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A COMMON TRANSITION IN MTHFR GENE AND MALE INFERTILITY: A META-ANALYSIS IN IRANIAN POPULATION

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ABSTRACT

Male infertility is a main issue for juvenile couples. About 50% of infertility causes refer to male factors. Genetic factors such as genetic polymorphisms in key genes could affect male infertility. One of key gene polymorphisms is MTHFR-C677T which may influence male infertility. There are three case-control study about the association of C677T transition with male infertility in Iranian population, but the results are approximately inconclusive.

Therefore, we performed a meta-analysis in Iranian population about the association of C677T transition with male infertility. We found the eligible studies by search in suitable databases. Then, the data was extracted from included studies and was analyzed by Open Meta [analyst] Software. Our data revealed that there is a significant association of MTHFR-C677T with male infertility in TT vs. CC (OR= 2.197, 95%CI= 1.431- 3.372, p< 0.001, $P_{heterogeneity}$= 0.526, I2= 0%) and CT vs. CC (OR= 1.472, 95%CI= 1.156-1.875, p= 0.002, $P_{heterogeneity}$= 0.767, I2= 0%) models within Iranian population. According to our results, MTHFR-C677T may be a strong biomarker for screening of susceptible infertile men in Iranian population.

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Introduction

Infertility refer to lack of ability to pregnancy after one year in couples with unprotected sexual intercourse [1,2]. About 13-18% of couples are infertile. Infertility can be due to hormonal, age, obesity or related infectious diseases [3,4]. Infertility can be due to immunological, physiological or the result of surgery or obstruction and can also be due to certain abnormalities in the gametes (eg sperm abnormal parameters) [5]. Although in many cases diagnosis of infertility is not possible simply, lack of ovulation, preventing mechanical, defects in sperm and age of parents are a major cause of infertility. 20 percent of couples are infertile, however, reason of their diseases is simply not justified [6]. A significant number of infertility phenotypes associated with certain genetic disorders [7]. Diverse genetic causes of infertility are including chromosomal abnormalities, single-gene disorders, and multifactorial phenotypes. Some genetic factors in particular could affect on men whereas some others influence on men and women [8]. For example, chromosomal translocation occurs in both sexes, while Klinefelter syndrome and its related phenotype occurs in men. One of other genetic factors which can influence the male infertility is genetic polymorphisms [9]. Genetic polymorphisms in key genes such as protamines [10], MTR [11], MTHFR [12, 13], and etc. could influence male infertility. There are three common polymorphism in the MTHFR gene (C677T; A1298C, and G1793A). Among these, C677T is more common rather than two others. There are three genetic association study regard to the association of C677T transition with male infertility in Iranian men, but the results are roughly inconclusive. Therefore, this study was aimed to investigate the association of C677T transition with male in a meta-analysis approach in Iranian population.

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Material and methods

Search strategy

We employed some suitable universal databases such as PubMed, Google Scholar, ScienceDirect, and some Persian databases such as Magiran and Scientific Information (SID) databases to find out the related papers. We used keywords such as MTHFR, Polymorphism, Male infertility, Iran, C677T, Ala222Val, A222V, and SNP to discover appropriate studies.

Study selection and data extraction

Irrelevant and duplicated articles were omitted, and abstracts of the residual papers were then assessed to decide whether the full-text could be studied. Allied studies were carefully chosen via following inclusion principles: 1- Assessed the association of C677T with male infertility. 2- Case-control design. 3- The diagnosis of male infertility was confirmed by WHO criteria. 4- Documents should comprise the odds ratios (ORs) and 95% confidence intervals (CIs). The data such as the name of the authors, publication year, and genotype frequencies in fertile and infertile groups were extracted from included studies.

Statistical analysis

At first step, Hardy-Weinberg equilibrium (HWE) was estimated for fertile groups of all three studies by a Chi square test. The association of C677T and male infertility risk was assessed by ORs within 95% CI. Meta-analysis was done in the TT vs. CC and CT vs. CC models. The estimated I^2 score and Q test were applied to compute the heterogeneity scale [14], and when the *p*-value of the Q test was <0.1, the random-effect model was considered [15,16], otherwise, we used the fixed-effect model [17, 18]. The Open Meta [Analyst] software were used for the statistical analysis.

Results

After search and screen of potential eligible articles, we found that three article are suitable for meta-analysis [19, 20, 12] Some characteristics of these three papers such as genotype frequencies and name of author, and years of publication are summarized in table 1. The genotype frequencies in all of three aforementioned studies were in Hardy-Weinberg equilibrium ($p< 0.05$).

