

## ASSOCIATION OF *AHRR* rs2292596 WITH MALE INFERTILITY IN 422 VIETNAMESE INDIVIDUALS

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### SUMMARY

Male infertility is a reproductive disease in men caused by multiple factors ranging from harmful lifestyle habits to endogenous genetic elements. This study aimed to investigate the association between the polymorphism *AhRR* rs2292596 and male infertility. Total DNA was extracted from blood of 422 Vietnamese samples including 218 non-obstructive azoospermic and oligozoospermic patients and 204 healthy controls. The genotypes of the polymorphism were determined by PCR-RFLP method. The distribution of genotypes and their relationship with male infertility were analyzed by statistical methods. The results indicated that rs2292596 *AhRR* followed Hardy-Weinberg equilibrium ( $p$ -value > 0.05). However, there was association between the rs2292596 polymorphism and male infertility in the three models (additive, dominant, and recessive) ( $p$ -value > 0.05). The investigation would help enrich the knowledge about the influences of genetic factors on male infertility in the Vietnamese population.

**Keywords:** Male infertility, *AhRR*, Vietnam, rs2292596, PCR-RFLP

### INTRODUCTION

Deterioration in reproductive health is an increasing global concern since 9% of couples of child-bearing ages, i.e. nearly 186 million people worldwide, are struggling with the disease (Inhorn, Patrizio, 2015). Male factor is assumed to account for at least 50% of infertile cases (Mélodie, Christine, 2018). Among the potential etiologies, genetic disorders, ranging from chromosomal aberrations to single-gene alterations, are responsible for approximately 15% of the cases (Fainberg, Kashanian, 2019; Krausz *et al.*, 2015). However, determining the genetic cause of male infertility is complicated because more than 2000 genes are involved in spermatogenic processes (Krausz, Riera-

Escamilla, 2018). To identify the idiopathic etiology of male infertility, genes with common cellular functions such as DNA repair, xenobiotic metabolism, meiosis, and endocrine regulation were investigated in addition to spermatogenic genes. At least 300 SNPs disseminated in more than 123 genes had been described as related to male infertility, but the data remain controversial and inconsistent (Araujo *et al.*, 2019; Krausz *et al.*, 2015).

Xenobiotics (Gk. Xenos – "foreigner"), also called environmental chemicals, are found but not produced in organisms (Thi Trang, Huyen, 2018). They are mostly produced for human occupational activities in the form of drugs, drug metabolites, synthetic pesticides, herbicides,

industrial pollutants, food additives, etc. Widespread usage of such chemicals in daily life and their leakage into the surrounding environment were supposed to be a putative peril for male fertility (Oliva *et al.*, 2001). By forming covalent bonds with endogenous macromolecules such as DNA and protein, they could interfere in enzymes and transporter activities; weaken DNA transcription; or generate mutations, proteins malfunction, resulting in cell death, tissue toxicity, and reproductive system impairment in men (Schuppe *et al.*, 2000; Thi Trang *et al.*, 2018). Endocrine-disrupting chemicals (EDCs), which constitute a major group of xenobiotics, are exogenous agents with the ability to imitate endogenous hormones (Henriques *et al.*, 2018; Tang *et al.*, 2018; Taşkurt Hekim *et al.*, 2020). One of the most common representatives of EDCs is 2,3,7,8-tetrachlorodibenzo-p-dioxins or TCDD, the most toxic of all dioxins and dioxin-like compounds (Olson, Morton, 2019). These foreign chemicals are mediated in the human body by aryl hydrocarbon receptor (AhR) signaling cascade, which includes 3 major molecules: aryl hydrocarbon receptor (AhR), aryl hydrocarbon receptor repressors (AhRR), aryl hydrocarbon receptor nuclear translocator (ARNT). The xenobiotics are then further metabolized by phase I and phase II xenobiotic enzymes.

