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Case Control Study

Association of rs1137101 with hypertension and type 2 diabetes mellitus in ethnic Mongolian and Han Chinese from the Inner Mongolia region

Association of rs1137101 with hypertension+T2DM

Keyu Zhao, Menglu Yuan, Yunna Wu, Hongwei Cui, Wenyan Han, Jing Wang, Xiulan Su

Abstract

BACKGROUND

Hypertension (HTN) and type 2 diabetes mellitus (T2DM) are often coincident and each condition is considered a risk factor for the other. Both occur frequently in the Inner Mongolia region of China. It's not known why there are differences in risk between Han and Mongolian ethnic groups. *Lepr* gene and its polymorphism rs1137101 (Gln223Arg), both are proved as the potential risk factories to occur HTN and T2DM. But the role of rs1137101 in occurrence of HTN+T2DM remain not yet fully elucidated for Mongolian and Han in Inner Mongolia region.

AIM

To investigates the relationship between rs1137101 and the occurrence of HTN with T2DM in Mongolian and Han populations in Inner Mongolia

METHODS

A total of 2652 subjects of Han and Mongolian ethnic origins were enrolled in the current study, including 908 healthy controls, 1061 with HTN patients and 683 HTN patients with T2DM.

RESULTS

The association between the rs1137101 polymorphism and HTN with T2DM was analyzed and differences between Han and Mongolian individuals assessed. There was a significant correlation between rs1137101 with both HTN (co-dominant model, dominant model, over-dominant model and log-additive model) and HTN plus T2DM (co-dominant model, dominant model, over-dominant model and log-additive model) after adjustment of sex and age in individuals of Mongolian origin. The result shown that rs1137101 was significant associated with HTN (co-dominant model, recessive model and log-additive model) and HTN+T2DM (co-dominant model, dominant model, over-dominant model and log-additive model) in Han Chinese population.

CONCLUSION

Mongolian and Han subjects with HTN who had rs1137101 were protected against the development of T2DM and Han Chinese population of Inner Mongolia. Allele A plays opposite roles in the occurrence of HTN in Mongolian and Han Chinese populations.

Key Words: rs1137101; Mongolian; Han Chinese; hypertension; type 2 diabetes mellitus; associate study

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Core Tip: Hypertension (HTN) and type 2 diabetes mellitus (T2DM) are often coincident and each condition is considered a risk factor for the other.It's not known why there are differences in risk between Han and Mongolian ethnic groups. Lepr gene and its polymorphism rs1137101 (Gln223Arg), both are proved as the potential risk factories to occur HTN and T2DM. The current study investigates the relationship between rs1137101 and the occurrence of HTN with T2DM in Mongolian and Han populations in Inner Mongolia.Differences between the two populations are analyzed. Scientific data to promote advanced metabolic disease research is presented.

INTRODUCTION

The causes of hypertension (HTN) are multifactorial and the condition is, in turn, a risk factor for cardiovascular disease and nephropathy [1]. Current estimates put a global figure of 1.3 billion [2,3] on the number of people with high blood pressure, an estimate that is set to rise to 1.6 billion by 2025 [2,4]. Advanced age, gender, obesity and genotype are all risk factors for HTN [2]. Diabetes mellitus (DM) is another public health problem which has increased rapidly over recent years with 80%-90% patients having

Type 2 diabetes mellitus (T2DM) [5,6]. Epidemiological studies have shown that HTN is a major risk factor for T2DM [7]. One third of HTN patients also have T2DM and are at increased risk of cardiovascular disease and mortality [8,9].

The leptin (LEP) receptor (LEPR) is a transmembrane protein encoded by the *lepr* gene. Several variants have been characterized and there is widespread expression throughout the body's tissues [10]. The LEP hormone is known to have roles in the regulation of hunger, energy balance, metabolism, reproduction and insulin secretion mediated by binding to LEPR [11,12]. Binding of LEP to its hypothalamic receptor has been shown to raise blood pressure in mice and blockade of LEPR resulted in lower values of blood pressure [13,14]. LEPR has roles in insulin secretion and its activity is relevant to the development of insulin resistance [12,15]. Indeed, a recent study has correlated *lepr* polymorphisms with DM and HTN [16,17]. Among the Han Chinese population, the *lepr* gene polymorphism, rs13306519, has been associated with DM and rs12037879 with HTN [5]. Moreover, rs1137100 (Arg109Lys) and rs8179183 (Lys656Asn) have been associated with both DM and HTN [15,18].

