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Original Article

Frequency of CYP1A1 Gene Polymorphisms in Infertile Men with Non-obstructive Azoospermia

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ABSTRACT

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Background and Aims: The cytochrome P450 1A1 (CYP1A1) plays a curial role in phase I metabolism of polycyclic aromatic hydrocarbons to their ultimate biologically active intermediates that have potential reproductive toxicity in men. Reproductive functions in men may be impaired by many environmental, physiologic, and genetic factors. The majority of the environmental factors are xenobiotics. Metabolic active xenobiotics exert adverse effects via covalent interactions between intermediate metabolites and cellular macromolecules such as DNA or protein.

Materials and Methods: Genotyping two polymorphisms, CYP1A1*2A and CYP1A1*2C, was done using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) assay in a case–control study including 105 infertile men and104 healthy fertile subjects.

Results: The results showed that frequency of CYP1A1*2A was significantly different between the patients and the controls (p = 0.036). Analysis indicated that CYP1A1*2A CC genotype was significantly associated with an increased risk of male infertility (OR = 5.4, CI=1.12-26.04; 95%) compared with the AA genotype. No significant association was detected between CYP1A1*2C polymorphism and male infertility.

Conclusions: The CYP1A1*2A single nucleotide polymorphism can be considered as an effective agent in azoospermia.

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Introduction

Infertility refers to sexual intercourse without pregnancy within 12 months, and this problem affects 10-15% of couples in the United States [1]. Male factor infertility is partially or fully responsible for approximately 30-55% cases of infertility [2, 3]. Azoospermia, which is the complete absence of sperm in the ejaculate, accounts for 10-15% of male infertility cases and generally affects 1% of the male population [3-5]. One of the most important mechanisms involved in genetic studies is attention to the cytochrome P4501A1 (CYP1A1), which plays a curial role in phase I metabolism of polycyclic aromatic hydrocarbons to ultimate biologically active intermediates. It has potential reproductive toxicity in men [6, 7]. CYPlAl, is involved in the metabolism of substrates through catalysing the hydroxylation of 17b-estradiol at the C-2 position [8]. The polymorphic gene CYP1A1 (CYP1A1*2A CC genotype) encodes CYP1A1 enzyme. The catalyzes of polycyclic aromatic hydrocarbons (PAHs) are able to form DNA adducts. The DNA adducts in sperm cells can cause severe DNA damage and interfere with meiotic division during spermatogenesis. It can be related with infertility in men [9]. It has been recently reported that the genetic polymorphisms CYP1A1*2C of xenobiotic-metabolizing enzymes may possibly play an important role in male factor infertility [10]. Cytochrome P4501A1 gene, located on chromosome 15q22-q24, is 5987-bp long and encodes 512 amino acid protein. Two polymorphisms have been identified in CYP1A1 gene in the Han-Chinese population [11, 12] CYP1A1*2A (T to C substitution at nucleotide 3801 in the 3´-non-coding region, rs4646903) and CYP1A1*2C (Ile462Val, A to G substitution at nucleotide 2455 leading to an amino acid change of isoleucine to the homeostasis of male reproductive valine at codon 462 in exon 7, rs1048943). CYP1A1*2A is most prevalent in the Asian population. T⁄C polymorphism has been proposed to be a functional-related site [13, 14]. These reports implied an essential role for the two polymorphisms. CYP1A1 is a key enzyme in phase I bioactivation of the series of PAHs, which have reproductive toxicity. It can be associated with the risk of male infertility. Thus, the present study analysed genotyping of CYP1A1*2A and CYP1A1*2C polymorphisms in infertile male referring to Yazd Reproductive Sciences Institute, to evaluate any correlation between these genes and impair spermatogenesis.

Materials and Methods

Subjects

One hundred and five infertile men with non obstructive azoospermia who had referred to Yazd Reproductive Sciences Institute were studied. One hundred and four fertile men were included in this study as controls. All patients and controls were Iranian. Infertile men with known causes (cytogenetic, hormonal and Y-chromosomal deletions) were excluded from the study. All cases and controls signed inform consent form and then entered to this study. The precedure was approved by Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran. Blood samples were taken from all of them and DNA was extracted for genetic tests. Isolation of genomic DNA from peripheral lymphocytes was carried out using Salting out method, and the DNA stored at 4ºC in the refrigerator until laboratory analysis was performed.

