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THE RS1801131 AND İDİOPATHİC MALE İNFERTİLİTY İN IRANİAN POPULATİON: A META-ANALYSİS

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ABSTRACT

Methylene tetrahydrofolate reductase (MTHFR) gene is a key regulatory enzyme in folate pathway which is involved in male reproductive system. There are many single nucleotide polymorphism (SNP) in this gene. One of key gene polymorphisms is rs1801131 which may influence male infertility.
The aim of this study is to investigate the association of rs1801131 with male infertility in Iranian population by a meta-analysis approach.
To find out eligible studies, we searched appropriate universal (PubMed, Google Scholar, and ScienceDirect) and Persian (SID and Magiran) databases.
After screening of articles, we analyzed the extracted data by Meta Analyst software. After meta-analysis, we didn't find any significant association of rs1801131 with male infertility within Iranian population in CC vs. AA (OR= 1.088, 95%CI= 0.668-1.772, p= 0.735) and AC vs. AA (OR= 1.021, 95%CI= 0.742-1.406, p=0.897) genetics models.
According to the result, we concluded that rs1801131 could not be a suitable biomarker for idiopathic male infertility in Iranian population.

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Introduction

Methylene tetrahydrofolate reductase (MTHFR) is the rate-limiting enzyme in methyl cycle, which is encoded by the gene MTHFR (Goyette et al., 1994). Methylene tetrahydrofolate reductase catalysis the conversion of 10, 5- methylene tertrahydrofolate to 5- methyl tetrahydrofolate. 5-methyl tetrahydrofolate is a substrate for remethylation of homocystein to methionine. This methyl group from the methionine is used to construction of S adenosylmethionine which is used to DNA methylation (Kakkoura et al., 2015; Födinger et al., 1999; Friso et al., 2002). Folate is essential for DNA methylation and DNA synthesis. Homocysteine is a sulfur-containing amino acid that is a metabolite from methionine essential amino acid (Karimian and Hosseinzadeh Colagar, 2016; Karimian and Hosseinzadeh Colagar, 2017). The enzyme is involved in a biochemical interaction in the folate cycle, between methionine and S- adenosylmethionine (Smulders et al., 2007). Researchers have reported that folate deficiency causes increased DNA fragmentation (Koury et al., 1997). Several mechanisms could explain the association between serum folate and male infertility. Serum folate levels are inversely related to the concentration of homocysteine (Hcy) of serum (Ganji and Kafai, 2004). Reduction in serum levels of vitamin B increases the re-methylation of homocysteine resulting in disruption of the methylation cycle that ultimately disrupts the

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synthesis, repair, and DNA methylation (Friso and Choi, 2005). All of aforementioned notes could explain the main role of folate pathway and MTHFR gene in male infertility. The rs1801131 polymorphism which located on exon 8 of MTHFR gene may affect the DNA methylation, DNA repair and DNA synthesis (Karimian and Colagar, 2016; Nikzad et al., 2015). Some studies investigated the association of rs1801131 with male infertility in Iranian population (Safarinejad et al., 2011; Karimian and Colagar, 2016). In this study we investigate the association of this polymorphism with male infertility within Iranian population in a meta-analysis approach.

Material And Methods

Meta-analysis

At November 2016, a deep search was completed by ScienceDirect, PubMed, and Google Scholar, and also two Persian SID and Magiran databases for the following keywords: "male infertility", "Iran", "MTHFR", "polymorphism", "SNP", "rs1801131", and "A1298C". The inclusion criteria which used to choice of paper are as follow: 1- investigation of rs1801131 and male infertility risk; 2- case-control study; and 3- adequate data to calculate the odds ratios (ORs) and 95% confidence intervals (95%CIs). The following information was extracted from all included articles: the name of first author, year of publication, frequencies of genotypes for fertile and infertile men, and method of genotyping. The extracted data from included studies in meta-analysis are detailed in table 1.

Table 1. Distribution of A1298C in included studies

Genotype frequencies						HWE P[a]	Genotyping method	Reference
Control			Case					
AA	AC	CC	AA	AC	CC			
149	141	38	75	70	19	0.60	PCR-RFLP	Safarinejad et al., 2011
70	48	14	59	44	15	0.19	PCR-RFLP	Karimian and Colagar, 2016

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

Statistical Analysis

In meta-analysis, the pooled ORs within 95% CIs were estimated for the two following genetic models: 1- CC vs. AA (Codominant model), 2- AC vs. AA (Codominant model). A $\chi 2$ test based on Q test, was used to evaluated the heterogeneity assumption and a $p<0.1$ considered as a significant difference (Higgins et al., 2003). In the absence of true heterogeneity, the fixed-effect model was employed for evaluation of the pooled OR (Mantel and Haenszel, 1959; Sharif et al., 2016), if not the random-effect model was used for calculation of the OR (DerSimonian and Laird, 1986; Sharif et al., 2017).

