Effect of interaction between occupational stress and polymorphisms of MTHFR gene and SELE gene on hypertension

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The G98T polymorphism of SELE gene (c^2=6.776, P=0.034), the C677T (χ^2=7.130, P=0.028) and A1298C (c^2=12.036, P=0.002) loci of MTHFR gene and the degree of occupational stress (c^2=11.921, P=0.003) were significantly different between the case group and the control group. The genotypes GT at the G98T polymorphism of the SELE gene (*OR*=2.151, *95%CI*: 1.227-3.375), and the dominant model(AC/CC versus AA, OR=1.925, *95%CI*: 1.613-3.816); AC and CC at the A1298C polymorphism of the MTHFR gene (*OR*$_{AC}$=1.917, *95%CI*: 1.064-3.453; *OR*$_{CC}$=2.233, *95%CI*: 1.082-4.609), the additive model (CC versus AA, OR=2.497, *95%CI*: 1.277-4.883) and the dominant model(AC/CC versus AA, OR=2.012, *95%CI*: 1.200-3.373); at the C677T polymorphism of the MTHFR gene CT and TT (*OR*$_{CT}$=1.913, *95%CI*: 1.085-3.375; *OR*$_{TT}$=3.117, *95%CI*: 1.430-6.795), the additive model (CC versus AA, OR=1.913, *95%CI*: 1.085-3.375) and the dominant model(AC/CC versus AA, OR=2.012, *95%CI*: 1.200-3.373), which could increase hypertension risk (P<0.05). The gene-gene interaction showed that there was a positive interaction between the A1298C and C677T sites of the MTHFR gene, and the gene-occupational stress interaction showed that there was a positive interaction between the A1298C and C677T sites of the MTHFR gene and the occupational stress. **[Conclusion]** The interaction of gene mutation and occupational stress in Xinjiang oil workers maybe increase the risk of hypertension.

Effect of interaction between Occupational stress and Polymorphisms of MTHFR Gene and SELE Gene on Hypertension

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Abstract

[Background] Gene-environment interaction is related to the prevalence of hypertension, but the impact of genetic polymorphisms on hypertension may vary due to different geography and population.

[Objective] To explore the impact of the interaction among occupational stress and MTHFR gene and SELE gene polymorphism on the prevalence of hypertension in Xinjiang oil workers.

[Methods] A case-control study was conducted on 310 oil workers. In an oilfield base in Karamay City, Xinjiang, 155 hypertensive patients aged 18~60 years old with more than one year of service were selected as the case group, and 155 oil workers without hypertension were selected as the control group according to the 1:1 matching principle (matching conditions: the gender and shift were the same. The age is around 2 years old). The Occupational Stress Scale was used to evaluate the degree of occupational stress, PCR technique was used to detect MTHFR and SELE gene polymorphism, Logistic regression analysis was used to analyze the effects of gene and occupational stress on hypertension, and gene-gene and gene-environment interactions were analyzed by generalized multi-factor dimension reduction method.

[Results] The G98T polymorphism of SELE gene (χ^2=6.776, P=0.034), the C677T (χ^2=7.130, P=0.028) and A1298C (χ^2=12.036, P=0.002) loci of MTHFR gene and the degree of occupational

35   stress (χ^2=11.921, *P*=0.003) were significantly different between the case group and the control

36   group. The genotypes GT at the G98T polymorphism of the SELE gene (*OR*=2.151, *95%CI*:

37   1.227-3.375), and the dominant model(AC/CC versus AA, OR=1.925, *95%CI*: 1.613-3.816); AC

38   and CC at the A1298C polymorphism of the MTHFR gene (OR_{AC}=1.917, *95%CI*: 1.064-3.453;

39   OR_{CC}=2.233, *95%CI*: 1.082-4.609), the additive model (CC versus AA, OR=2.497, *95%CI*: 1.277-

40   4.883) and the dominant model(AC/CC versus AA, OR=2.012, *95%CI*: 1.200-3.373);   at the

41   C677T polymorphism of the MTHFR gene CT and TT (OR_{CT}=1.913, *95%CI*: 1.085-3.375;

42   OR_{TT}=3.117, *95%CI*: 1.430-6.795), the additive model (CC versus AA, OR=1.913, *95%CI*: 1.085-

43   3.375) and the dominant model(AC/CC versus AA, OR=2.012, *95%CI*: 1.200-3.373), which

44   could increase hypertension risk (*P*<0.05). The gene-gene interaction showed that there was a

45   positive interaction between the A1298C and C677T sites of the MTHFR gene, and the gene-

46   occupational stress interaction showed that there was a positive interaction between the A1298C

47   and C677T sites of the MTHFR gene and the occupational stress.

48   **[Conclusion]** The interaction of gene mutation and occupational stress in Xinjiang oil workers

49   maybe increase the risk of hypertension.