Deoxyribonucleic acid isolation and genotyping

Each subject donated 5 mL of blood for genomic DNA extraction. The genomic DNA was extracted from the peripheral blood lymphocytes, using salting out method [15]. The CYP1A1*2A and CYP1A1*2C polymorphisms were determined using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method.

The primers used for CYP1A1*2A polymorphism PCR were prepared using a 380 bp DNA synthesizer (Pishgam company, Tehran City, Iran) sequences of primers derived from the published sequence of CYP1A1 were as follows with primers:

5´- TAGGAGTCTTGTCTCATGCCT-3´ and 5´- CAGTGAAGAGGTGTAGCCGCT-3 ´[16].

CYP1A1*2A polymorphism PCR

The genotypes of CYP1A1 were detected using designed RFLP [16]. Briefly, the PCR reaction mixture contained approximately 1 µl of genomic DNA, 10 µl (Taq 2x Master Mix RED 1.5 mM MgCl2), 0.7 µl of a pair of primers and 16.2 µl H2O reaction using a thermal cycler (Eppendorf-Germany) was at 95°C for 10 min. to effect initial denaturation, followed by 35 cycles of denaturation at 95°C for 1 min., annealing at 62°C for 1 min., and extension at 72°C for 10 min.

Detection of CYP1A1*2A Polymorphism using designed RFLP

Ten µl of PCR product was digested with *Msp I* (New England Biolabs, USA) at 37°C for 4.5 h. Restriction digestion occurred in the presence of the C allele, thus yielding fragments of 200 and 140 bp as visualized after fractionation by agarose gel electrophoresis. In the presence of the T allele, the PCR product remained intact. After digestion, the products were subjected to agarose gel (1.5%) electrophoresis, followed by safe staining. The gels were photographed using an ultraviolet light transilluminator (Figure 1).

CYP1A1*2C polymorphism PCR

The primers used for CYP1A1*2C polymorphism PCR were prepared using a 248 bp DNA synthesizer (Pishgam company, Tehran City, Iran). Sequences of primers derived from the published sequence of CYPIAI were as follows with primers:

5´-TTCATGGTTAGCCCATAGATG-3´ and 5´-TACAGGAAGCTATGGGTCAAC-3´[17].

The genotypes of CYP1A1 were detected using designed RFLP [17]. Briefly, the PCR reaction mixture contained approximately 5 µl of genomic DNA. The DNA concentration in the PCR reaction was between 5-50 ng/µl, 10 µl (Taq 2x Master Mix RED 1.5 mM MgCl2), 0.7 µl of a pair of primers, and 16.2 µl H_2O reaction using a thermal cycler (Eppendorf-Germany) was at 95°C for 10 min. to effect initial denaturation, followed by 35 cycles of denaturation at 95°C for 1 min., annealing at 64°C for 1 min., and extension at 72°C for 10 min.

Detection of CYP1A1*2C Polymorphism using designed RFLP

Ten µl of PCR product was digested with *BsrdI* (New England Biolabs, USA) at 57°C for 4.5 h. In the presence of the A allele, the PCR product was cleaved into two fragments (133 and 115 bp) while with the G allele, the original fragment remained intact. After digestion, the products were subjected to agarose gel (1.5%) electrophoresis, followed by safe staining. The gels were photographed using an ultraviolet light transilluminator (Fig. 2).

Statistical analysis of data

The frequency differences of both polymorphisms were tested by Chi-square test between cases and controls, and odds ratio in 95% confidence intervals were determined using SPSS (ver. 16).

