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Energy metabolism and whole-exome sequencing-based analysis of Sasang constitution: a pilot study

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ABSTRACT

Background: Traditional Korean Sasang constitutional (SC) medicine categorizes individuals into four constitutional types [Tae-eum (TE), So-eum (SE), Tae-yang (TY), or So-yang (SY)] based on biological and physiological characteristics. As these characteristics are closely related to the bioenergetics of the human body, we assessed the correlation between SC type and energy metabolism features.

Methods: Forty healthy, young (22.3 ± 1.4 years) males volunteered to participate in this study. Participants answered an SC questionnaire, and their face shape, voice tone, and body shape were assessed using an SC analysis tool. Thirty-one participants (10 TE, 10 SE, 3 TY, and 8 SY) were selected for further analysis. Collected blood samples were subjected to blood composition analysis, mitochondrial function analysis, and whole-exome sequencing.

Results: The SY type showed significantly lower total cholesterol and high-density lipoprotein cholesterol levels than the SE type. Cellular and mitochondrial Adenosine triphosphate (ATP) levels were similar across types. All types showed similar basal mitochondrial oxygen consumption rates, whereas the TE type showed a significantly lower ATP-linked oxygen consumption rate than the other types. Whole-exome sequencing identified several genes variants that were exclusively detected in particular SC types, including 19 for SE, seven for SY, 11 for TE, and six for TY.

Conclusion: SC type-specific differences in mitochondrial function and gene mutations were detected in a small group of healthy, young Korean males. These results are expected to greatly improve the accurate screening and utilization of SC medicine.

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1. Introduction

Sasang constitutional medicine (SCM) is a Korean medical tradition that classifies physiological and pathological traits into four constitutional types: Tae-yang (TY), So-yang (SY), Tae-eum (TE), and So-eum (SE). The concept that constitution can be "typed" is the most basic underlying paradigm described in the *Donguisusebowon*.[1] Unlike Westernized diagnostic tools based on molecular biological evidence, SCM emphasizes integrative and holistic characteristics of the individual.[1] SCM is not only used for the clinical diagnosis of individual constitution but is also widely used in the SC type-specific treatment of disease.[2] Thus, the SCM tradition can be considered as a complement to the current "personalized medicine" approach.[3,4]

SCM considers balances between food intake and waste discharge, energy consumption and storage, and catabolism and anabolism.[2] TY, SY, TE, and SE types display different hyper- and hypoactive organs. For example, the TE type shows a tendency toward a hyperactive liver and hypoactive lung, whereas the TY type shows the opposite tendency. In the same manner, the SY and SE types also show opposite tendencies toward hyper- and hypoactive organs; the SY type has a hyperactive spleen and hypoactive kidney, whereas the SE type has a hypoactive spleen and hyperactive kidney.[2] Beyond single organ-specific characteristics, SCM is deeply concerned with various biological processes such as food intake, digestion, waste excretion, and energy storage in multiple organs as well as catabolism and anabolism balance at the cellular level. The detailed biological characteristics and bodily features of different SC types have previously been described.[2] According to the SCM theory, the imbalance of energy metabolism under pathological conditions affects the sensitive hypoactive organ of each type, which can cause disease.[2] Because SC types are reflected by integrative systemic features and are closely associated with metabolic status, SCM can facilitate the diagnosis and treatment of metabolic syndromes or diseases including obesity, hyperlipidemia, diabetes, and hypertension.[5–10] These previous studies provide strong evidence of correlations between SC types and particular diseases, suggesting the value of SC types as holistic biomarkers for a wide range of diseases.

SC types are determined by professional oriental medical doctors based on traditional diagnostic methods including seeing, listening, questioning, and touching. However, these traditional diagnostic methods are based on subjective observations and are catechetic methods, making them difficult to objectify and quantify.[1] To overcome difficulties in traditional diagnosis and to establish an evidence-based diagnostic tool, we developed the Sasang constitution analysis tool (SCAT),[11] a system designed to provide objective information for determining the SC type. In addition to the SCAT, several genomic approaches have been used to identify the genetic loci or pathways responsible for different SC types.[12,13] Won et al[12] found a significant link between the constitution and chromosomes 8q11.22–23 and 11q22.1–3 based on a genome-wide scan of a Korean family. Kim et al[13] not only performed a genome-wide association analysis but also analyzed the pathways involved in SC. These studies, therefore, suggest the possibility of genomic differences among SC types.

Next-generation sequencing is a novel and powerful genomics tool that can be used to rapidly sequence whole or specific regions of an individual human genome and provide integrative genomic information about the individual.[14] Whole-exome sequencing (WES) is the most widely used targeted sequencing method, as the exome contains the majority of known disease-causing variants. WES enables the selective capture and sequencing of the protein-coding portion of the genome to understand relationships between gene variants and their associated phenotypes.[15–17] Based on this advantage, we aimed to use WES to identify gene variants of SC types and to link this genomic information to the morphological and physiological characteristics of each SC type.[18]

In the bodies of mammals, intracellular organelles, called the mitochondria, play an essential role in the production, storage, and transformation of biological energy molecules, known as Adenosine triphosphate (ATP), and the regulation of catabolic and anabolic pathways.[19–22] Impaired mitochondrial function results in an imbalance of energy metabolism and an increase in oxidative stress in major organs, including the heart, liver, kidney, and brain, which cause a wide range of diseases including inflammatory diseases, neurodegenerative diseases, metabolic syndromes, cancers, and cardiovascular diseases.[23–28] Recent studies by Shim et al[29,30] show that the TE type has reduced mitochondrial metabolism and an obesity-prone tendency. Therefore, we hypothesized that variations in mitochondrial energy metabolism are associated with different SC types and phenotypic characteristics. The aim of this study was to identify SC type-specific energy metabolic and/or genetic variants that can be used for the precise diagnosis of SC type. We measured the energy status-related metabolites in blood samples, as well as mitochondrial oxidative phosphorylation, and identified SC type-specific gene variants in 31 healthy individuals.

2. Methods

2.1. *Participants*

This study was approved by the Institutional Review Board and Ethics Committee of Inje University Paik Hospital, Busan, Korea (15-0287). The study was performed in accordance with previously established experimental protocols and guidelines. Informed consent was obtained from all participants. Forty healthy males were recruited through posters placed on community boards in the College of Medicine, Inje University. The study included 31 participants after excluding nine individuals for the following reasons: (1) diagnosis of diabetes, hypertension, hyperlipidemia, or other chronic disease, (2) drug supplementation within 3 months of the study, (3) results of initial screening interviews, or (4) SC type diagnosis based on SCAT score and the opinion of a medical doctor with expertise in SCM.

2.2. *SCAT*

The SCAT was used to diagnose the SC type of 40 males at the College of Medicine, Inje University. The diagnosis of constitution was based on face pictures, voice recordings, body