AhR, AhRR, and ARNT are identified as the members of the basic helix-loop-helix (bHLH) Per-ARNT-Sim (PAS) family of transcriptional regulators (Hollie, 2011). While the bHLH domain is responsible for DNA binding, the PAS domains (PAS-A and PAS-B) are involved in protein-protein interaction and ligand binding, which is in the PAS-B domain of AhR but not in AhRR (Sakurai *et al.*, 2017). *AhRR*, located on 5p15.33, contains 12 exons spanning over 166 kb. The gene encodes protein participating in the AhR ligand-triggered pathway and is involved in the regulation of cell growth and differentiation. The *AhRR*, whose expression is upregulated by activated AhR, negatively represses the activity of AhR and also regulates the expression of drug-

metabolizing *CYP1A1* (Fujii-Kuriyama, Kawajiri, 2011). Previously, polymorphism in *AhRR* had been demonstrated to be associated with various diseases in different cohorts; such as rheumatoid arthritis (Cheng *et al.*, 2017), oral cancer (Cavaco *et al.*, 2013), germ cell cancer (Brokken *et al.*, 2013), and also reproductive diseases: endometriosis (Tsuchiya *et al.*, 2005; Watanabe *et al.*, 2001) and micropenis (Fujita *et al.*, 2002; Soneda *et al.*, 2005). Among the studies, the polymorphism *AhRR* rs2292596 was proposed to be crucial in the function of the signaling pathway. However, publications on the correlation of polymorphism with male infertility in several populations (Japanese, Iranian, and Estonian) generated inconsistent results. To interpret the relationship between the gene and reproductive impairment in males, we conducted a case-control association study of polymorphism *AhRR* rs2292596 (NG\_029834.2:g.123665C>G) in the Vietnamese population.

## MATERIALS AND METHODS

### Study participants

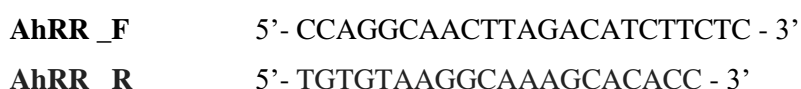
The study consisted of 422 subjects (218 male infertile patients and 204 controls). Patients were selected by the criteria of (1) experiencing childless status after at least 12 months of regular unprotected sexual intercourse; (2) being diagnosed with azoospermia or oligospermia (< 15 million sperms/ ml); and (3) non-obstructive azoospermia (NOA); (4) normal karyotype, and no AZF region disorders; (5) no medical history of diseases including shrinkage of testicles caused by mumps, transmitted diseases, and drug addiction. Controls were selected among men having at least 1 child without seeking assisted reproductive technology (ART). All subjects that fulfilled the essential above requirements gave informed consent for the blood collection. The study was approved by the Institutional Review Board of the Institute of Genome

Research, Vietnam Academy of Science and Technology.

## Methods

### Extraction of total DNA from blood samples

Whole blood samples were extracted by GeneJET Whole Blood Genomic DNA Purification Kit (Thermo Fisher). After isolation, 2  $\mu$ L of DNA samples were checked by electrophoresis in 0.8–1% agarose gel. Additionally, the quality and quantity of total DNA were also assessed by the absorbance-



The total volume of PCR reaction was 10  $\mu$ L including: 6.95  $\mu$ L of nuclease-free water (H<sub>2</sub>O); 1  $\mu$ L of Dream Taq Buffer (10X); 0.6  $\mu$ L of dNTPs (2.5 mM); 0.05  $\mu$ L Taq DNA polymerase (5U/ $\mu$ L); 0.2  $\mu$ L primer F/R (10 pmol); and 1  $\mu$ L of DNA template (~2.5 ng/  $\mu$ L). The PCR the thermal cycle was: 95°C/5 minutes, 35 cycles of 95°C/30 seconds, 57°C/35 seconds, 72°C/45 seconds, 72°C/5 minutes. 2  $\mu$ L of PCR products were evaluated for quality by electrophoresis in 1.2% agarose gel.

PCR products were digested with restriction enzyme *Bsu*RI (*Hae*III) (Thermo Fisher). The total volume of digestion reaction was 5  $\mu$ L based on the protocol suggested by the manufacturer: 3  $\mu$ L of PCR products; 1.4  $\mu$ L of nuclease-free water (H<sub>2</sub>O); 0.3  $\mu$ L Buffer R (10X); and 0.3  $\mu$ L of *Bsu*RI (*Hae*III) (10U/  $\mu$ L).

based nucleic acid quantification method using NanoDrop One/ One<sup>c</sup> machine with DNA volume of 1  $\mu$ L. DNA samples were then diluted from the initial concentration to the required concentration (~2.5 ng/  $\mu$ L) to obtain standard working DNA samples. All the samples were then stored at -20°C.

