·研究论文·

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# 赤峰市汉族和蒙古族孕期女性 MTHFR 与 MTRR 的基因多态性分布研究

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**摘 要**: 针对赤峰市汉族和蒙古族孕期女性开展分子流行病学调查, 研究叶酸代谢关键酶 5,10- 亚甲基四氢叶酸还原酶(5,10-methylenetetrahydrofolate reductase, MTHFR) C677T、A1298C 以及甲硫氨酸合成酶还原酶(methionine synthase reductase, MTRR) A66G 的基因多态性在该地区汉族及蒙古族中的分布。以孕期保健的 853 名女性为研究对象, 其中汉族 647 人、蒙古族 206 人。采集口腔黏膜上皮脱落细胞, 抽提基因组 DNA, 使用荧光定量 PCR 方法检测 MTHFR C677T、A1298C 和 MTRR A66G 的基因多态性, 并进行统计学分析。结果显示: 1) 入组对象的基因多态性分布符合遗传平衡; 2) 汉族和蒙古族孕期女性 MTHFR C677T 位点基因型 CC、CT、TT 的频率分别为 15.61%、52.40%、31.99%与 23.79%、50.97%、25.24%, 差异具有统计学意义($P$<0.05)。汉族和蒙古族孕期女性 MTHFR A1298C 位点基因型 AA、AC、CC 的频率分别为 76.04%、22.10%、1.86%与 74.27%、23.30%、2.43%, 差异无统计学意义($P$>0.05)。汉族和蒙古族孕期女性 MTRR A66G 位点基因型 AA、AG、GG 的频率分别为 58.42%、36.63%、4.95%与 50.48%、40.78%、8.74%, 差异具有统计学意义($P$<0.05); 3) 汉族和蒙古族孕期女性 MTHFR C677T和 A1298C 两位点连锁有 6 种组合, 频率最高的是 CT/AA, 之后依次是 TT/AA、CT/AC、CC/AA、CC/AC、CC/CC, 没有 CT/CC、TT/AC 和 TT/CC 组合。两位点间存在完全连锁不平衡。本研究获取的赤峰市汉族、蒙古族孕期女性 MTHFR 和 MTRR 基因多态性的群体遗传学特征, 为指导科学增补叶酸营养、实施个性化孕期保健提供了依据。

**关键词**: 基因多态性; 亚甲基四氢叶酸还原酶(MTHFR); 甲硫氨酸合成酶还原酶(MTRR); 出生缺陷干预研究

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# Study of Genetic Polymorphisms of MTHFR and MTRR in Han and Mongolian Women During Pregnancy in Chifeng City

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**Abstract:** A molecular epidemiological survey was conducted among Han and Mongolian women during pregnancy in Chifeng City to study the genetic polymorphism distribution of key folate metabolism enzymes 5,10-methylenetetrahydrofolate reductase (MTHFR) C677T, A1298C, and methionine synthase reductase (MTRR) A66G. A total of 853 pregnant women were analyzed in this study, including 647 Han people and 206 Mongolians. Exfoliated oral mucosal epithelial cells were collected, genomic DNA was extracted, and

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the polymorphisms of MTHFR C677T, A1298C and MTRR A66G were detected by real-time quantitative PCR. The results showed that the genetic polymorphism distribution of the enrolled subjects conformed to the genetic balance. The genotype frequencies of MTHFR C677T CC, CT and TT in Han women during pregnancy were 15.61%, 52.40% and 31.99%, respectively, and those in Mongolian women during pregnancy were 23.79%, 50.97% and 25.24%, respectively, and the difference between them was statistically significant ($P$<0.05). The genotype frequencies of MTHFR A1298C AA, AC and CC in Han women during pregnancy were 76.04%, 22.10% and 1.86%, respectively, and those in Mongolian women during pregnancy were 74.27%, 23.30% and 2.43%, respectively, and the difference was not statistically significant ($P$>0.05). The genotype frequencies of MTRR A66G AA, AG and GG in Han women during pregnancy were 58.42%, 36.63% and 4.95%, respectively, and those in Mongolian women during pregnancy were 50.48%, 40.78% and 8.74%, respectively, and the difference was statistically significant ($P$<0.05). The two loci, MTHFR C677T and A1298C had six combinations, with CT/AA the highest frequency, followed by TT/AA, CT/AC, CC/AA, CC/AC, CC/CC and there were no CT/CC, TT/AC and TT/CC combinations. They were in complete linkage disequilibrium. By this study, the population genetic characteristics of MTHFR and MTRR genetic polymorphisms were obtained in pregnant Han and Mongolian women in Chifeng City, providing a basis for guiding the scientific supplementation of folic acid nutrition and implementing personalized pregnancy care.