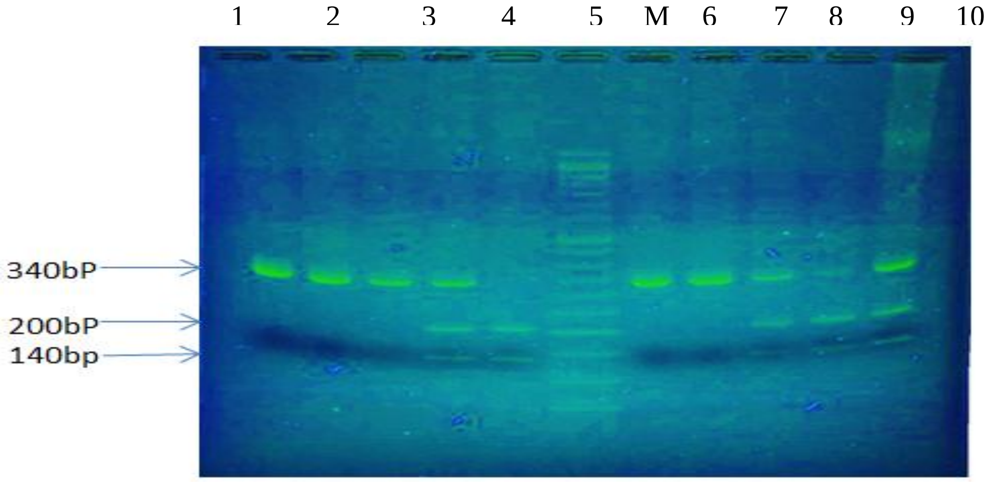

Fig. 1. Analysis of CYP1A1*2A polymorphism by PCR-RFLP. Lane 5,10: CC homozygous (200 and140 bp); lane 4,9,11: TC heterozygous (340, 200 and 140 bp); lane 1,2,3,6,7: TT homozygous(340 bp).

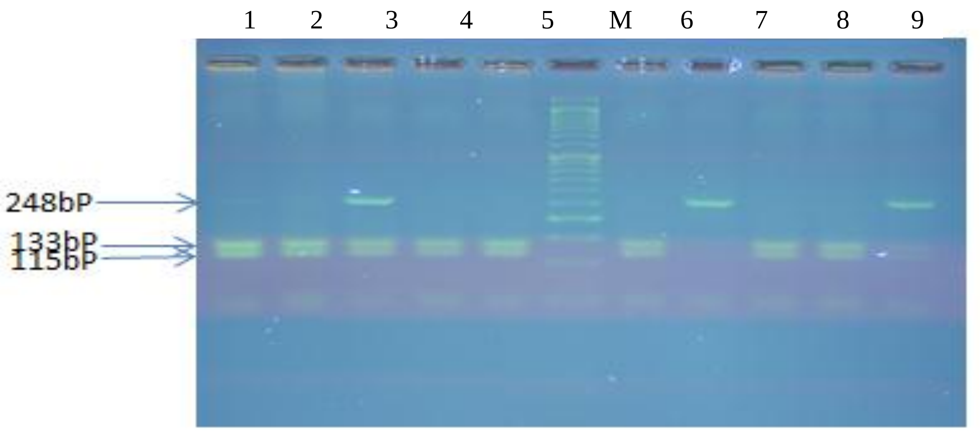

Fig. 2. Analysis of CYP1A1*2C polymorphism by PCR-RELP. Lane 1,2,4,5,6,8,9: AA homozygous (133 and 115 bp); lane 3: AG heterozygous (248, 133 and 115 bp); lane 7,10: GG homozygous (248 bp)

Results

The frequencies of the TT, TC and CC genotypes of CYP1A1*2A polymorphism in cases and controls are shown in tables 1 and 2. The statistical analysis of the gene frequencies showed that CC genotype is associated with increased risk of male infertility (OR=5.4, 95% CI=1.12-26.04). The frequency of these polymorphisms is in the Hardy-Weinberg equilibrium. The frequencies of CYP1A1*2C genotypes in the patients (9.5, 84.8 and 5.7% for AA, AG and GG, genotypes respectively) were non-significantly different from those in controls (4.8, 94.2 and 1.0% for AA, AG and GG genotypes, respectively) (p=0.364 and p=0.164), as shown in tables 3 and 4.