### SNP Genotyping

PCR amplification was performed with working DNA samples and a pair of specific primer as follows:

The mixture was incubated at 37°C in a water bath or shaking heat blocks for 4 – 6 hours. Digested products were further verified for quality by electrophoresis in 2.5% agarose gel. Depending on the number of DNA bands acquired from enzymatic digestion of PCR products, the genotype of *AhRR* rs2292596 was determined (Table 1). To verify the digestion results of PCR-RFLP method, 5% (20 samples) out of 422 samples were selected randomly to be purified by GeneJET PCR Purification Kit (Thermo Fisher) and subsequently sequenced by Sanger technique using ABI PRISM 3500 Genetic Analyzer (Applied Bio-systems, Carlsbad, CA, USA). The obtained sequencing results were then compared with the reference sequence (NG\_029834.2) of *AhRR* using the bioinformatics software SnapGene Viewer.

**Table 1.** Number and size of DNA bands of 3 genotypes of *AhRR* rs2292596.

Genotypes	Number of DNA bands	Size of DNA bands (bp)
CC	2	229; 163
CG	3	229; 163; 130
GG	2	229; 130

### Statistical analysis

Data obtained from PCR-RFLP method were analyzed using SPSS software version 26 (IBM,

New York, NY, USA) and Microsoft Excel (Microsoft Corp., Washington, DC, USA). Chi-square test ( $\chi^2$ ) was carried out to examine the Hardy-Weinberg equilibrium (HWE) of the

population and to assess the correlation between genotype and allele type of polymorphism with male infertility probability. The correlation was investigated in 3 test models: additive, dominant, and recessive and was estimated by OR (odds ratio) index with a confidence interval of 95%. The estimation was considered to be statistically significant if  $p$ -value < 0.05.

**RESULTS**

**Genotype identification of polymorphism *AhRR* rs2292596**

The DNA region containing the polymorphism *AhRR* rs2292596 was amplified by a specific pair of primers *AhRR\_F* and *AhRR\_R*. Electrophoresis results of the PCR products indicated distinct, sharp, and bright band DNA with correct molecular weight (437 bp) and a minimum amount of primer-dimers. PCR products were then digested with restriction enzymes *BsuRI* (*HaeIII*). Electrophoresis results showed six samples (Fig. 1).

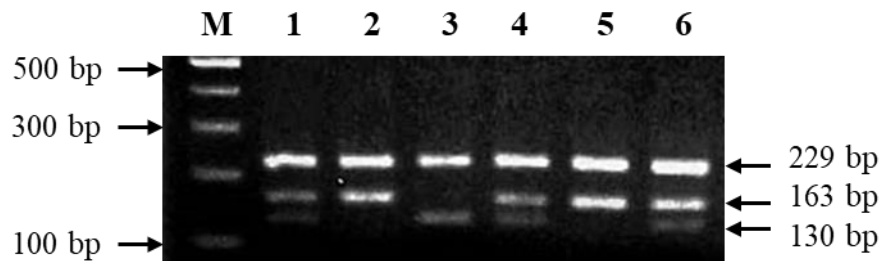
The genotypes and allele frequencies of all 422 samples were described in Table 2. Allele G (minor allele) was less common than allele C in

the case group with a frequency of 0.333 and 0.667, respectively. A similar pattern occurred in the control group with a minor allele frequency of 0.368. No clear discrepancy between minor alleles of both research groups has been detected due to their approximately similar frequencies. Additionally, the distribution of all 3 genotypes of polymorphism *AhRR* rs2292596 was followed Hardy-Weinberg equilibrium (HWE) with  $p$ -values of 0.519 (case group), 0.898 (control group), and 0.739 (whole population).

Verification of 20 samples (10 cases and 10 controls) by Sanger sequencing showed consistent outcomes with PCR-RFLP method (Fig. 2).

**Analysis of the correlation between *AhRR* rs2292596 and male infertility**

Three test models (additive, dominant, and recessive) were used to assess the relationship between genotypes of *AhRR* rs2292596 and male infertility (Table 3). The  $p$ -values were higher than 0.05, suggesting no statistically significant association between genotypes and male infertility.