Results

After analysis of Hardy-Weinberg equilibrium, we found that the distribution of genotype frequencies in control groups of both included studies met the Hardy-Weinberg criteria ($p>0.05$). Our genetic association study revealed that there is no significant association between rs1801131 and male infertility in Iranian population in both CC vs. AA (OR= 1.088, 95%CI= 0.668-1.772, p= 0.735) and AC vs. AA (OR= 1.021, 95%CI= 0.742-1.406, p= 0.897) genetic models. Also, heterogeneity analysis revealed there is no true heterogeneity in both CC vs. AA (I2= 0%, Pheterogeneity= 0.634) and AC vs. AA (I2= 0%, Pheterogeneity= 0.774) models.

Table 2. Results of meta-analysis

Genetic model	**Analysis model**	**OR (95%CI)**	**P-value**	**tau^2**	**Q(df=1)**	**PH**	**I^2**
CC vs. AA (Codominant model)	Random effect	1.088 (0.667-1.776)	0.736	0.000	0.227	0.634	0%
	Fixed effect	1.088 (0.668-1.772)	0.735	-	0.227	0.634	0%
AC vs. AA (Codominant model)	Random effect	1.021 (0.742-1.406)	0.897	0.000	0.082	0.774	0%
	Fixed effect	1.021 (0.742-1.406)	0.898	-	0.082	0.774	0%

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

Discussion

Infertility involved 10-15% of couples all around the world. About 50% of infertility causes are related to male factors (Ferlin et al., 2006; Abbasalizadeh et al., 2008; Rafatmanesh et al., 2017). With advances in molecular biology, many genes

involved in male infertility are known. Defects in genes involved in spermatogenesis can lead to infertility (Ferlin et al., 2006; Karimian et al., 2015; Talebi et al., 2017). It is known that autosomal polymorphisms in the genes such as protamine, MTR, MTRR, and MTHFR and has an important role in male infertility (Jamali et al., 2016; Nikzad et al., 2015). The rs1801131 is an exonic variety in MTHFR gene. The aim of this study was to investigate the association of this polymorphism with male infertility in Iranian men in a meta-analysis. Our data revealed that there is no significant association between rs1801131 and male infertility in Iranian population. However, further studies are required to obtain more accurate data.

Some possible mechanisms can explain the role of MTHFR in male reproductive system. MTHFR is a key enzyme in folate pathway which is involved in many process such as DNA methylation, DNA synthesis, and DNA repair (Bailey and Gregory, 1999). On the other hand these three process is very closely related to spermatogenesis (Messerschmidt et al., 2014). Therefore any changes in the sequence of this gene may disrupt male fertility. Methylation of DNA has several vital roles in human cells such as increasing stability of the genome and gene expression suppression (Montjean et al., 2011; Ravel et al., 2009). Moreover, if methylation of DNA is obstructed by 5-azacytidine during the spermatogenesis process, the count of spermatids and spermatozoa reduce in the testis, which can result in asthenozoospermia and teratozoospermia in humans (Benchaib et al., 2003). Increased level of homocysteine may lead to auto-oxidation process by H2O2 production, a damaging reactive oxygen (Makker et al., 2009). Moreover, reactive oxygen species (ROS) might be correlated with homocysteine-mediated DNA destruction. Intracellular H2O2 increase by homocysteine, and this encourages program cell death produced by DNA damages (Abd-Elmoaty et al., 2010). Oxidative stress is damaging for sperm and this results in DNA damage and plasma membrane via peroxidation of lipid (Ross et al., 2010). In previous studies, we explained the effects of SNPs on gene expression, RNA structure and protein function (Mazaheri et al., 2017; Soleimani et al., 2017; Raygan et al., 2016; Ebrahimi et al., 2017). The effect of rs1801131 polymorphism on MTHFR enzyme could be evaluated by in silico analysis. A big limitation of this study was the low number of included studies in the meta-analysis. Therefore more case-control studies with different ethnicities are required to obtain more accurate data. In addition, these similar studies could be performed in cancer field which involved with environmental and genetic factors (Khamechian et al., 2013; Sharif et al., 2017).

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