Table 1. Genotype frequencies of CYP1A1*2A polymorphisms in cases and the controls

	Genotypes	Cases N (%)	Control N (%)	OR	CI	P-value
CYP1A1*2A	TT	55 (52.4%)	66 (63.5%)	ref	--	--
	CC	9 (8.6%)	2 (1.9%)	5.4	(1.12-26.04)	0.036
	TC	41 (39.0%)	36 (34.6%)	1.37	(0.77-2.42)	0.285
	Sum	105	104			

OR= Odds ratio; CI= Confidence interval

Table 2. Allel frequencies of CYP1A1*2A polymorphisms in cases and thecontrols

	Alleles	Cases N (%)	Control N (%)	OR	CI	P-value
CYP1A1*2A	T	151 (71/90%)	168 (80/77%)	0.61	(0.38-0.96)	0.034
	C	59 (28/1%)	40 (19/23%)			

OR= Odds ratio; CI= Confidence interval

Table 3. Genotype frequencies of CYP1A1*2C polymorphisms in cases and the controls

	Genotypes	Cases N (%)	Control N (%)	OR	CI	P-value
CYP1A1*2C	AA	10 (9.5%)	5 (4.8%)	ref	--	--
	GG	6 (5.7%)	1 (1.0%)	3.00	(0.28-32.21)	0.364
	AG	89 (84.8%)	98 (94.2%)	0.45	(0.15-1.38)	0.164
	Sum	105	104			

OR= Odds ratio; CI= Confidence interval

Table 4. Allele frequencies of CYP1A1*2C polymorphisms in cases and the controls

	Allele	Cases N (%)	Control N (%)	OR	CI	P-value
CYP1A1*2C	A	109 (51/90%)	108 (51/92%)	0.99	(0.68-1.46)	0.997
	G	101 (48/1%)	100 (48/08%)			

OR= Odds ratio; CI= Confidence interval

Discussion

In this study, frequency of the two single nucleotide polymorphisms of CYP1A1 gene of infertile men, was tested. Genetic studies have shown that cytochrome P4501A1 (CYP1A1) plays a curial role in phase I metabolism of polycyclic aromatic hydro-carbons, which have potential reproductive toxicity in men [6, 7]. Despite significant advancements in the diagnostic workup of infertile men, the cause in approximately 50% of cases remains unknown [18-20].

Reproductive functions in men may be impaired by many environmental, physiologic, and genetic factors [21-23]. The majority of the environmental factors are xenobiotics [6, 24]. Metabolic active xenobiotics exert adverse effects via covalent interactions between intermediate metabolites and cellular macro-molecules such as DNA [25] and protein [26]. These compounds are not only metabolized by CYPlAl but are also capable of inducing the activity of the enzyme. Apart from xenobiotic metabolism, CYPlA1 can participate in inactivation of testosterone [27] and, therefore, an increased enzyme activity could affect testicular function. To date, the impact of genetic variability to metabolize xenobiotic on male reproductive functions has not been extensively studied. The relation between environmental and genetic factors and infertility has not been shown clearly. In the present study, we determined the relation between these CYP1A1 poly- morphisms, which are related to xenobiotic-metabolizing enzymes in nonobstructive azoospermia referring to Yazd Reproductive Sciences Institute. Thus, the individuals carrying CYP1A1*2A CC allele were found to have an increased risk of infertility. Since the original identification of the CAYP1A1 polymorphisms, a number of studies have investigated the genetic effect of the polymorphisms on susceptibility to human complex diseases, such as various cancers [28, 29] polycystic ovary syndrome [30], chronic kidney disease [31], coronary artery disease [32] and systemic lupus erythematosus [33]. Association between polymorphisms of CPY1A1 and susceptibility to male infertility has also been reported in different populations with polymorphisms of CPY1A1 gene. Previous study found that individuals with CYP1A1 mutations have significantly increased risk for the development of idiopathic male infertility in Indian and Chinese populations [34, 35]. However Yarosh et al. revealed that CYP1A1 variants have no effect on the male infertility [36]. Recently, the important influence of estrogen in the development of male infertility has been acknowledged [36, 37]. It is well recognized that estrogens are metabolized by CYP1A1, as an estrogen-metabolizing gene, and converted into catecholestrogens 2-hydroxyestradiol and 4-hydroxyestradiol [38]. CYP1A1 is also involved in inactivation of xenobiotic metabolism, and activation of environmental toxins. There is a complex interaction circuit between CYP1A1, estrogen receptor alpha, and aryl hydrocarbon receptor with anti-estrogenic properties [39, 40]. CYP1A1 is induced by diverse exogenous and endogenous chemicals through the aryl hydrocarbon receptor [41]. Moreover, CYP1A1 expression interacts with the aryl hydrocarbon receptor and estrogen receptor alpha expression [42]. CYP1A1 polymorphisms can alter the activity and expression of the enzyme [43, 44]. They can regulate the expression level of aryl hydrocarbon receptor and estrogen receptor alpha, resulting in male reproduction disorders. In addition, association of CYP1A1 and estrogen polymorphisms with impaired spermatogenesis implies that both genetic and environmental factors contribute to testicular dysfunction, which can lead to sperm damage, deformity, and eventually male infertility [45]. In the present study the frequency of the CYP1A1*2A CC genotype in cases was higher than controls, indicating that the individuals carrying this allele have an increased risk of infertility independent of seminal parameters. Other studies also indicate that polymorphism in the gene CYP1A1 has been shown to be associated with male factor infertility [35,46,47]. These results suggest that genetic polymorphisms of xenobiotic-meta-bolizing enzymes can play an important role in infertility. Therefore, CYP1A1 polymorphisms, in the standard semen analysis, might be taken as important parameters for prediction of fertility potential.