The polymorphism, rs1137101, of the *lepr* gene is located on chromosome 1p31 and involves a substitution of the 223rd amino acid residue, gln (Q), for Arg (R). This mutation affects the ObR Ig domain, according to the PFAM database (http://pfam.xfam.org/protein/P48357; Figure 1A and Table 1). Construction of a 3D model of the region including amino acids 126 to 533 using Swiss-model software (https://swissmodel.expasy.org/) reveals a consequent change in protein structure (Figure 1B). These predictions imply that the rs1137101 mutation may influence protein structure and have an impact on protein function. Previous studies have associated rs1137101(Gln223Arg) with obesity, cancer, HTN and DM [9,19,20]. It also has been shown to be a risk factor for HTN and T2DM in the Chinese population [21,22]. The current study investigates the relationship between rs1137101 and the occurrence of HTN with T2DM in Mongolian and Han populations in Inner Mongolia.

MATERIALS AND METHODS

Study subjects

A total of 2652 subjects, including 908 healthy controls, 1061 HTN patients and 683 patients with HTN + T2DM, were randomly selected from adult residents of Mongolia (Hohhot, Wuhai, Xilinhot) and enrolled in the study. Study participants were unrelated and the ethnic composition was 1357 Han and 1305 Mongolian. All participants provided written informed consent. The study was performed in accordance with the declaration of Helsinki and approved by the ethical committee of the affiliated hospital of Inner Mongolia Medical University.

T2DM and HTN were diagnosed according to the following criteria established by the World Health organization (WHO): HTN: Systolic Blood Pressure (SBP) ≥140 mmHg and/or Diastolic Blood Pressure (DBP) ≥90 mmHg or current prescription for antihypertensive medication[23]. Participants with chronic renal disease, renal artery stenosis, primary hyperaldosteronism, thyroid disease, Cushing syndrome, phaeochromocytoma or other diseases known to cause HTN were excluded; T2DM: Fasting Blood Sugar (FBS) ≥ 7.0mmol /L or postprandial blood glucose (PBG) ≥ 11.1mmol/L or current definitive diagnosis of T2DM[24]. Participants with Type 1 diabetes mellitus, cancer or other severe metabolic disease were excluded.

Data collection

Age, weight and medical history were collected by questionnaire. Body Mass Index (BMI) was calculated according to the formula: mass (kg)/ height^2 (m^2). Blood pressure was measured on the right arm using a mercury sphygmomanometer. Blood samples of HTN, T2DM and HTN+T2DM groups were collected after an 8 h fast. Genomic DNA was isolated from whole blood used Maga bio plus whole blood genomic DNA purication Kit II (Hangzhou Bioer Technology co. Ltd, China), according to the manufacturer's instructions. FBS, triglyceride (TG), cholesterol (CHO), High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL) of every group were measured after plasmapheresis.

Genotyping

rs1137101(Gln223Arg) polymorphisms were assessed by PCR amplification. The primers used were Forward: 5′-TTCCCCAAAAAGGCAGTTTTCA-3′ and Reverse: 5′-AGAAGCCACTCTTAATACCCCCAGT -3′. The target DNA sequences were amplified using a multiplex PCR method. Thermal cycling was performed for rs1137101 Loci in Gene Amp PCR system 9600 (PerkinElmer, Waltham, MA, USA). Then the fluorescent products of ligase detection reaction were differentiated by 3130xl genetic analyze (Applied Biosystems, CA, USA). To verify the accuracy of the genotyping results for SNPs.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 (SPSS Inc., Chicago, IL) and SNPStats (https://www.snpstats.net/start.htm) [25] software. Categorical variables were presented as frequencies. Continuous data were reported as the mean ± standard deviation. Student's t-test were used to analyze age, weight, height, BMI, FBS, SBP, DBP, TG, CHO, HDL and LDL, and statistical hypotheses were tested using the 2-tailed t-test. Chi-square test were used to analyze ethnic and gender. Logistic regression was used to compute the Odds ratio (OR) by adjusting for age and sex, and the adjusted OR was presented together with a 95% confidence interval (CI). Logistic regression, Hardy Weinberg Equilibrium (HWE) and five genetic models (co-dominant, dominant, recessive, over-dominant and log-additive), were calculated using SNPStats software. A value of $p<0.05$ was considered to be significant.