50

Introduction

52   High systolic blood pressure is a leading cause of death from ischemic heart disease, found

53   in Global Burden of Disease Study 2019 (*GBD 2019 risk factors collaborators, 2020*). Therefore,

54   the effective prevention and control of hypertension in the population has become a major public

55   health issue. Data from a cardiovascular disease risk screening study of 170,000 urban and rural

56   residents showed that the detection rate of age-specific hypertension in people aged 35-75 was as

57   high as 37% (*Lu et al., 2017*). However, the etiology of hypertension is complex and diverse, and

58   has not yet been comprehensively studied. It has been shown that genetic and environmental

59   interactions result in an increased risk of developing hypertension (*Huang et al., 2019; Kokubo et

60   al., 2019*). Heritability studies have confirmed that genetic variation among individuals with

61   hypertension accounts for approximately 30-60% of the variation (*Liu et al., 2015*). In recent years,

62   a number of investigators have focused on the association of *MTHFR* gene (*McNulty et al., 2017*)

63   *SELE* gene (*Liao et al., 2016*) polymorphisms with hypertension, but the findings have been

64   inconsistent. Evidence from both the GWAS *(Lu et al., 2015)* and epidemiological studies

65   (*Amenyah et al., 2020; Ji et al., 2019*) suggests that MTHFR gene polymorphisms are associated

66   with the risk of developing hypertension, but polymorphisms at the C677T and A1298C loci of

67   the MTHFR gene are not consistent in all populations. A case-control study in Orléans found that

68   the prevalence of hypertension in the Algerian population was not associated with the MTHFR

69   gene (*Amrani-midoun et al., 2016*). Many studies have also confirmed that subjects carrying the

70   677CC genotype are at significantly increased risk of developing hypertension, while the C677T

71   gene polymorphism leads to lower blood pressure (*Ghogomu et al., 2016*). Meta-analysis suggests

72   that carriers of the C allele of the A561C polymorphism of the SELE gene may contribute to an

73   increased risk of hypertension in the Chinese Han population (*Ouyang et al., 2015*). In addition, a

74   significant association between G98T polymorphism and hypertension has also been found (*Chen*

75   *et al., 2008*). From this it is clear that the probability of developing cardiovascular risk varies

76   geographically due to genetic polymorphisms. Oil workers in Karamay, Xinjiang, are often

77   associated with the occurrence of occupational stress due to the nature of their special occupation,

78   which in turn affects their physical and mental health. A number of studies have now shown that

79   occupational stress may cause an increase in blood pressure through the neurological response of

80   individuals (*Tao et al., 2018*).

81   Therefore, considering the variation in the results of studies conducted in different

82   populations, this study will comprehensively investigate the effects of the interaction among

83   MTHFR gene and SELE gene polymorphisms and occupational stress on hypertension, that aim

84   to provide new ideas for the prevention and control of hypertension in oil workers.

85

86   Materials & Methods

87   **Study Subjects**

88   In the case-control study, a total of 183 oil workers with hypertension according to the results of

89   physical examination in 2020 at the central hospital in Karamay, excluding 28 people with

90   incomplete information (missing questionnaire information, no blood samples, low DNA

91   extraction concentration, etc.), and finally including 155 hypertensive patients aged between 18-

92   60 years with 1 year of work experience as the case group, and 155 non-hypertensive patients were

93   selected as the control group according to the 1:1 matching principle with gender, age (±2 years),

94   and shift status as matching factors. All participants signed a written informed consent. The study

95   was approved by the Ethics Review Committee of the First Affiliated Hospital of Xinjiang Medical

96   University (No. 2015006).

97   **Methods**

98   **General Information and Occupational Stress Survey**

99   A structured questionnaire was used to collect information on gender, age, educational level, shift

100   work, smoking and alcohol consumption (Smoker: smoking $\geq$ 1 cigarette per day for six months

101   or more; drinker: drinking ≥ 2 times a week with alcohol intake ≥ 50 g per drinking session
102   regularly ≥ 1 year (*Xing et al., 2018*)), marital status, working age, personal income per month and
103   BMI among oil workers. Among them, the Occupational Stress Inventory Revised Edition (OSI-
104   R) was used to assess the level of occupational stress. The scale consists of the Occupational Role
105   Questionnaire (ORQ), the Personal Strain Questionnaire (PSQ), and the Personal Resources
106   Questionnaire (PRQ). The occupational stress of oil workers in this study was assessed by the
107   ORQ, which consists of six dimensions with 10 entries in one dimension and using a scale of 1 to
108   5 and summarized, with higher ORQ scores representing higher levels of occupational stress.
109   According to the scoring principle of the scale, occupational stress was classified as: "Low"
110   (ORQ>160), "Middle" (120≤ORQ≤160), and "High" (ORQ<120).

111   **Diagnosis of hypertension and diagnostic criteria**

112   Blood pressure was measured by a professional physician at the Karamay Central Hospital during
113   a routine physical examination of the oil workers. After the oil workers rested for 10 min, blood
114   pressure was measured twice at 5 min intervals using a zeroed standard mercury
115   sphygmomanometer to take the mean value, and when the difference was greater than 5 mmHg,
116   the mean value was taken after the third measurement. In this study, hypertension was defined
117   according to the Chinese Guidelines for the Prevention and Treatment of Hypertension (2018
118   revision) (*Chinese Journal of Cardiovascular Medicine, 2019*) as (1) systolic blood pressure (SBP)
119   ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg and (2) self-reported hypertension
120   diagnosed by a physician, and being treated with antihypertensive therapy within the past two
121   weeks.

122   **Sample collection**

123   4 ml venous blood sample was collected from each subject after 8 h fasting period. The samples
124   were put into the ethylenediaminetetraacetic acid (EDTA) anticoagulation tubes. The serum and
125   plasma were separated by centrifugation at 4°C, 8 000 r/min (20 mm radius), for 3 min, and then
126   stored at -20°C for future and used to extract the genomic deoxyribonucleic acids (DNAs) and
127   ribonucleic acids (RNAs).