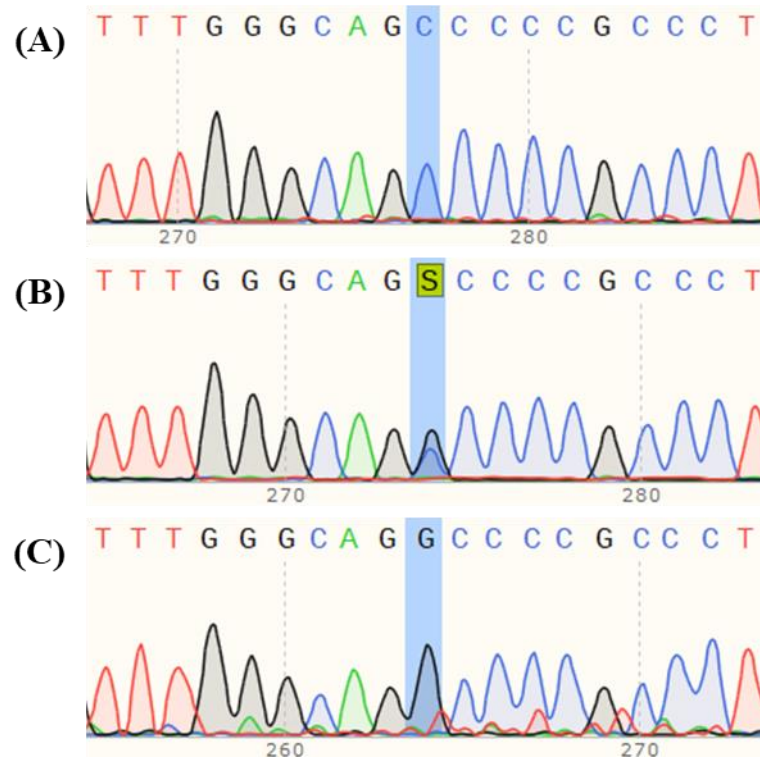


**Figure 1.** Image of 6 *BsuRI*-digested PCR products on agarose gel 2.5%. M: Marker 100 bp; 1, 4, and 6: Heterozygous GC (3 bands with 229 bp, 163 bp, and 130 bp); 2, and 5: Wildtype CC (2 bands with 229 bp, and 163 bp); 3: Homozygous GG (2 bands with 229 bp, and 130 bp).

**Table 2.** Quantity summary of rs2292596 genotypes and allele frequencies.

	Genotypes			Allele frequencies		HWE $p$ -value
	CC	CG	GG	G	C	
<b>Case (n = 218)</b>	95	101	22	0.333	0.667	0.519
<b>Control (n = 204)</b>	82	94	28	0.368	0.632	0.898
<b>Total</b>	177	195	50	0.350	0.650	0.739

Note: n: number of participants. HWE: Hardy-Weinberg equilibrium.



**Figure 2.** Genotyping *AhRR* rs2292596 using Sanger sequencing. (A): Wildtype form CC; (B): Heterozygous form CG; (C) Homozygous form GG.

**Table 3.** Correlation between rs2292596 and male infertility.

Test model	Case group (n = 218)	Controls (n=204)	OR	95% CI	p-value
<b>Additive</b>					
CC	43.58%	40.20%	1.000		0.481
CG	46.33%	46.08%	1.078	0.717 - 1.621	0.717
GG	10.09%	13.73%	1.474	0.784 - 2.773	0.228
<b>Dominant</b>					
CC	43.58%	40.20%	1.000		
CG + GG	56.42%	59.80%	1.149	0.780 - 1.693	0.482
<b>Recessive</b>					
CC + CG	89.91%	86.27%	1.000		
GG	10.09%	13.73%	1.417	0.782 - 2.568	0.250

**Note:** n: number of participants; OR: odds ratio; 95% CI: 95% confident intervals; p-value is measured using Chi-square test.

## DISCUSSION

Male infertility is a growing international health issue. It is a complex multifactorial

disease caused by either non-genetic factors (stress, over intake of alcohol, smoking, reproductive tract infection, overexposure to

detrimental environmental chemicals, etc.) or genetic factors (chromosome duplication, transversion, microdeletion, mutation, etc.) (Asha, 2017; Krausz *et al.*, 2015; Mélodie, Christine, 2018). Despite the enormous efforts in identifying the underlying causes of reproductive impairment in males, at least 30% of infertile cases remain unknown cause or classified as idiopathic cases. Recent trends in the path of hunting for “hidden” genetic cause of male infertility had led the researchers to the promising explanation lying in polymorphisms of both spermatogenic genes and xenobiotic metabolism genes in autosomal or sex chromosome. In fact, it is hypothesized that the causes of reproductive problems in men might be associated with exposure to environmental chemicals or xenobiotics such as dioxin or dioxin-related compounds.

