Sirtuin 1 gene polymorphisms are associated with body fat and blood pressure in Japanese

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Sirtuin 1 (SIRT1) **is a longevity gene that protects cells against oxidative and genotoxic stress. This study aimed to investigate the associations of *SIRT1* gene single nucleotide polymorphisms (SNPs), rs7895833, rs7069102, and rs2273773, with various laboratory data in 1279 Japanese health checkup examinees. The genotyping was performed using a polymerase chain reaction (PCR) with confronting 2-pair primers (CTPP) assay. Concerning rs7895833 (A allele frequency: 0.290), body fat ratio and body mass index were high in the AA carriers of male subjects, and diastolic blood pressure was high in the AA carriers of female subjects. Concerning rs7069102 (G allele frequency: 0.181), body fat ratio and systolic blood pressure were high in the GG carriers of male subjects. Concerning rs2273773 (C allele frequency: 0.323), fasting glucose and body fat ratio were high in the TT carriers of male subjects, and systolic and diastolic blood pressures were high in the CC carriers of male subjects. Thus, the A allele of rs7895833, G allele of rs7069102, and T allele of rs2273773 carried a high risk for obesity in men. Furthermore, the A allele of rs7895833 in women, and the G allele of rs7069102 and C allele of rs2273773 in men, carried a high risk for hypertension. The T allele of rs2273773 in men carried a high risk for hyperglycemia. In conclusion, these *SIRT1* gene polymorphisms are associated with high body fat and blood pressure in Japanese, especially in men. The allele frequencies of rs7895833 and rs7069102, which are different from Caucasians, might explain why Japanese show less marked obesity compared with Caucasians. (Translational Research 2011;157:339–347)**

Abbreviations: γ-GTP = γ-glutamyl transpeptidase; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FOXO = forkhead transcription factor; HDL = high density lipoprotein; LDL = low density lipoprotein; NAD = nicotinamide adenine dinucleotide; PCR = polymerase chain reaction; PCR-CTPP = PCR with confronting 2-pair primers; PGC-1α = peroxisome proliferator-activated receptor γ coactivator 1α; PPAR-γ = peroxisome proliferator-activated receptor γ; *SIRT1* = *sirtuin 1*; SNP = single nucleotide polymorphism

The silent information regulator Sir2 (an nicotinamide adenine dinucleotide [NAD]-dependent histone deacetylase) protein is related to longevity in lower organisms such as yeast, flies, and worms.[1,2] Sir2 has also been concerned in life-span extension during caloric restriction in these organisms.[3-5] Humans have 7 sirtuins *(SIRT1-7)*,[6] in which *SIRT1* is most homologous to yeast Sir2 and has been studied extensively.

SIRT1 can deacetylate a variety of substrates and is, therefore, involved in a broad range of physiologic

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AT A GLANCE COMMENTARY

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Background

Sirtuin 1 (SIRT1) is a longevity gene that protects cells against oxidative and genotoxic stress by binding to and deacetylating several substrates such as p53 and forkhead transcription factors (FOXOs). This study aimed to investigate the association of *SIRT1* gene single nucleotide polymorphisms (SNPs) rs7895833, rs7069102, and rs2273773, with various laboratory data in 1279 Japanese healthy subjects by using polymerase chain reaction (PCR) with confronting 2-pair primers (CTPP) assay.

Translational Significance

This study demonstrated that *SIRT1* gene polymorphism is associated with body fat and blood pressure in Japanese healthy subjects. The A allele of rs7895833 and the G allele of rs7069102 are related to obesity. The different allele frequencies of the *SIRT1* polymorphisms between Japanese and Caucasians might explain why Japanese show less marked obesity compared with Caucasians.

functions. *SIRT1* deacetylates forkhead transcription factor 1 (FOXO1) and promotes its activity.[7,8] FOXO1 may have protective or negative effects on insulin resistance and vascular function.[9-11] *SIRT1* also deacetylates peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and increases its acivity.[12-14] PGC-1α is involved in a wide variety of biologic responses, including adaptive thermogenesis, mitochondrial biogenesis, glucose and lipid metabolism, fiber type-switching in skeletal muscle, and heart development.[15]

SIRT1 controls numerous physiologic processes and protects cells against oxidative stress.[16-18] Its activity is dependent on NAD that affects electronic transmission of mitochondria and cellular oxygen supply. A decrease in NAD and *SIRT1* activity is responsible for high p53 acetylation and c-Jun N-terminal kinase activation, which are related to cell activation, inflammation, and atherosclerosis. These pathways can be prevented by the antioxidant resveratrol.[19]

SIRT1 also has an important function in endocrine signaling, specifically in glucose and lipid metabolism.[13,20-23] Li et al[24] demonstrated that *SIRT1* activates liver X receptor (LXR) proteins α and β, and that it plays an important role in the regulation of blood lipid metabolism. Increased hepatic *SIRT1* activity enhances gluconeogenesis and inhibits glycolysis.[13,21] *SIRT1* stimulates insulin secretion in the pancreas.[22,23] In adipose tissue, *SIRT1* interacts with peroxisome proliferator-activated receptor (PPAR)-γ to repress its transcriptional activity, leading to inhibition of adipogenesis.[20]

Only a few human genetic association studies on *SIRT1* have been published. A variation in the *SIRT1* gene was not associated with longevity in a case-control study comparing long-lived individuals with younger subjects,[25] and all-cause mortality was not influenced by *SIRT1* genetic variation in the Leiden 85-plus Study.[26,27] *SIRT1* genetic variation is related to obesity.[27,28] Carriers of *SIRT1* polymorphisms showed increased whole-body energy expenditure among healthy nondiabetic offspring of type 2 diabetic patients.[14]

We genotyped common single-nucleotide polymorphisms (SNPs) of *SIRT1* to determine the association with various laboratory data in Japanese healthy subjects. Three SNPs, rs7895833, rs7069102, and rs2273773 were selected because they seemed to cover almost 100% of the common variation of the *SIRT1* gene in Japanese. [28]

METHODS

Study subjects. This study included Japanese subjects who underwent a health evaluation at Nagoya University Hospital in Nagoya and in Yakumo, Hokkaido. In Nagoya, 476 subjects agreed to provide their blood for genetic tests. In Yakumo, 803 subjects agreed to participate in the study. Altogether, 1279 examinees participated in this study. Those undergoing a "basic health evaluation" with blood tests were invited to participate in our polymorphism study. The general characteristics of the subjects are as follows: The subjects included 571 men and 708 women. The mean age was 57.0 $\pm$ 12.6 years. Almost all the laboratory parameters were within the normal range for Japanese (Table I). Written informed consent was obtained from all subjects, and the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. The subject enrollment was approved by Ethics Committee of Nagoya University School of Medicine in 2004 for Nagoya University Hospital and in 2003 for Yakumo city.

Anthropometric, laboratory measurement. Height, weight, and systolic and diastolic blood pressures were measured for all participants. Body mass index