Table 1. Distribution of 677C>T in included studies

Genotype frequencies						HWE *P*[a]	Genotyping method	Reference
Control			Case					
CC	CT	TT	CC	CT	TT			
144	148	36	58	80	26	0.83	PCR-RFLP	[19]
77	52	3	51	59	8	0.09	PCR-RFLP	[20]
144	98	13	109	109	24	0.48	PCR-RFLP	[12]

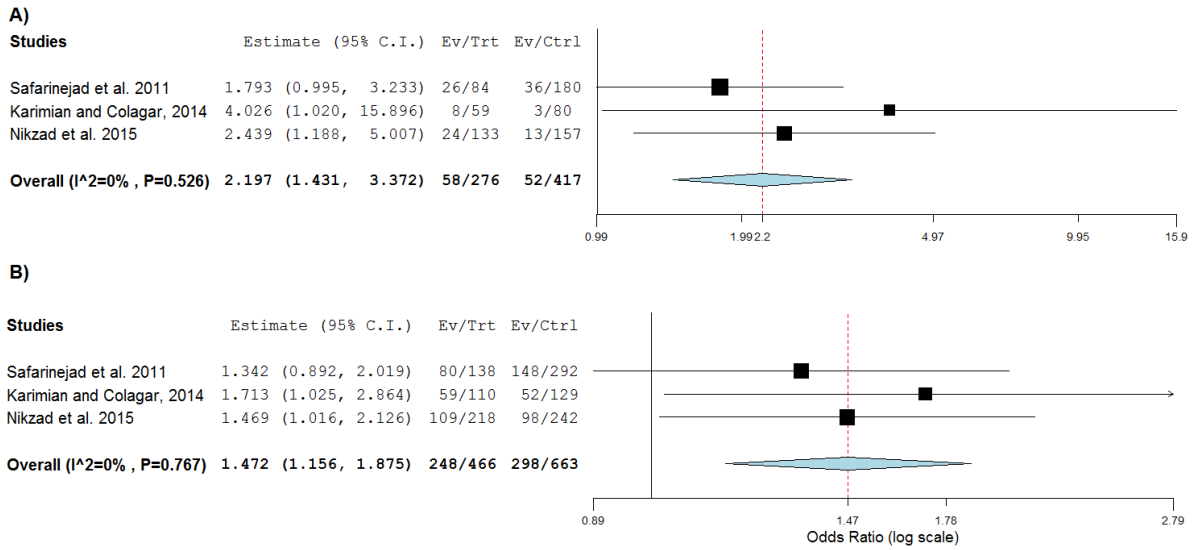
PCR=polymerase chain reaction; RFLP=restriction fragment length polymorphism.
The control groups were in Hardy–Weinberg equilibrium.

Table 2. Results of meta-analysis

Genetic model	Analysis model	OR (95%CI)	*P*-value	tau^2	Q(df=2)	*P*H	I^2
TT *vs*. CC (Codominant model)	Random effect	2.172 (1.409-3.348)	< 0.001	0.000	1.282	0.527	0%
	Fixed effect	2.197 (1.431- 3.372)	< 0.001	-	1.285	0.526	0%
CT *vs*. CC (Codominant model)	Random effect	1.473 (1.156-1.875)	0.002	0.000	0.531	0.767	0%
	Fixed effect	1.472 (1.156-1.875)	0.002	-	0.531	0.767	0%

OR, odds ratio; CI, confidence interval; *P*H, *P*-values for heterogeneity from Q test

The meta-analysis results about the association of MTHFR C677T and male infertility risk were detailed in table 2. As shown in table 2, we found a strong significant association between MTHFR-C677T with male infertility in Iranian population in both TT vs. CC (OR= 2.197, 95%CI= 1.431- 3.372, p< 0.001, $P_{heterogeneity}$= 0.526, I2= 0%) and CT vs. CC (OR= 1.472, 95%CI= 1.156-1.875, p= 0.002, $P_{heterogeneity}$= 0.767, I2= 0%) models (Figure 1).



Forest plot. Results of meta-analysis in TT vs. CC (A) and CT vs. CC (B) models.

Discussion

Infertility affects about 10-15% juvenile couples. About 50% of infertility reasons are related to male factors. Anatomic, immunologic, and hormonal abnormalities and also environmental factors could affect male reproduction. Some other factors also could influence male fertility which are idiopathic. These comprises about 25-30% of male infertility factors [21]. Recently, molecular genetic reasons of male infertility have attracted much attention, because there many genes are recognized which are involved in spermatogenesis process. Then any abnormalities in these genes could affect male reproductive capacity. Genetic factors comprise about 30% of male infertility causes [22]. Genetic factors involved in male infertility are classified in three groups: 1- chromosomal aneuploidy, 2- micro deletions, and 3- single gene abnormalities [23, 24,2]. Genetic polymorphisms are a group of genetic factors which can influence male infertility [10, 25]. Polymorphisms in key pathways such as genome packaging proteins and folate metabolizing genes can disrupt spermatogenesis [26, 27]. One of key genetic polymorphisms which may involve in male infertility is MTHFR C677T. There are some evidences that show this SNP is involved in male infertility in Iranian population, but the results are approximately inconclusive. Therefore we performed a meta-analysis in Iranian population. Our data revealed that there is a significant association between MTHFR C677T and male infertility in both TT vs. CC and CT vs. CC genetic models within Iranian population. Therefore, it could be a risk factor for male infertility and it could be considered as a biomarker for screening of susceptible men for infertility. Genetic polymorphisms can alter gene expression, RNA structure and protein function [27, 29,30]. Our previous study revealed that there is MTHFR C677T could affect protein function and RNA structure [31, 12]. In addition, these similar studies could be performed in cancer field which involved with environmental and genetic factors [32] Finally, there are some limitations in our study which should be considered. For example the number of studies which included in our study is low. Also, the included studies in our meta-analysis are limited to some ehnithity of Iranian population. Therefore, more studies with larger sample sizes are required to obtain more accurate results.

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