**Key words:** gene polymorphism; methylenetetrahydrofolate reductase (MTHFR); methionine synthase reductase (MTRR); birth defect intervention study

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叶酸是人体重要的营养素, 叶酸摄入不足或代谢障碍会造成体内同型半胱氨酸升高和甲基化降低。孕期叶酸营养不足会导致胎儿神经管畸形[1]、先天性心脏病[2]、唐氏综合征[3]、唇腭裂[4]等出生缺陷, 并与流产[5]、早产[6]等不良妊娠结局以及妊娠期糖尿病[7]、妊娠期高血压[8]等疾病密切相关。5,10-亚甲基四氢叶酸还原酶(5,10-methylenetetrahydrofolate reductase, MTHFR)和甲硫氨酸合成酶还原酶(methionine synthase reductase, MTRR)是叶酸代谢通路中的关键酶, 基因多态性决定了不同的酶活性以及叶酸利用能力。本研究针对赤峰市汉族和蒙古族孕期女性开展分子流行病学调查, 研究MTHFR C677T、A1298C 和 MTRR A66G 的基因多态性分布, 并获取本地区的群体遗传学特征。

## 1 资料与方法

### 1.1 研究对象

选取 2019 年 4 月至 9 月到赤峰市妇产医院进行孕期检查的健康女性, 依据知情同意原则采集口腔黏膜细胞。入组对象共 853 人, 其中汉族 647 人、蒙古族 206 人。

### 1.2 检测方法

利用硅胶吸附法提取口腔黏膜细胞样本的基因组 DNA。采用荧光定量 PCR 技术, 检测MTHFR C677T、A1298C 和 MTRR A66G 的基因多态性。DNA 抽提试剂盒、荧光定量 PCR 仪等相关试剂、仪器均购自美国 ABI 公司。

### 1.3 统计学分析

采用 Haploview 4.2 软件进行单核苷酸多态性(single nucleotide polymorphism, SNP)的 Hardy-Weinberg 平衡、连锁不平衡(linkage disequilibrium, LD)分析。采用 SPSS 19.0 软件分析基因型频率和等位基因频率, 两组间数据的比较采用卡方检验, $P$<0.05 为差异具有统计学意义。

## 2 结果

### 2.1 Hardy-Weinberg 平衡分析

入组对象 MTHFR C677T、A1298C 和 MTRR A66G 的基因多态性分布见表 1。汉族和蒙古族孕期女性的叶酸代谢相关基因位点分布均符合遗传平衡($P$>0.05), 说明样本数据符合孟德尔定律, 样本具有群体代表性。

### 2.2 基因型频率分析

入组对象 MTHFR C677T、A1298C 和 MTRR A66G 的基因型频率分布见表 2。汉族和蒙古族女性 MTHFR C677T、MTRR A66G 的基因型频率具有统计学差异($P$<0.05), MTHFR A1298C 的基因型频率无显著性差异($P$>0.05)。

### 2.3　等位基因频率分析

入组对象 MTHFR C677T、A1298C 和 MTRR A66G 的等位基因频率分布见表 3。汉族和蒙古族女性 MTHFR C677T、MTRR A66G 的等位基因频率具有统计学差异($P<0.05$), MTHFR A1298C 的等位基因频率无统计学差异($P>0.05$)。

