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The reduction of vascular disease risk mutations contributes to longevity in the Chinese population

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ABSTRACT

Aim: Genetic factors play important roles in determining human lifespan. Although some "longevity genes" have been identified to be implicated in human longevity, many disease-associated variants were also observed in the long-lived individuals. The oldest old and their offspring usually have a lower prevalence of age-related diseases, which is likely attributed to a reduction or an absence of disease risk variants.

Methods and results: To test this hypothesis, 23 disease risk single nucleotide polymorphisms (SNPs), identified by previous genome-wide association studies (GWASs), were selected and genotyped in 1074 samples consisting of 574 longevity subjects (over 90 years old) and 500 younger controls. Our results revealed that 5 SNPs (rs2144300, rs1864163, rs2200733, rs1967017, and rs7193343) displayed significantly lower allelic frequencies and odds ratios (ORs) in the longevity group than that in the control group. The frequencies of homozygous mutation genotypes and corresponding ORs of the rs1864163, rs2200733, rs127430, rs1967017, and rs12413409 were lower in the longevity subjects. Interestingly, most of the abovementioned SNPs

Abbreviations: AD, Alzheimer Disease; CHB, Chinese Han Beijing; CVD, cardiovascular disease; GWAS, genome-wide association study; MAF, minor allele frequency; OR, odds ratio; PD, Parkinson Disease; PCR, polymerase chain reaction; SNP, single nucleotide polymorphism.

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convey susceptibility to cardiovascular disease (CVD), which is the leading cause of deaths in old adults but shows a much lower incidence in the longevity individuals and their offspring.

Conclusion: Taking into account the observation that the longevity subjects and their offspring have lower rate of cardiovascular mortality, it is then most plausible that the lack of disease risk variants, especially the CVD, is a genetic contributor to longevity in the Chinese population.

Introduction

Human lifespan is influenced by multiple determinants, including various environmental and genetic factors. Though the non-genetic factors, such as diet, health habits, physical activity, and psychosocial factors are important, the role of heritability in determining human lifespan is attracting more and more attention. Age at death in adulthood has a heritability of approximately 25% (Murabito et al., 2012), and the heritability of living to at least 100, i. e. centenarians, has been estimated at 0.33 in women and 0.48 in men (Sebastiani and Perls, 2012). Epidemiological investigations reveal that the oldest old and their offspring usually have a delayed or reduced prevalence of age-related diseases, such as cardiovascular disease (CVD), Alzheimer Disease (AD), Parkinson Disease (PD), cancers and some metabolic diseases (Franceschi and Bonafe, 2003; Hitt et al., 1999; Terry et al., 2003; Terry et al., 2004), suggesting that the long-lived individuals may have some special genetic basis to help them to delay or escape these senile diseases.

In the past decade, a number of genes, e.g. *daf-2*, *daf-16* and *sir-2*, were discovered, in which some specific genetic alterations confer advantage in extending the organisms' lifespan (Kenyon et al., 1993; Lin et al., 1997; Tissenbaum and Guarente, 2001), indicating the existence of longevity genes. Only very few longevity genes are confirmed to be valid for human beings (Brooks-Wilson, 2013), which is difficult to explain the significantly reduced incidence of age-related diseases in the longevity subjects and their offspring. Alternatively, given the recognition that all common complex diseases increase with age, it is plausible that the low prevalence of age-related diseases in the long-lived people is attributed to a much lower frequency of risk alleles. Indeed, there is increasing evidence showing a lower frequency of disease risk alleles in the longevity subjects (Pinos et al., 2013; Ruiz et al., 2012; Schachter et al., 1994). However, inconsistent observation comes from a recent study on the age-related disease risk variants in the longevity subjects (Beekman et al., 2010), causing it highly controversial whether the long-lived people do contain a lower frequency of disease risk alleles. To provide more evidence, we selected 23 age-related disease risk variants with high prevalence and mortality rates in the elderly and had them genotyped in 1074 samples consisting of 574 longevity subjects (over 90 years) and 500 younger controls for the study. Our study reveals that the SNPs related to cardiovascular disease (CVD) show a much lower frequency in the longevity individuals than the controls, suggesting that the lack/scarcity of disease gene mutations could be a genetic contributor to longevity.

Methods

Subjects

total of 1074 Chinese subjects consisting of 574 longevity subjects (over 90 years, mean age 93.8 years) and 500 controls (mean age 51.7 years) were collected from Sichuan province of China in 2010. All of the longevity subjects had no severe life-threatening illness, such as heart attack, cerebellar hemorrhage, and cancer, according to the medical examination. Only some of them had decreased vision or hearing loss as reported previously (He et al., 2014; Ye et al., 2009). The control subjects were all healthy with no severe medical history. Blood samples for DNA isolation were obtained after a 12 h fasting period. The investigation conformed with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee at Kunming Institute of Zoology, Chinese Academy of Sciences. Written informed consent was obtained from each of the participants prior to the study.