128   **Genotyping method of MTHFR and SELE gene polymorphisms**

129   DNA in blood was quantified using spectrophotometric analysis, and a polymerase chain reaction-
130   restriction fragment length polymorphism (PCR-RELP) technique to amplify the target fragment
131   and digest the PCR amplified product with specific endonucleases for SNP typing, As follow:
132   First, the genomic DNA was extracted using a TIANamp Blood DNA Kit (TIANGEN, China) in
133   accordance with the manufacturer's instructions. Microspectrophotometer was used to detect the
134   concentration and purity of the DNA samples for the subsequent experiments. Concentration >100

135   μg/μl, 1.70 <260OD/280OD <2.0 means that the sample is qualified. Second, all DNA samples
136   were genotyped through polymerase chain reaction (PCR)–ligase detection reaction. Table 1
137   presents the primers and restriction endonuclease for amplifying the PCR of the target SNPs for each
138   participant.
139
140   **Statistical analysis**
141   Comparison of rates and genotypes between groups for each polymorphism were performed using
142   chi-square tests, all in SPSS 25.0. SHEsis software was used for Hardy-Weinberg equilibrium test.
143   The effect of each gene polymorphism and occupational tension on hypertension was analyzed by
144   logistic regression, and forest plots were drawn with R. Gene-gene and gene-occupational tension
145   interactions were modeled by applying generalized multifactor downscaling (GMDR) software,
146   and dendrograms were drawn with Multifactor dimensionality reduction (MDR) method.
147
148   # Results
149   **Distribution of basic demographic characteristics of the case and control groups**
150   In this study, 310 oil workers (155 in the case group and 155 in the control group) were
151   investigated, of whom 200 were male and 110 were female in Table 2. The comparison of
152   hypertension among demographic characteristics showed that the differences between different
153   personal income per month (χ^2=5.684, P=0.017), smoking (χ^2=27.01, P<0.001), drinking alcohol
154   (χ^2=8.903, P=0.003), and BMI (χ^2=5.845, P=0.016) were statistically significant, while the
155   differences between different ethnic group, educational level, professional title, marital status, and
156   working age groups were not statistically significant (P > 0.05).
157   **Distribution of SELE and MTHFR genotypic loci and occupational stress between the case**
158   **group and control group**
159   The distribution of SELE and MTHFR genotype loci and occupational stress degree between the
160   case group and the control group is shown in Table 3. Hardy-Weinberg genetic balance test showed
161   that the distribution of G98T and A561C loci of SELE gene, A1298C and C677T loci of MTHFR
162   gene were consistent with expected values in case group and control group. The G98T
163   polymorphism of SELE gene (χ^2=6.776, P=0.034), the C677T (χ^2=7.130, P=0.028) and A1298C
164   (χ^2=12.036, P=0.002) loci of MTHFR gene and the degree of occupational stress (χ^2=11.921,
165   P=0.003) were significantly different between the case group and the control group.
166
167

168 **Logistic regression analysis of the relationship between genetic and occupational stress with**

169 **hypertension**

170 The association of SELE and MTHFR genes and occupational stress with hypertension was

171 analyzed using binary logistic regression and is shown in Table 4. After adjusting for personal

172 income per month, smoking, drinking alcohol, and BMI, genotypes GT at the G98T polymorphism

173 of the SELE gene (*OR*=2.151, *95%CI*: 1.227-3.375), and the dominant model(AC/CC versus AA,

174 OR=1.925, *95%CI*: 1.613-3.816); AC and CC at the A1298C polymorphism of the MTHFR gene

175 (OR_{AC}=1.917, *95%CI*: 1.064-3.453; OR_{CC}=2.233, *95%CI*: 1.082-4.609), the additive model (CC

176 versus AA, OR=2.497, *95%CI*: 1.277-4.883) and the dominant model(AC/CC versus AA,

177 OR=2.012, *95%CI*: 1.200-3.373); at the C677T polymorphism of the MTHFR gene CT and TT

178 (OR_{CT}=1.913, *95%CI*: 1.085-3.375; OR_{TT}=3.117, *95%CI*: 1.430-6.795), the additive model (CC

179 versus AA, OR=1.913, *95%CI*: 1.085-3.375) and the dominant model(AC/CC versus AA,

180 OR=2.012, *95%CI*: 1.200-3.373), which could increase hypertension risk (*P*<0.05).

181 **Effect of gene-gene and gene-occupational tension interactions on hypertension**

182 GMDR software was used to analyze the effects of gene-gene and gene-occupational tension

183 interactions on hypertension. The gene-gene interaction showed the best interaction model

184 between the MTHFR gene A1298C and C677T loci with a training set precision of 0.6677 and a

185 test set precision of 0.6639, a sign test *P*=0.001, and a cross-validation agreement coefficient of

186 10/10, as shown in Table 5 and Figure 1. the dendrogram showed a strong positive interaction

187 between the MTHFR gene A1298C polymorphism and the C677T loci, see Figure 2. The gene-

188 occupational tension interaction showed the best interaction model between MTHFR gene

189 A1298C polymorphism, C677T polymorphism and occupational tension with a training set

190 precision of 0.7662, test set precision of 0.7440, sign test *P*=0.001, and cross-validation

191 consistency coefficient of 10/ 10, see Figure 3. The dendrogram showed a strong positive

192 interaction between the C677T polymorphism of the MTHFR gene and occupational tension, see