**表 1　Hardy–Weinberg 平衡分析**
**Table 1　Hardy–Weinberg equilibrium analysis**

| Nationality | | MTHFR C677T | | | $\chi^2$ | $P$ | MTHFR A1298C | | | $\chi^2$ | $P$ | MTRR A66G | | | $\chi^2$ | $P$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | CC | CT | TT | | | AA | AC | CC | | | AA | AG | GG | | |
| Han | Actual frequency | 101 | 339 | 207 | 3.82 | 0.051 | 492 | 143 | 12 | 0.18 | 0.669 | 378 | 237 | 32 | 0.44 | 0.508 |
| | Estimated frequency | 113 | 315 | 219 | | | 491 | 145 | 11 | | | 381 | 231 | 35 | | |
| Mongolian | Actual frequency | 49 | 105 | 52 | 0.08 | 0.778 | 153 | 48 | 5 | 0.28 | 0.597 | 104 | 84 | 18 | 0.03 | 0.860 |
| | Estimated frequency | 50 | 103 | 53 | | | 152 | 50 | 4 | | | 103 | 85 | 17 | | |

**表 2　汉族、蒙古族女性 MTHFR C677T、A1298C 和 MTRR A66G 的基因型频率**
**Table 2　MTHFR C677T, A1298C and MTRR A66G genotype frequencies of Han and Mongolian women**

*n* (percentage, %)

| Nationality | MTHFR C677T | | | $\chi^2$ | $P$ | MTHFR A1298C | | | $\chi^2$ | $P$ | MTRR A66G | | | $\chi^2$ | $P$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CC | CT | TT | | | AA | AC | CC | | | AA | AG | GG | | |
| Han | 101 | 339 | 207 | 8.35 | 0.02 | 492 | 143 | 12 | 0.42 | 0.81 | 378 | 237 | 32 | 6.29 | 0.04 |
| | (15.61) | (52.40) | (31.99) | | | (76.04) | (22.10) | (1.86) | | | (58.42) | (36.63) | (4.95) | | |
| Mongolian | 49 | 105 | 52 | | | 153 | 48 | 5 | | | 104 | 84 | 18 | | |
| | (23.79) | (50.97) | (25.24) | | | (74.27) | (23.30) | (2.43) | | | (50.48) | (40.78) | (8.74) | | |

**表 3　汉族、蒙古族女性 MTHFR C677T、A1298C 和 MTRR A66G 的等位基因频率**
**Table 3　MTHFR C677T, A1298C and MTRR A66G allele frequencies of Han and Mongolian women**

*n* (percentage, %)

| Nationality | MTHFR C677T | | $\chi^2$ | $P$ | MTHFR A1298C | | $\chi^2$ | $P$ | MTRR A66G | | $\chi^2$ | $P$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C | T | | | A | C | | | A | G | | |
| Han | 541 | 753 | 7.08 | 0.01 | 1 127 | 167 | 0.37 | 0.54 | 993 | 301 | 5.78 | 0.02 |
| | (41.81) | (58.19) | | | (87.09) | (12.91) | | | (76.74) | (23.26) | | |
| Mongolian | 203 | 209 | | | 354 | 58 | | | 292 | 120 | | |
| | (49.27) | (50.73) | | | (85.92) | (14.08) | | | (70.87) | (29.13) | | |

### 2.4　MTHFR C677T 和 A1298C 的连锁及单倍型分析

MTHFR C677T 和 A1298C 两位点的连锁情况见表 4、表 5。它们在汉族和蒙古族女性都有 6 种组合, 其中, 频率最高的均为 CT/AA, 之后依次均为 TT/AA、CT/AC、CC/AA、CC/AC、CC/CC, 均没有 CT/CC、TT/AC 和 TT/CC 组合。

**表 4　汉族女性 MTHFR C677T 和 A1298C 的连锁型分布**
**Table 4　MTHFR C677T and A1298C linkage type distribution in Han women**

*n* (percentage, %)

| MTHFR C677T | MTHFR A1298C | | |
|---|---|---|---|
| | AA | AC | CC |
| CC | 53 (8.19) | 36 (5.56) | 12 (1.86) |
| CT | 232 (35.86) | 107 (16.54) | 0 (0) |
| TT | 207 (31.99) | 0 (0) | 0 (0) |

**表 5　蒙古族女性 MTHFR C677T 和 A1298C 的连锁型分布**
**Table 5　MTHFR C677T and A1298C linkage type distribution in Mongolian women**