RESULTS

Baseline demographic characteristics

Baseline demographic characteristics of the study population are summarized in Table 2. Significant differences were found in ethnicity, gender, age, weight, height, FBS, SBP, DBP and HDL between cases with HTN, those with both HTN + T2DM and controls. No significant deviation from the HWE was detected (Table 3). Allele frequency was not significant in the Han population but significant differences between Mongolian groups were observed (Table 4).

***lepr* gene polymorphisms and HTN in ethnic Han and Mongolian Chinese**

The correlation between the *lepr* gene polymorphism, rs1137101, and HTN in ethnic Han and Mongolian Chinese subjects was analyzed. A total of 861 subjects of Han origin (control=455; HTN=406) and 1108 subjects of Mongolian origin (control=453; HTN=655) were assessed. We used logistic regression analysis to evaluate whether rs1137101 was independently associated with HTN after adjusting for the sex and age (Table 5). After analysis for five inheritance models, codominant, dominant, recessive, over-dominant and log-additive, could be found co-dominant (A/G) model: OR=0.88 (0.62-1.27), co-dominant (A/A) model: OR= 0.21 (0.05-0.80) and recessive (A/A) model: OR= 0.21 (0.05-0.82) statistically significant for hypertensive Han subjects compared with controls. Results for Mongolian subjects were: codominant (A/G) model: OR= 1.49 (1.12-1.97); codominant (A/A) model: OR= 1.47 (0.64-3.34); dominant (A/G-A/A) model: OR= 1.49 (1.13-1.95); over-dominant (A/A) model: OR= 1.47 (1.11-1.95) and log-additive model: OR= 1.40 (1.10-1.79). An association between rs1137101 and HTN was established for subjects of Mongolian ethnic origin.

The correlation between rs1137101 and HTN with T2DM in Han and Mongolian subjects

The association of rs1137101 with HTN + T2DM was analyzed. A total of 683 subjects, composed of 197 Mongolian and 496 Han were included. The same five genetic models (codominant, dominant, recessive, over-dominant and log-additive) were used to analyze associations between HTN + T2DM as described above for HTN. OR (Adjusted for sex and age) for the five genetic models in Mongolian subjects were: codominant (A/G): 0.70 (0.44-1.11); codominant (A/A): 1.06 (0.27-4.25); dominant (A/G-A/A): 0.72 (0.46-1.13); recessive (G/G-A/G): 1.15 (0.29-4.57), over-dominant (A/G): 0.70 (0.44-1.11) and log-additive: 0.78 (0.52-1.16). OR (Adjusted for sex and age) for the five genetic models in Han subjects were: codominant (A/G): 0.59 (0.40-0.87); codominant (A/A): 0.38 (0.14-1.08); dominant (A/G-A/A): 0.56 (0.39-0.82); recessive (G/G-A/G): 0.43 (0.15-

1.21), over-dominant (A/G): 0.61 (0.41-0.89) and log-additive: 0.60 (0.43-0.83). No significant differences were found in Mongolian, but we found genotypes GA and AA was significantly decrease the risk of HTN+T2DM in Han subjects (Table 6). Thus, the LEPR polymorphism is associated with the occurrence of HTN + T2DM in Han Chinese populations but not Mongolian.

A comparison was made between patients with HTN and those with HTN + T2DM to analyze the correlation between the *lepr* polymorphism and the occurrence of these disorders in Mongolian and Han populations. OR (95%CI) (Adjusted for sex and age) for Han subjects for the same five genetic models were: codominant (A/G): 0.65 (0.46-0.92); codominant (A/A): 1.61 (0.41-6.28); dominant (A/G-A/A): 0.68 (0.49-0.96); recessive (A/A): 1.77 (0.46-6.87); over-dominant (A/G): 0.65 (0.46-0.91) and log-additive: 0.75 (0.55-1.02). All values were non-significant. For Mongolian subjects, OR (Adjusted for sex and age) were: codominant (A/G): 0.54 (0.36-0.81); codominant (A/A): 0.55 (0.17-1.79); dominant (A/G-A/A): 0.54 (0.36-0.80); recessive (A/A): 0.65 (0.20-2.11); over-dominant (A/G): 0.55 (0.37-0.82) and log-additive: 0.59 (0.41-0.84). The codominant A/G model, dominant A/G-A/A model, over-dominant A/G model and log-additive model were all associated with a significantly decreased risk of HTN+T2DM in Mongolian and Han patients (Table 7).