193 Figure 4.

194

195 # Discussion

196 Hypertension is a major risk factor for cardiovascular disease and has a low control rate due to its

197 complex and diverse etiology (*Gheorghe et al., 2018*). Many researchers have done numerous

198 studies on environmental and genetic aspects and found that occupational stress is one of the risk

199 factors for hypertension, but MTHFR gene and SELE base polymorphisms may lead to different

200 levels of individual susceptibility to hypertension depending on geographical regions and

201 ethnicity. Previous studies have also suggested the utility of hypertension susceptibility genotypes

202 in Mendelian randomization (*Fu et al., 2019*). However, it has been argued that a single genotype
203 in the MTHFR gene and SELE gene should not be used as independent markers in a Mendelian
204 randomization design, but rather the study should be expanded to include gene-environment
205 interactions. Therefore, this study not only explored the effect of genes, but also the effect of gene-
206 environment interactions on hypertension.

207 Studies about some populations in the three northeastern provinces of China have found that
208 polymorphisms in the MTHFR genes A1298C and C677T are not significantly associated with
209 hypertension (*Liu et al., 2019*). In this case-control study of oil workers in Karamay, Xinjiang,
210 adjusting for confounding factors, mutant genes at the A1298C polymorphism and the C677T
211 polymorphism of the MTHFR gene were found to be susceptible genotypes for hypertension,
212 which is consistent with the findings of and *Alghasham et al* (*2012*). The human MTHFR gene is
213 located on chromosome 1 (1P36.3) and has 11 exons, and the SNP sites that have a greater impact
214 on enzyme activity are found at the C677T and A1298C loci, which are in the coding region.
215 The C677T polymorphism is a point mutation at the position 677 on MTHFR gene with the
216 substitution of cysteine to thymine nucleotide at that position. This point mutation causes the
217 substitution of alanine to valine in the MTHFR enzyme. The single nucleotide polymorphism of
218 this gene reduces the thermostability of the MTHFR enzyme due to the decreased activity of the
219 enzyme at 37℃ or higher. MTHFR enzyme activity in homozygous subjects is 50-60% lower at
220 37℃ and 65% lower at 46℃ compared with normal non-mutated controls (*Rosenberg et al., 2002*).
221 The inability of the MTHFR enzyme to catalyse the conversion of 5,10-methylenetetrahydrofolate
222 to 5-methyltetrahydrofolate leads to the rise of plasma homocysteine levels in the homozygous
223 mutated subjects. Some researchers postulated that homocysteine could cause atherogenesis and
224 thrombogenesis leading to substantialfibrosis and muscle cell hyperplasia,which in turn can be
225 a risk factor for coronary artery disease (*Stanger et al., 2004*). In addition, The MTHFR C677T
226 polymorphism was also reported to be associated with increased risk of myocardial infarction in
227 young/middle-aged Caucasians. Individuals with the MTHFR 677TT genotype and a low folate
228 status had a significantly higher risk of coronary heart disease. A recent study also reported the
229 association between MTHFR C677T gene polymorphism and essential hypertension which is
230 closely related to the increased level of Hcy (Ren et al., 2018).

231 The present study also yielded such results. Numerous studies have confirmed that
232 homocysteine (HCY) is an independent risk factor for cardiovascular disease and can cause
233 vascular lesions in the body, and HCY accumulation caused by MTHFR mutations may increase
234 the risk of vascular complications in hypertensive patients. Scholars have demonstrated that HCY
235 levels are significantly elevated in individuals carrying the 677TT genotype, suggesting that the

236   mechanism of MTHFR C677T and the development of hypertension maybe related to abnormal
237   HCY metabolism due to decreased mutant enzyme activity, which impairs the normal biological
238   function of endothelial cells, thereby inducing oxidative stress that exacerbates the inflammatory
239   response and puts the blood vessels in a persistent inflammatory state, etc. It has been suggested
240   that the A1298C mutation does not inherently affect blood pressure levels but may play a
241   regulatory role when individuals are accompanied by the MTHFR C677T mutation. In contrast,
242   the present study showed that the mutant gene at the A1298C polymorphism of the MTHFR gene
243   is a susceptible genotype for hypertension, which may be due to different geographical and ethnic
244   differences.

245   When the A-C mutation occurs in the A1298C polymorphism, the transcriptionally expressed
246   glutamate will be converted to alanine, which will affect the catalytic regulation of the enzyme. A
247   case-control study found the A1298 C polymorphisms were related to depression severity (*Chen*
248   *et al., 2021*). It has been suggested that although the A1298C mutation itself does not affect blood
249   pressure levels, it may play a regulatory role when individuals are accompanied by the MTHFR
250   C677T mutation. In contrast, the present study showed that the mutated gene with the A1298C
251   polymorphism in the MTHFR gene is a susceptible genotype for hypertension, which may be due
252   to differences across geography and ethnicity. The difference in the association of C677T and
253   A1298C with hypertension may be due to their gene polymorphism, with the C677T mutation site
254   present in the MTHFR gene The C677T mutation site is found in exon 4 of the MTHFR gene and
255   is involved in encoding the catalytic structural domain of the N-terminal part of the enzyme, which
256   directly affects the catalytic activity of the enzyme, whereas the A1298C mutation site is found in
257   exon 7 of the MTHFR gene and encodes the C-terminal regulatory domain.