*n* (percentage, %)

| MTHFR C677T | MTHFR A1298C | | |
|---|---|---|---|
| | AA | AC | CC |
| CC | 25 (12.14) | 19 (9.22) | 5 (2.43) |
| CT | 76 (36.89) | 29 (14.08) | 0 (0) |
| TT | 52 (25.24) | 0 (0) | 0 (0) |

汉族、蒙古族女性 MTHFR C677T 和 A1298C 两个位点构建的单倍型均存在 3 种组合: TA、CA、CC, 两位点间存在完全连锁不平衡(表 6)。

## 3　讨论

MTHFR 和 MTRR 的基因多态性分布具有地

**表 6 汉族、蒙古族女性 MTHFR C677T 和 A1298C 的单倍型分布频率**

**Table 6 Distribution frequency of haplotypes of MTHFR C677T and A1298C in Han and Mongolian women**

| Nationality | Haplotype/(%) | | | $D'$ | LOD | $r^2$ |
|---|---|---|---|---|---|---|
| | TA | CA | CC | | | |
| Han | 58.20 | 28.20 | 13.60 | 1.0 | 40.34 | 0.219 |
| Mongolian | 50.70 | 35.20 | 14.10 | 1.0 | 11.24 | 0.169 |

注: $D'$为连锁不平衡系数, 用于度量观察到的单倍型频率与平衡状态下期望频率的偏差; LOD 指在一定重组率条件下, 两个位点相连锁的似然性和不连锁的似然性比值的对数值, LOD≥3 时, 肯定连锁; $r^2$ 表示一个位点可反映另一位点信息量的程度。

Notes: $D'$represents linkage disequilibrium coefficient, used to measure the deviation between the observed haplotype frequency and the expected frequency in equilibrium; LOD refers to the logarithm of likelihood ratio of two sites linked and non-linkage under a certain recombination rate. When LOD≥3, it is definitely linked; $r^2$ indicates the degree to which one site can reflect the amount of information in another site.

域和民族差异[9]。近年来该领域的报道大多为汉族人群, 鲜有蒙古族人群的调查研究。根据 2010 年第六次全国人口普查数据, 我国蒙古族人口约 650 万, 其中 423 万分布在内蒙古自治区。内蒙古自治区常住人口中, 汉族占 79.5%, 蒙古族占 17.1%且分布于各盟市。本研究调查了赤峰市汉族及蒙古族 MTHFR 和 MTRR 的基因多态性分布。调查显示赤峰市蒙古族女性 MTHFR C677T 位点 TT 基因型频率为 25.24%, T 等位基因频率为 50.73%, 低于汉族女性的 31.99%和 58.19%, 差异具有统计学意义($P$<0.05)。这与裴丽君等[10]报道的包头市蒙古族和汉族人群的比较结果类似。此外, 赤峰市蒙古族女性 MTRR A66G 位点 GG 基因型频率为 8.74%, G 等位基因频率为 29.13%, 高于汉族女性的 4.95%和 23.26%, 差异具有统计学意义($P$<0.05)。

本研究的检测结果显示, 赤峰市汉族女性 MTHFR C677T 位点 TT 的基因型频率为 31.99%, T 等位基因频率为 58.19%, 高于已有报道的新疆阿克苏(21.9%, 47.1%)[11]、湖北宜都市(12.2%, 36.8%)[12]、广东佛山市(5.6%, 21.5%)[13]等地, 低于山东淄博市(43.6%, 65.6%)[14]、河南新乡市(38.9%, 62.0%)[15]、河北廊坊市(37.8%, 60.9%)[16]等地。

总的来讲, 通过调查各地区汉族及少数民族叶酸代谢关键酶的基因多态性分布, 可以为基于群体遗传特征的出生缺陷病因学研究和临床干预研究提供依据。从全国范围内来看, 赤峰市汉族及蒙古族女性叶酸代谢关键酶基因位点的风险型 MTHFR 677TT 占比较高, 尤其是汉族女性, 叶酸利用能力偏低, 这提示对育龄妇女进行叶酸代谢障碍相关基因位点筛查, 识别叶酸利用能力低下的人群, 有助于指导相关人群科学增补叶酸营养, 从而实现个性化保健。

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