



Short Communication

Disease-associated marked hyperalphalipoproteinemia



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ABSTRACT

Marked hyperalphalipoproteinemia (HAL) is a heterogeneous syndrome. To clarify the pathophysiological significance of HAL, we compared clinical profiles between marked HAL subjects with and without cholesteryl ester transfer protein (CETP) deficiency. CETP deficiency was associated with cardiovascular diseases and strokes in the HAL population, particularly in female. HAL women without CETP deficiency tended to have higher prevalence with cancer history. HAL may not always be a longevity marker, but be sometimes accompanied with pathological conditions.

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1. Introduction

Hyperalphalipoproteinemia (HAL) had been regarded as a longevity syndrome. Matsuzawa et al. reported that a man with HAL unexpectedly had a corneal opacity which is a clinical sign for

high density lipoprotein (HDL) deficiency [1]. Following studies revealed that genetic deficiency of cholesteryl ester transfer protein (CETP) is a major cause for HAL in Japan [2,3]. CETP is a plasma glycoprotein which facilitates the transfer of cholesteryl ester from HDL to apolipoprotein

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B-containing lipoproteins, then determine the plasma levels of HDL-cholesterol and low-density lipoprotein (LDL)-cholesterol levels [4]. This protein also regulates the lipid composition and particle size of lipoproteins.

CETP deficiency presents marked HAL and relative decrease in LDL-cholesterol level [5]. Such lipid profiles are generally believed protective for cardiovascular diseases (CVDs) and strokes, however, there has been a controversy whether this genetic deficiency is overall anti- or pro-atherogenic [6–8]. In addition, it is noteworthy that some clinical trials with CETP inhibitors recently failed and terminated [9], suggesting that further understanding pathophysiological significance for HAL is obviously required.

Here, we examined the prevalence of CVDs and strokes in HAL subjects with and without CETP deficiency along with their respective lipid profiles in a specific community, Akita Prefecture, Japan, where we reported that genetic CETP deficiency accumulates [10].

2. Subjects and methods

2.1. Subjects

The surveyed population comprised residents aged over 20-years-old in a community in Daisen City, Akita Prefecture, Japan (<http://www.city.daisen.akita.jp/content/docs/english/>), which includes Omagari area where genetic CETP deficiency accumulates [9,10].

After the opt-out in the community journal, we directly sent a request letter to 343 people with marked HAL (HDL-C > 100 mg/dL) based upon the annual health examination for the last three years. Unrelated 181 individuals (53%) agreed to participate in this study. Physical examination, blood test, and interview for medical histories and records of CVDs and strokes were performed. Based upon the analyses of the CETP gene and the protein levels, the subjects with HAL were divided into CETP-deficient and non-CETP-deficient groups.

This study was approved by the ethical committee in Osaka University.

2.2. Medical interview

We performed interviews on smoking, alcohol consumption, and medical histories for CVDs, stroke, diabetes mellitus, hypertension, hyperlipidemia, and cancer.

Diagnoses of hypertension and diabetes mellitus were made according to the criteria of Japanese Society of Hypertension and Japan Diabetes Society. CVDs include non-fatal myocardial infarction, angina pectoris, congestive heart failure, and arteriosclerosis obliterans. Strokes include cerebral infarction and cerebral hemorrhage, but exclude subarachnoid hemorrhage and strokes associated with atrial fibrillation. Cancers included any malignant tumors treated previously and currently.

2.3. CETP gene analyses

We performed direct sequencing of the DNA fragments amplified by polymerase chain reaction to detect two common CETP gene mutations [11,12]: intron 14 splicing defect (c.1321 + 1G>A, rs5742907) and missense mutation in exon 15 (c.1376A>G, rs2303790).

2.4. CETP protein mass

CETP protein mass was measured by the commercial available ELISA kit according to the manufacturer's protocol [13,14].

2.5. Criteria for CETP deficiency

Criteria of CETP deficiency was one of the following: 1) either of the common genetic mutations with c.1321 + 1G>A or c.1376A>G. We previously reported that these two CETP gene mutations contributed to approximately 90% of the genetic CETP deficiency in Japan (13, 14); 2) CETP mass was below 2.0 µg/mL.

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