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ORIGINAL ARTICLE

Associations of polymorphisms in circadian genes with abdominal obesity in Chinese adult population

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Summary
Objective: Circadian rhythm, which is controlled by circadian genes, regulates metabolic balance including the circulating levels of glucose, fatty acids, triglycerides, various hormones and so on. The study aimed to investigate the impact of potential polymorphisms in circadian genes on abdominal obesity among Chinese Han adults.
Methods: A total of 260 cases with abdominal obesity and 260 controls were recruited by individual matching. Demographic characteristics and lifestyle information were collected by a validated questionnaire, and anthropometric parameters was measured by physical examination. Twenty-three single nucleotide polymorphisms (SNPs) in three circadian genes, *CLOCK*, *CRY1* and *CRY2*, were genotyped by MassArray technique.
Results: Five SNPs significantly deviated from Hardy–Weinberg equilibrium (HWE) among controls, so eighteen SNPs were taken into logistic regression analysis. Independently, *CLOCK* rs10002541 (CC genotype vs. TT genotype: OR: 0.45, 95% CI: 0.23–0.86), *CLOCK* rs6850524 (CC genotype vs. GG genotype: OR: 0.50, 95% CI: 0.25–0.99) and *CRY1* rs10861688 (TT genotype vs. CC genotype: OR: 0.50, 95% CI: 0.25–0.97) were negatively associated with the risk of abdominal obesity. Haplotype analysis showed that the haplotypes of CG and TG for *CLOCK* rs10002541 and rs4864546 had significant associations with abdominal obesity. Compared with the

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carriers of TA, those of CG were observed to have a lower risk (OR: 0.74, 95% CI: 0.56—0.99) of abdominal obesity, and those of TG presented a higher risk (OR: 1.70, 95% CI: 1.03—2.81).

Conclusions: Our findings suggest that *CLOCK* and *CRY1* polymorphisms might be involved in individual susceptibility to abdominal obesity in Chinese Han population.

Introduction

Obesity is one of the most serious public health problems today, with at least 2.8 million people dying each year as a result of being overweight or obese [1]. In regard to the definition of obesity, body mass index (BMI) and waist circumference (WC) are widely used. Compared with overall adiposity recognised by BMI, abdominal adiposity measured by WC might be more meaningful as it reflects the accumulation of abdominal fat, which associates with cardiovascular diseases, metabolic disorders and death more closely [2].

Numerous studies have focused on the factors contributing to the development of obesity. It has been found that a certain lifestyle is associated with obesity. For example, people with less sleep are more likely to be obese, which has been shown in different subsets of subjects [3—6]. Cigarette smokers and alcohol drinkers also tend to become obese [7—9]. Tea drinking might play a protective role in preventing obesity [10]. As our knowledge and understanding of circadian rhythm evolved, there has been increasing interest in the role of circadian rhythm in metabolic phenotypes, such as obesity. Some studies have supported a positive link between the disruption of circadian rhythm and the incidence of obesity [11]. However, limited studies on the relation of circadian rhythm with abdominal obesity have been reported [12,13].

Circadian rhythm is biological rhythm which follows a relatively fixed time period between 20 h and 28 h, and its disruption tends to result in energy imbalance [14]. At the molecular level, circadian rhythm is regulated by suprachiasmatic nucleus (SCN), which conducts a complex system by feedback loops [15]. The core components of the loops are positive (*CLOCK* and *BMAL1*) and negative (*PER* and *CRY*) limbs [16,17]. CLOCK—BMAL1 heterodimers bind to the enhancer (E-box) which located in the promoter region of *CRY* genes to activate the transcription of *PER* and *CRY* genes, subsequently the corresponding proteins (PER and CRY) form heterodimers to inhibit CLOCK—BMAL1 [18]. In mammals, many metabolic pathways are rhythmically coordinated by the circadian clock. The core elements of the circadian clock (*CLOCK*, *BMAL1*, *PER* and *CRY*) can either directly regulate rhythmic transcription of metabolic genes or drive rhythmic expression of transcription factors that regulate expression of metabolic genes on a second hierarchical level [19].

Single nucleotide polymorphism (SNP), which is one kind of the most common genetic variants, might affect the process of gene transcription, translation and modification. It has been demonstrated that certain polymorphisms in circadian genes might change the susceptibility to overall adiposity [20], but there is limited evidence to validate the relationship between polymorphisms in circadian genes and abdominal obesity. In the present study, we assessed whether genetic polymorphisms in three selected circadian genes (*CLOCK*, *CRY1* and *CRY2*) are associated with abdominal obesity. Furthermore, we analysed the associations between haplotypes in *CLOCK*, *CRY1*, *CRY2* and abdominal obesity.

Materials and methods

Subjects

The source population has been described in our previous study [21]. Briefly, the residents with ≥ 35 years of age living in Jiashan County, Zhejiang Province who chose to attend the free biennial health checkups between 2010 and 2011 were invited to participate in our cross-sectional survey. A face-to-face interview was conducted by trained interviewers with a questionnaire to collect demographic characteristics (age and gender) and lifestyle information (sleep duration, smoking, alcohol drinking and tea drinking). The definition of smoker was those who had smoked at least 1 cigarette per day for more than 1 year, or more

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