Conclusions

With regard to the results of the association between a polymorphism of CYP1A1*2A and azoospermia this single nucleotide polymorphism can be recognized as an effective agent in azoospermia, although their function is dependent on other genetic and environmental factors. Molecular studies are needed at other genetic levels to better understand its precise genetic role.

Conflict of Interest

The authors declare that they have no competing interests.

Acknowledgment

There is no acknowledgement to declare.

References

[1]. Bhasin S, de Kretser DM, Baker HW. Clinical review 64: Pathophysiology and natural history of male infertility. J Clin Endocrinol Metab. 1994; 79(6): 1525-529.

[2]. Bablok L, Dziadecki W, Szymusik I, Wolczynski S, Kurzawa R, Pawelczyk L, et al. Patterns of infertility in Poland: multicenter study. Neuro Endocrinol Lett. 2011; 32(6):799-804.

[3]. Jarow JP, Sharlip ID, Belker AM, Lipshultz LI, Sigman M, Thomas AJ, et al. Best practice policies for male infertility. J Urol. 2002; 167(5): 2138-144.

[4]. Jarvi K, Lo K, Fischer A, Grantmyre J, Zini A, Chow V, et al. CUA Guideline: The workup of azoospermic males. Can Urol Assoc J. 2010; 4(3): 163-67.

[5]. Jarow JP, Espeland MA, Lipshultz LI. Evaluation of the azoospermic patient. J Urol. 1989; 142(1): 62-5.

[6]. Schuppe HC, Wieneke P, Donat S, Fritsche E, Kohn FM, Abel J. Xenobiotic metabolism, genetic polymorphisms and male infertility. Andrologia. 2000; 32 (4-5): 255-62.

[7]. Fritsche E, Schuppe HC, Dohr O, Ruzicka T, Gleichmann E, Abel J. Increased frequencies

