domains and the N-terminus.17,19 Subjects with FHD have mutations in only one ABCA1 allele (i.e., they are Tangier disease heterozygotes),20 which accounts for the less severe HDL deficiency and cellular lipid transport defect in this disorder.21 ABCA1 mutations and polymorphisms are likely to be prevalent in the general population of subjects with low HDL levels. The type of mutation in the ABCA1 gene may influence the severity of the lipid transport defect and HDL deficiency.19

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Reverse cholesterol transport from peripheral cells to the liver involves in the first step small particles of discoidal shape, named preb-HDL, synthetized in liver and small intestine, or resulting from hydrolysis of triglyceride-rich particles. These preb-HDL uptake cholesterol from peripheral cells, and their shape change to spherical particles, named HDL3, then HDL2, as they become enriched in esterified cholesterol (via an esterifying enzyme, lecithin cholesterol acyl transferase (LCAT) associated with preβ-HDL particles) and phospholipids. The final uptake of HDL2 by the liver involves a selective receptor, named scavenger receptor B1 (SR-B1).22

ABCA1 allows the transmembrane transport of free cholesterol and phospholipids from peripheral cells into pre-HDL.23 In patients with Tangier disease, the presence of one or several mutations leads to conformational changes of the transporter, which impede the lipid transfer to nascent HDL particles.

Huang et al found more than one mutations of ABCA1 gene in two sisters with Tangier disease.24 Pisciotta et al reported that six novel mutations of ABCA1 gene found in subjects with severe HDL deficiency with and without premature coronary artery disease and belonging to six unrelated families.25

There were some studies about relationship between lipid metabolism and ABC transporter genes except Tangier disease and familial HDL deficiency.26-28 Xiao et al showed that their results exhibited an interaction of PON1 A/B192 and ABCA1 R219K on serum lipid levels in 680 patients with stroke.26

In another study was observed that ABCA1 K219R K allele is an antiatherogenic allele with increased cholesterol efflux activity. Also, V771M M allele appears to be antiatherogenic allele although the frequency of the M771 allele is low.27 Hodoglugil et al examined polymorphisms in ABCA1 gene in Turks, a population characterized by low HDL levels. They observed that the rare alleles of C14T and V771M polymorphisms were associated with higher HDL levels in men and, in combination with the rare alleles of R219K and I883M respectively with higher HDL in both sexes.28

Alterations of plasma lipid levels play a key role in the pathogenesis of atherosclerotic diseases.29 Previous studies demonstrated the effects of ABCA1 on lipid profile and cardiovascular disease.30-33

Harada et al provided evidence that I/M 823 variant, not R/K 219 variant, in ABCA1 is one of the determinants of HDL level, suggesting the importance of this gene on lipid metabolism in Japanese patients with coronary artery disease.33

Tregouet et al found that ABCA1 R219K variant was associated with MI risk.31 It was showed that ABCA1 V825I and M883I variants were associated with coronary artery disease status in Malays.32

Liu et al suggested that The -191G/C SNP in the promoter region of ABCA1 is associated with increased CAD and the C allele may relate to the stability of CAD without detectable changes in plasma lipids.33

Hong et al found that ABCA1 G2265T variant may lead to decreased HDL-C, associated evidence of early atherosclerosis was not confirmed.34

ABCA1 gene and protein are expressed in minimally atherosclerotic human arteries. Albrecht showed that ABCA1 gene expression was significantly elevated in atherosclerotic plaques.35

Porchay et al suggested that ABCA1 gene polymorphisms modulate HDL-C concentrations, in interaction with BMI, and, thus, they might influence cardiovascular risk in the general population.36

Zwarts et al found that ABCA1 C69T and G191C variations in non-coding disease – lipids – polymorphisms – risk factors regions of ABCA1 may significantly alter the severity of atherosclerosis.37

References