The biological effect of 2,3,7,8-tetrachlorodibenzo-p-dioxins (TCDD) is mediated by *AhR* signaling cascade, comprising *AhR*, *AhRR*, and *ARNT*; therefore, polymorphisms in such genes are assumed to be related to susceptibility to male infertility. Among the studied polymorphisms, *AhRR* rs2292596 demonstrated the correlation with infertility in males in 3 different cohorts. The reasons this SNP is associated with male infertility remain unknown. However, the SNP is located in the heterodimerization domain of *AhRR*, which ranges from about amino acid 27 to 280 (Sakurai *et al.*, 2017). Consequently, it may alter the function of *AhRR* protein, leading to weaker negative feedback and exacerbating the toxic effects of environmental chemicals (Merisalu *et al.*, 2007; Watanabe *et al.*, 2004).

Although studies on the polymorphism rs2292596 (Pro185Ala) of the *AhRR* gene suggested that it is correlated with male infertility in different models, the results remained discordant. Watanabe and others (2004) conducted a study on a Japanese cohort of 123 infertile and 112 fertile men and concluded that the allele Pro185 is associated with an incidence of male infertility (Watanabe *et al.*, 2004). On the contrary, a study on the Estonian

population concluded that allele Ala185 rather than Pro185 is related to male infertility (Merisalu *et al.*, 2007). Additionally, the study also revealed a negative association between the appearance of genotype Ala/Ala and sperm count. Inconsistent with the study on Japanese population, an investigation of an Iranian population consisting of 111 patients and 110 healthy men also proposed that the wild-type allele Pro185 is associated with both susceptibility and severity of infertility, and can be used as a genetic marker in the prediction of male infertility (Mohammad-Hasani *et al.*, 2019). Meanwhile, in the present study, no association between polymorphism *AhRR* rs2292596 and male infertility was recognized in Vietnamese population with any model ( $p > 0.05$ ). This result is in contrast to all 3 previous publications, showing the inconsistency of relation between infertility susceptibility and polymorphism Pro185Ala in different ethnic populations worldwide, which may be explained by the genetic background differences, environmental factors, etc. Also, we compared our minor allele (allele G) frequency with the genome aggregation database (GnomAD) of 7 different populations. While the frequency of allele G (0.345) in the Vietnam population was higher than in African (0.143) and Latino (0.254), it is smaller than other cohorts comprising Ashkenazi Jewish (0.430), East Asian (0.395), Finnish (0.455), non-Finnish European (0.399), and South Asian (0.45).

## CONCLUSION

In this study, we analyzed the correlation of the variant rs2292596 in the gene *AhRR* with infertility in the Vietnamese population. Results revealed the frequencies of the genotypes CC, CG, and GG are 0.419, 0.462, and 0.118, respectively, and they were all followed Hardy-Weinberg Equilibrium. However, the statistical analysis showed that rs2292596 is not associated with male infertility. This study is considered as a pilot study in assessing the correlation of the *AhRR* gene with male infertility in Vietnam.

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## MỐI LIÊN QUAN CỦA *AhRR* rs2292596 VỚI BỆNH VÔ SINH NAM Ở 422 CÁ THỂ NGƯỜI VIỆT NAM

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### TÓM TẮT

Vô sinh ở nam giới là một bệnh gây ra bởi nhiều yếu tố, bao gồm các yếu tố xuất phát từ lối sống không lành mạnh và các yếu tố liên quan đến di truyền. Với mục đích đánh giá sự liên quan của đa hình rs2292596 trên gen *AhRR* với bệnh vô sinh nam ở người Việt Nam, chúng tôi đã thu thập và tách chiết DNA tổng số của 422 mẫu máu (218 mẫu bệnh và 204 mẫu đối chứng). Kiểu gen của đa hình được xác định bằng phương pháp PCR-RFLP. Sự phân bố kiểu gen cũng như mối liên hệ với bệnh vô sinh nam được đánh giá bằng phương pháp thống kê sinh học. Kết quả cho thấy phân bố kiểu gen của rs2292596 tuân theo định luật Hardy-Weinberg ( $p$ -value > 0,05). Tuy nhiên, chúng tôi đã không tìm thấy mối liên quan giữa đa hình này với vô sinh ở nam giới trên quần thể người Việt Nam khi phân tích thống kê trên cả ba mô hình (cộng gộp, trội và lặn) ( $p$ -value > 0,05). Nghiên cứu này đã góp phần vào việc xác định ảnh hưởng của các nhân tố di truyền đến bệnh vô sinh nam tại quần thể người Việt Nam.

**Từ khóa:** Vô sinh nam, *AhRR*, Việt Nam, rs2292596, PCR-RFLP