of cytochrome P4501A1 polymorphisms in infertile men. Andrologia 1998; 30(3): 125-28.
[8]. Yager JD. Molecular mechanisms of estrogen carcinogenesis. Annu Rev Pharmacol Toxicol. 1996; 36(1): 203-32.
[9]. Gaspari L, Chang SS, Santella RM, Garte S, Pedotti P, Taioli E. Polycyclic aromatic hydrocarbon-DNA adducts in human sperm as a marker of DNA damage and infertility. Mutation Res. 2003; 535(2): 155-60.
[10]. Aydos SE, Taspinar M, Sunguroglu A, Aydos K. Association of CYP1A1 and glutathione S-transferase polymorphisms with male factor infertility. Fertil Steril. 2009; 92(2): 541-47.
[11]. Huang CS, Chern HD, Chang KJ, Cheng CW, Hsu SM, Shen CY. Breast cancer risk associated with genotype polymorphism of the estrogen-metabolizing genes CYP17, CYP1A1 and COMT: a multigenic study on cancer susceptibility. Cancer Res. 1999; 59(19):4870-875.
[12]. Huang CS, Shen CY, Chang KJ, Hsu SM, Chern HD. Cytochrome P4501A1 polymorphism as a susceptibility factor for breast cancer in postmenopausal Chinese women in Taiwan. Br J Cancer. 1999; 80(11): 1838-843.
[13]. Landi MT, Bertazzi PA, Shields PG, Clark G, Lucier GW, Garte SJ, et al. Association between CYP1A1 genotype, mRNA expression and enzymatic activity in humans. Pharmacogenetics 1994; 4(5): 242-46.
[14]. Taioli E, Bradlow HL, Garbers SV, Sepkovic DW, Osborne MP, Trachman J, et al. Role of estradiol metabolism and CYP1A1 polymorphisms in breast cancer risk. Cancer Detect Preven. 1999; 23(3): 232-37.
[15]. Gaaib JN, Nassief AF, Al-Assi A. Simple salting-out method for genomic DNA extraction from whole blood. Tikrit J Pure Sci. 2011; 16(2): 1813-662.
[16]. Zhao B, Seow A, Lee EJ, Poh WT, Teh M, Eng P, et al. Dietary isothiocyanates, glutathione S-transferase-M1,-T1 polymorphisms and lung cancer risk among Chinese women in Singapore. Cancer Epidemiol Prevent Biomark. 2001; 10(10): 1063-1067.
[17]. Hayashi SI, Watanabe J, Nakachi K, Kawajiri K. Genetic linkage of lung cancer-associated MspI polymorphisms and amino acid replace-ment in the heme binding region of the human cytochrome P4501A1 gene. J Biochem. 1991;110: 407-11.
[18]. Guzick DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C, et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med. 2001; 345: 1388-393.
[19]. Dohle GR, Colpi GM, Hargreave TB, Papp GK, Jungwirth A, Weidner W. EAU guidelines on male infertility. Eur Urol. 2005;48:703-11.
[20]. Forti G, Krausz C. Clinical review 100: evaluation and treatment of the infertile couple. J Clin Endocrinol Metab 1998;83:4177-188.
[21]. Pourmasumi S, Ghasemi N, Talebi AZ, Sabeti P. The effect of vitamin E and selenium on sperm chromatin quality in couples with recurrent abortion. International Journal of Medical Laboratory 2018; 5(1): 1-10.
[22]. Ashrafzadeh HR, Nazari T, Dehghan Tezerjani M, Khademi Bami M, Ghasemi-Esmailabad S, Ghasemi N. Frequency of TNFR1 36 A/G gene polymorphism in azoospermic infertile men: A case-control study. Int J Reprod Biomed. 2017; 15(8): 521-26.
[23]. Talebi AR, Vahidi S, Aflatoonian A, Ghasemi N, Ghasemzadeh J, Firoozabadi RD, et al. Cytochemical evaluation of sperm chromatin and DNA integrity in couples with unexplained recurrent spontaneous abortions. Andrologia. 2012; 44(S1): 462-70.
[24]. Wagner U, Schlebusch H, van der Ven H, van der Ven K, Diedrich K, Krebs D. Accumulation of pollutants in the genital tract of sterility patients. J Clin Chem Clin Biochem. 1990; 28(10): 683-88.
[25]. Bartsch H. DNA adducts in human carcino-genesis etiological relevance and structure-activity relationship. Mutat Res. 1996; 340(2-3): 67-79.
[26]. Basketter D, Dooms-Goosens A, Karlberg AT, Lepoittevin JP . The chemistry of contact allergy: why is amolecule allergenic? Contact Dermatitis 1995;32:65-73.
[27]. Oesch F, Wagner H, Platt KL, Arand M. Improved sample preparation for the testosterone hydroxylation assay using disposable extraction columns. J Chromatogr Biomed Appl. 1992; 582(1-2): 232-35.
[28]. Juarez-Cedillo T, Vallejo M, Fragoso JM, Hernandez-Hernandez DM, Rodriguez-Perez JM, Sánchez-García S, et al. The risk of developing cervical cancer in Mexican women is associated to CYP1A1 MspI polymorphism. Eur J Cancer. 2007; 43(10): 1590-595
[29]. Pandey SN, Choudhuri G, Mittal B. Association of CYP1A1 Msp1 polymorphism with tobacco-related risk of gallbladder cancer in a north Indian population. Eur J Cancer Prev. 2008; 17(2):77-81.
[30]. Akgul S, Derman O, Alikasifoglu M, Aktas D. CYP1A1 polymorphism in adolescents with polycystic ovary syndrome. Int J Gynaecol Obstet. 2011; 112(1): 8-10.
[31]. Siddarth M, Datta SK, Ahmed RS, Banerjee BD, Kalra OP, Tripathi AK. Association of CYP1A1 gene polymorphism with chronic kidney disease: a case control study. Environ Toxicol Pharmacol. 2013; 36(1): 164-70.
[32]. Taspinar M, Aydos S, Sakiragaoglu O, Duzen IV, Yalcinkaya A, Oztuna D, et al. Impact of genetic variations of the CYP1A1, GSTT1, and