258   The study also found that the mutant gene at the G98T polymorphism of the SELE gene was
259   the susceptible genotype for hypertension, which is consistent with the study of *Yesheng Wei et al*
260   (*2003*). The human SELE polymorphism, located on the long arm of chromosome 1, is a 13-kb
261   DNA sequence that is a vascular endothelial adhesion molecule and is a marker of vascular
262   endothelial function. Activation of the endothelium promotes atherosclerosis reduces the elasticity
263   of the arterial wall and alters the responsiveness of the endothelium to vascular stimuli, and
264   endothelial dysfunction maybe a major cause of hypertension. The G98T polymorphism is a single
265   nucleotide polymorphism in the coding region caused by the mutation of G to T in the 5'
266   untranslated region of exon 2 of the E-selectin gene at the site 98 (98bp downstream of the
267   transcription start site). It was found that T allele carriers are at high risk of hypertension and have
268   high blood pressure values. The G98T polymorphism mutation can enhance the expressed SELE
269   function by affecting the E-selectin 5' untranslated region structure, thus causing enhanced

270   adhesion, which in turn causes an inflammatory response, damage to endothelial cells, inhibition

271   of NO and prostaglandin production, and diminished vascular responsiveness to endothelium-

272   dependent vasotransfer substances, resulting in increased vascular resistance and, consequently,

273   hypertension (*Qiu et al., 2019; Srivastava et al., 2018*). There are fewer studies on SELE gene

274   polymorphisms in other diseases. The SELE gene also appears to be associated with

275   atherosclerosis, with monocytes adhering to vascular endothelial cells and migrating into the

276   endothelium to take up lipids and transform into foam cells as an early event in the formation of

277   atherosclerosis. Early events in the formation of atherosclerosis. Whereas there is no association

278   between A561C gene polymorphism and hypertension. The differences between these studies may

279   be due to epigenetic mechanisms involved in gene expression influenced by environmental

280   conditions (e.g., lifestyle and diet).

281   A Meta-study in a population of pregnant women found that the risk of hypertension was

282   significantly increased in the presence of high air pollution and mutations in the MTHFR gene

283   (*Yang et al., 2018*), and a study by Fu et al. in Chinese children confirmed that there was also an

284   interaction between the MTHFR gene and the effect of obesity on hypertension (*Fu et al., 2018*).

285   Wu Chuanyun et al. showed that the interaction between internal environmental factors may be a

286   potential factor contributing to elevated blood pressure (*Wu et al., 2015*). In this study, we used

287   GMDR software to construct risk models for the effects of gene-gene and gene-environment

288   associations on hypertension, and further analysis of the interactions between occupational stress

289   and the MTHFR and SELE genes found strong positive between the A1298C polymorphism of

290   the MTHFR gene and the C677T polymorphism, and between the C677T polymorphism of the

291   MTHFR gene and occupational stress *Taylor et al.* (*2010*) did interaction validation of different

292   genes with the environment and came to similar conclusions. The influence of genes on the

293   pathogenesis of hypertension may be the increased deposition of extracellular matrix components

294   and their altered structure or cell-extracellular matrix attachment, which causes structural changes

295   in the arterial wall. In contrast, the MTHFR gene is an important enzyme for folate metabolism,

296   and mutations in the MTHFR gene cause hyperhomocysteinemia and homocystinuria, indirectly

297   affecting changes in human blood pressure (*Bayramoglu et al., 2015*). SELE gene, on the other

298   hand, plays a key role in the binding of lymphocytes and monocytes to endothelial cells. Its genetic

299   polymorphisms may upregulate gene expression levels and thus affect the biological functions of

300   its proteins. Several lines of evidence have shown that A561C and G98T gene polymorphisms can

301   lead to a significant increase in blood pressure (*Farugue et al., 2011*). The special nature of oilfield

302   operations, which often involve shift work, job evaluation, and learning new technologies lead to

303   the occurrence of occupational stress as oilfield workers are often faced with loneliness, insomnia,

304 and depression separated from their families (*Yong et al., 2020*). When both genetic and
305 environmental factors are present, the risk of developing hypertension increases significantly.
306
307 ## Conclusions
308 In conclusion, the risk of hypertension among oil workers in Karamay, Xinjiang, maybe influenced
309 not only by environmental but also by genetic factors, and there is a strong interaction between the
310 two, which provides an updated vision for the prevention and control of hypertension. This study
311 demonstrated a strong interaction between gene-gene and gene-environment effects on
312 hypertension, but there are several potential limitations that should not be overlooked: first, the
313 sample size was small and there may be selection bias. Second, the genotyping method used in
314 this study may have potential bias, and there are reports demonstrating higher sensitivity and
315 accuracy of genotyping methods such as Mass Array and gene chips. Therefore, further sample
316 expansion and selection of more appropriate genotyping methods must be performed in the future
317 to confirm the results we observed in this study.
318