DISCUSSION

HTN and T2DM are major risk factors for cardiovascular and cerebrovascular diseases and both conditions are known to result from interactions between genetics and environment [26,27]. And the LEPR has been widely studied with respect to T2DM and HTN. We have previously demonstrated an association between rs1137101 and HTN in Han subjects and an association between rs7555955 and HTN in Mongolian subjects [28]. No association was found between rs1137101 and HTN or other metabolic traits in Mexican children [29] nor with HTN or cardiovascular disease in Iranian subjects [17]. A meta-analysis did show an association between rs1137101 and T2DM [30] and a Brazilian study suggested a relationship with T2DM and overweight [31]. Furthermore,

rs1137101 was correlated with T2DM, insulin change and overweight among the Punjabi population of North India [32]. These findings indicate that associations are very dependent on the origins of the population under study. Inner Mongolia is a vast territory with demarcation of urban, agricultural, pastoral and part-farming/part-pastoral areas. Each region has an individual life-style with specific eating habits, all of which have an impact on rates of HTN. Overlain on these variations are traditional risk factors, such as smoking, drinking and salt intake [33,34] plus environmental factors [35,36]. Results of the current study were not in accord with those of previous studies and discrepancies may be due to population and lifestyle differences.

The current study focused on the conditions of HTN and HTN + T2DM in ethnic Han and Mongolian populations in Inner Mongolia. There was significant association between rs1137101 with HTN and HTN + T2DM in Han Chinese subjects, the genotypes AA and GA may decrease risk of HTN and HTN+T2DM for control group and HTN group respectively. Whereas rs1137101 was associated with a significantly increased risk of HTN for control subjects, it was associated with a decreased risk of developing T2DM for HTN patients. Further investigations involving larger study populations with further data relating to environmental and lifestyle factors are required to substantiate interactions between genetics and the environment.

CONCLUSION

The current study investigated the impact of the SNP-driven polymorphism, rs1137101, on HTN in Mongolian subjects. There was significant correlation between control and HTN/ HTN+T2DM in Han and Mongolian subjects. Mongolian and Han subjects with HTN who had rs1137101 were protected against the development of T2DM. And we found that rs1137101 decrease the risk of HTN and HTN + T2DM for the Han Chinese population of Inner Mongolia. And different from the protect role in Han population, the polymorphism of rs1137101 could increase risk of HTN for Mongolian population.

ARTICLE HIGHLIGHTS

Research background

Hypertension (HTN) and type 2 diabetes mellitus (T2DM) are considered a risk factor for the other. Both occur frequently in the Inner Mongolia region of China. rs1137101 are proved as the potential risk factories to occur HTN and T2DM. But it's still not unknown the association between rs1137101 and HTN+T2DM in Mongolian and Han population in Inner Mongolia.

Research motivation

the role of rs1137101 in occurrence of HTN+T2DM remain not yet fully elucidated for Mongolian and Han in Inner Mongolia region.

Research objectives

To investigates the relationship between rs1137101 and the occurrence of HTN with T2DM in Mongolian and Han populations in Inner Mongolia. Illuminated the association between the rs1137101 polymorphism and HTN with T2DM was analyzed and differences between Han and Mongolia.

Research methods

We collected the blood samples, the information of blood pressure, weight, height and other body index among Inner Mongolia. Then we according to the data of SNP assay and other index (age, sex), used spss22.0 and SNPstats (https://www.snpstats.net/start.htm) to analysis the correlation between rs1137101 and HTN+T2DM in Mongolian and Han population among Inner Mongolia.

Research results

The association between the rs1137101 polymorphism and HTN with T2DM was analyzed and differences between Han and Mongolian individuals assessed. There was a significant correlation between rs1137101 with both HTN after adjustment of sex and

age in individuals of Mongolian origin. The result shown (OR were adjusted for age and sex) that rs1137101 was significant associated with HTN and HTN+T2DM in Han Chinese population.

Research conclusions

There was significant correlation between control and HTN/ HTN+T2DM in Han and Mongolian subjects. Mongolian and Han subjects with HTN who had rs1137101 were protected against the development of T2DM. And we found that rs1137101 decrease the risk of HTN and HTN + T2DM for the Han Chinese population of Inner Mongolia. And different from the protect role in Han population, the polymorphism of rs1137101 could increase risk of HTN for Mongolian population.

Research perspectives

This article analyzed the association between rs1137101 and HTN/HTN+T2DM by compared the control, HTN and HTN+T2DM groups. And found that rs1137101 may play a important role in HTN and HTN+T2DM in Mongolian and Han in Inner Mongolia. Further investigations involving larger study populations with further data relating to environmental and lifestyle factors are required to substantiate interactions between genetics and the environment.

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