GSTM1 genes on the risk of coronary artery disease. DNA Cell Biol. 2012; 31(2): 211-18.
[33]. Zhang J, Deng J, Zhang C, Lu Y, Liu L, Wu Q, et al. Association of GSTT1, GSTM1 and CYP1A1 polymorphisms with susceptibility to systemic lupus erythematosus in the Chinese population. Clin Chim Acta. 2010; 411(11–12): 878-81.
[34]. Vani GT, Mukesh N, Siva Prasad B, Rama Devi P, Hema Prasad M, Usha Rani P, et al. Association of CYP1A1*2A polymorphism with male infertility in Indian population. Clin Chim Acta. 2009; 410(1-2): 43-47.
[35]. Chen WC, Kang XX, Huang ZS, Wei YS, Pan Y. CYP1A1 gene polymorphism in oligozoospermic infertile patients of Zhuang population in Guangxi area. Guangdong Med ica l Journal. 2010; 31(13): 1669-671.
[36]. Parada-Bustamante A, Molina C, Valencia C, Flórez M, Lardone MC, Argandoña F, et al. Disturbed testicular expression of the estrogen-metabolizing enzymes CYP1A1 and COMT in infertile men with primary spermatogenic failure: possible negative implications on Sertoli cells. Andrology 2017; 5(3): 486-94.
[37]. Lucas TF, Pimenta MT, Pisolato R, Lazari MF, Porto CS. 17 betaestradiol signaling and regulation of Sertoli cell function. Spermatogenesis 2011; 1(4): 318-24.
[38]. Eugster HP, Probst M, Wurgler FE, Sengstag C Caffeine, estradiol, and progesterone interact with human CYP1A1 and CYP1A2. Evidence from cDNA-directed expression in Saccharomyces cerevisiae. Drug Metab Dispos. 1993; 21(1): 43-49.
[39]. Kisselev P, Schunck WH, Roots I, Schwarz D. Association of CYP1A1 polymorphisms with differential metabolic activation of 17beta-estradiol and estrone. Cancer Res. 2005; 65(7): 2972-978
[40]. Lai KP, Wong MH, Wong CK. Modulation of AhR-mediated CYP1A1mRNA and EROD activities by 17beta-estradiol and dexamethasone in TCDD induced H411E cells. Toxicol Sci. 2004; 78(1): 41-49.
[41]. Denison MS, Nagy SR . Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. Annu Rev Pharmacol Toxicol. 2003; 43: 309-34.
[42]. MacPherson L, Lo R, Ahmed S, Pansoy A, Matthews J. Activation function 2 mediates dioxin-induced recruitment of estrogen receptor alpha to CYP1A1 and CYP1B1. BiochemBiophys Res Commun. 2009; 385(2): 263-68.
[43]. Shah PP, Saurabh K, Pant MC, Mathur N, Parmar D. Evidence for increased cytochrome P450 1A1 expression in blood lymphocytes of lung cancer patients. Mutat Res. 2009; 670(1–2): 74-8
[44]. Agundez JA. Cytochrome P450 gene polymorphism and cancer. Curr Drug Metab. 2004; 5(3): 211-24.
[45]. Su MT, Chen CH, Kuo PH, Hsu CC, Lee IW Pan HA. Polymorphisms of estrogen-related genes jointly confer susceptibility to human spermatogenic defect. Fertil Steril. 2010; 93(1): 141-49.
[46]. Lu N, Wu B, Xia Y, Wang W, Gu A, Liang J. Polymorphisms in CYP1A1 gene are associated with male infertility in a Chinese population. Int J Androl. 2008; 31(5): 527-33.
[47]. Ramgir SS, Sekar N, Jindam D, Abilash VG. Association of CYP1A1*2A Polymorphism with Idiopathic Non-Obstructive Azoospermia in A South Indian Cohort. Int J Fertil Steril. 2017; 11(3): 142-47.