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321

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Primer sequences

No

1   Table1 The primers and restriction endonuclease for amplifying the PCR of the target SNPs

	SELE A 561C	SELE G98T	MTHFR C677T	MTHFR A1298C
Primer sequences	F:ATTAGCATCAAG GTTTAGGATAGGT R:TGAAGAAAGAG AGGCAAGAACCA	F:TGCCCAAAATC TTAGGATGC R:AAGCCCAGGGA AGAACACAT	F:TGAAGGAGAGG TGTCTGCGGGA R:AGGACGGTGCG GTGAGAGTG	F:CTTCTACCTGAAGAG CAAGTC R:CATGTCCACAGCATG GAG
Length	326bp	332bp	198bp	256bp
REE (μl)	PstI(0.2)	HphI(1)	HinfI(1)	MboII(1)
10x Buffer(μl)	2	2	2	2
ddH2O(μl)	3	8.5	7	7
PCR products	17	8.5	10	10
Temperature(℃)	37	37	37	37
Time(min)	15	240	10	60
Agarose gels	2.5%	2.5%	3%	3%
Voltage	110V	100V	110V	100V
Genotyping	CC:326bp AA:222+104bp AC:326+222+104bp	TT:332bp GG:194+138bp GT:332+194+138bp	CC:198bp TT:175+23bp CT:198+175+23bp	CC256bp AA:17+22+30+27bp AC:256+176+22+30+27bp

Amplification system

No

Table 1 Distribution of basic demographic characteristics of case group and control group

Item	N	Case group		Control group		χ^2	P
		n	%	n	%		
Gender						0.000	1.000
Male	200	100	50.0	100	50.0		
Female	110	55	50.0	55	50.0		
Age/years	310	46.20±5.458		46.21±5.469		0.010	0.992
Shift work						0.000	1.000
Yes	216	108	50.0	108	50.0		
No	94	47	50.0	47	50.0		
Ethnic group						1.741	0.187
Han	253	122	48.2	131	51.8		
Others	57	33	57.9	24	42.1		
Educational level						3.780	0.052
High school or below	173	95	549	78	45.1		
College or above	137	60	43.8	77	56.2		
Professional title						1.229	0.268
Junior or below	95	43	45.3	52	54.7		
Intermediate or above	215	112	52.1	103	47.9		
Marital status						1.303	0.521
Single	13	8	61.5	5	38.5		
Married	259	126	48.6	133	51.4		
Divorced/others	38	21	55.3	17	44.7		
Personal income per month/Yuan						5.684	**0.017**
< 5000	202	111	55.0	91	945.0		
≥ 5000	108	44	40.7	64	59.3		
Smoking						27.01	□**0.001**
Yes	183	114	62.3	69	37.7		
No	127	41	32.3	86	67.7		
Drinking alcohol						8.903	**0.003**
Yes	218	121	55.5	97	44.5		
No	92	34	37.0	58	63.0		
BMI (Body mass index / kg·m^{-2})						5.845	**0.016**

18.5~24	102	41	40.2	61	59.8		
> 24	208	114	54.8	94	45.2		
Working age/years						1.685	0.194
≤ 15	113	51	45.1	62	54.9		
> 15	197	104	52.8	93	47.2		
Total	310	155	50.0	155	50.0		

Amplification procedure

No

1   Table 2 Distribution of gene and occupational stress between case group and control group

Item	N	Case group		Control group		χ^2	P
		n	%	n	%	1.025	0.599
SELE A561C							
AA	213	103	48.4	110	51.6		
CC	15	9	60.0	6	40.0		
AC	82	43	52.4	39	47.6		
SELE G98T						6.776	**0.034**
GG	196	87	44.4	109	55.6		
TT	16	10	62.5	6	37.5		
GT	98	58	59.2	40	40.8		
MTHFR A1298C						12.036	**0.002**
AA	102	37	36.3	65	63.7		
CC	66	40	60.6	26	39.4		
AC	142	78	54.9	64	45.1		
MTHFR C677T						7.130	**0.028**
CC	116	50	43.1	66	56.9		
TT	52	34	65.3	18	34.6		
CT	142	71	50.0	71	50.0		
Occupational stress						11.921	**0.003**
Low	23	8	34.8	15	65.2		
Middle	127	52	40.9	75	59.1		
High	160	95	59.4	65	40.6		

Distribution of basic demographic characteristics of case group and control group

1   Table3 logistic regression analysis of the influence of genes and occupational stress on the prevalence of
2   hypertension

Gene	Unadjusted		Adjusted	
	OR(95%CI)	*P*	*OR(95%CI)*	*P*
SELE A561C				
AA	1.00		1.00	
AC	1.073(0.624-1.844)	0.800	1.161(0.654-2.058)	0.610
CC	1.519(0.496-4.652)	0.465	1.667(0.495-5.617)	0.409
Additive	1.751(0.547-5.601)	0.345	1.602(0.551-4.658)	0.387
Dominant	1.243(0.763-1.997)	0.392	1.337(0.800-2.235)	0.268
Recessive	0.653(0.227-1.882)	0.430	0.603(0.192-1.896)	0.387
SELE G98T				
GG	1.00		1.00	
GT	2.039(1.211-3.433)	0.007	2.151(1.227-3.375)	**0.008**
TT	2.756(0.924-8.216)	0.069	2.724(0.879-8.439)	0.082
Additive	2.088(0.730-5.971)	0.170	2.086(0.666-6.535)	0.207
Dominant	1.852(1.159-2.959)	0.010	1.925(1.163-3.186)	**0.011**
Recessive	0.584(0.207-1.648)	0.309	0.602(0.199-1.822)	0.369
MTHFR A1298C				
AA	1.00		1.00	
AC	2.223(1.279-3.864)	0.005	1.917(1.064-3.453)	**0.030**
CC	2.682(1.351-5.327)	0.005	2.233(1.082-4.609)	**0.030**
Additive	2.703(1.428-5.114)	0.002	2.497(1.277-4.883)	**0.007**
Dominant	2.303(1.414-3.752)	0.001	2.012(1.200-3.373)	**0.008**
Recessive	0.579(0.333-1.008)	0.054	0.610(0.337-1.104)	0.103
MTHFR C677T				
CC	1.00		1.00	
CT	1.683(0.990-2.860)	0.054	1.913(1.085-3.375)	**0.025**
TT	2.511(1.230-5.125)	0.011	3.117(1.430-6.795)	**0.004**
Additive	2.493(1.264-4.918)	0.008	2.936(1.398-6.166)	**0.004**
Dominant	1.557(0.980-2.575)	0.061	1.802(1.094-2.968)	**0.021**
Recessive	0.468(0.251-0.870)	0.017	0.437(0.225-0.849)	**0.015**
Occupational stress				
Low	1.00		1.00	
Middle	1.300(0.514-3.289)	0.580	0.753(0.277-2.051)	0.579
High	2.740(1.098-6.837)	0.031	1.629(0.610-4.352)	0.330

GMDR model of the influence of gene-gene, gene-occupational stress interaction on the prevalence of hypertension

GMDR model of the influence of gene-gene, gene-occupational stress interaction on the prevalence of hypertension

1   Table 4 GMDR model of the influence of gene-gene, gene-occupational stress
2   interaction on the prevalence of hypertension

Interaction model	Accuracy		Sign test (*P*)	CV consistency
	Training set	Testing set		
Gene-Gene				
A1298C	0.5903	0.5851	9(0.0107)	10/10
A1298C*C677T	0.6677	0.6639	10(0.0010)	10/10
A1298C*C677T*A561C	0.6929	0.6542	10(0.0010)	7/10
A1298C*C677T*A561C*G98T	0.7310	0.6340	10(0.0010)	10/10
Gene-Occupational stress				
Occupational stress	0.5993	0.5503	8 (0.0547)	7/10
Occupational stress*C677T	0.7010	0.6586	10 (0.0010)	9/10
Occupational stress*C677T*A1298C	0.7662	0.7440	10 (0.0010)	10/10
Occupational stress*C677T*A1298C*G98T	0.7958	0.7351	10 (0.0010)	10/10
Occupational stress*C677T*A1298C*G98T*A561C	0.8235	0.6916	10 (0.0010)	10/10

Figure 1

Forest plot of logistic regression analysis of the influence of genes and occupational
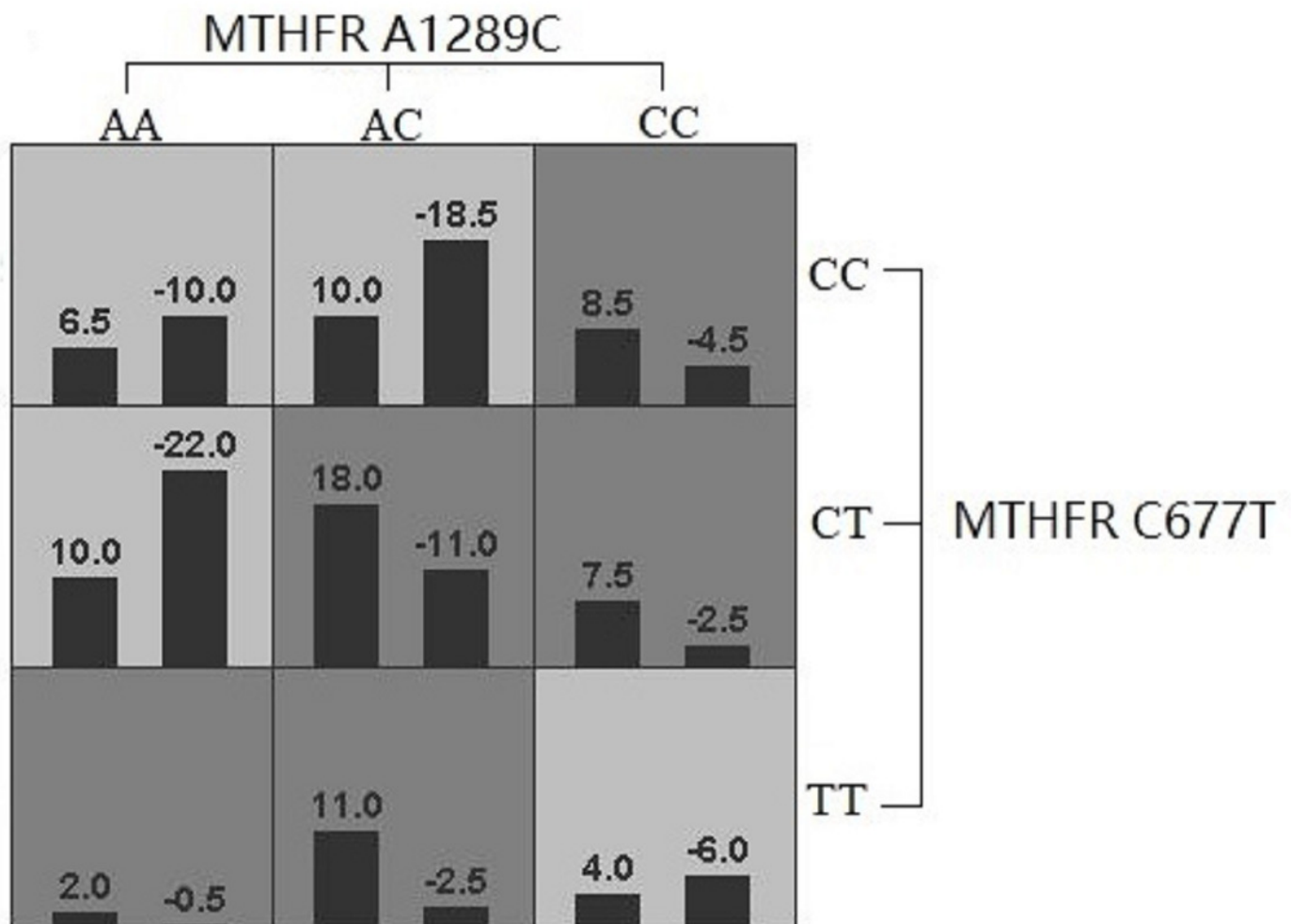
Figure 2

Gene-gene interaction model of MTHFR gene A1298C and C677T sites
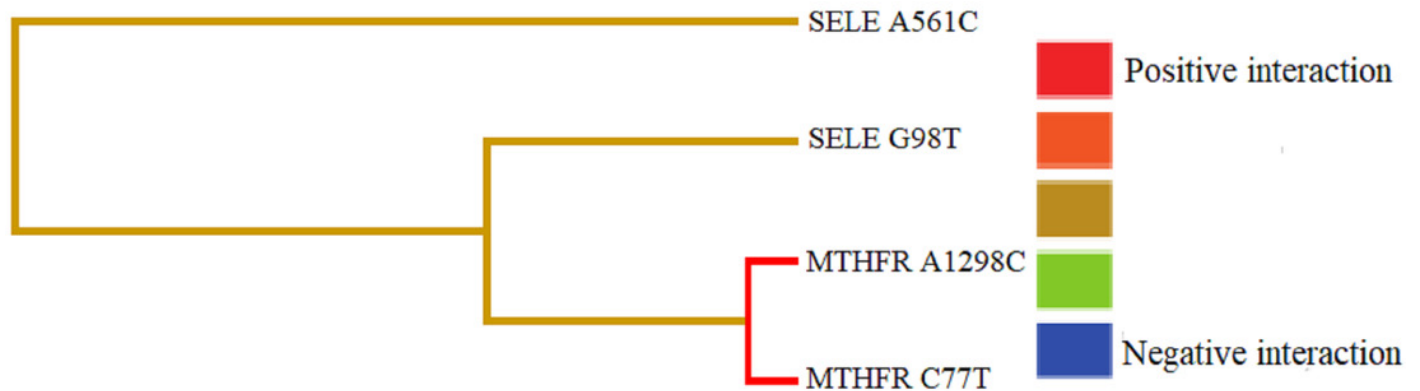
Figure 3

Gene-gene interaction dendrogram of MTHFR gene A1298C and C677T sites
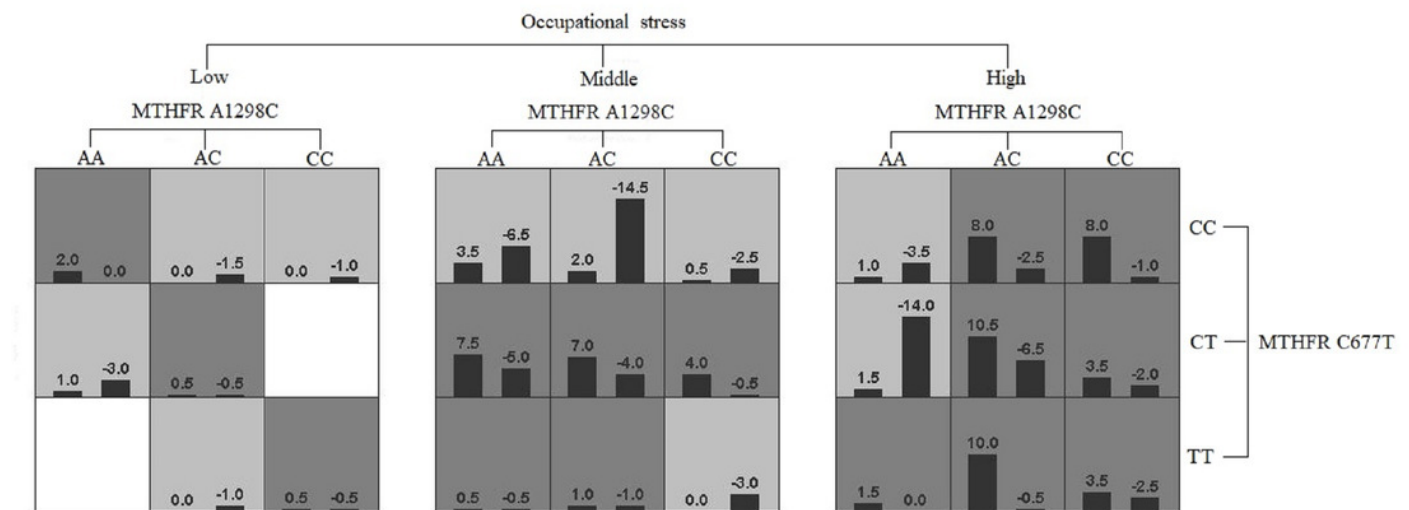
Figure 4

Gene-environment interaction model of MTHFR gene A1298C and C677T sites and occupational stress