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Association of *CYP19A1* Gene Polymorphism with Male Infertility in Khyber Pakhtunkhwa Population, Pakistan

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ABSTRACT

Male infertility is a multifactorial disease that is controlled by genetic, hormonal, and semen factors. In this research, the authors examined the relationship that exists between the *CYP19A1* gene polymorphisms, semen parameters, and hormone profiles in male infertility. **Objectives:** To determine the Polymorphism *CYP19A1* Gene and Male Infertility among the Khyber Pakhtunkhwa Population, Pakistan. **Methods:** 186 men were recruited into the study, consisting of 106 infertile men and 80 healthy controls. Sanger sequencing was done on three *CYP19A1* SNPs (rs17703883, rs726546, and rs10046). ELISA was used to determine serum hormonal levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and testosterone, and semen parameters, such as sperm count, morphology, and motility. **Results:** Genotype and allele frequency analysis showed a significant relationship between male infertility and the polymorphisms of the following: rs 17703883 and rs 726546, and not the polymorphism of rs10046 ($p>0.05$). Nonetheless, none of the SNPs that were researched were significantly correlated with serum testosterone levels. **Conclusions:** These observations indicate that the same *CYP19A1* gene (rs17703883 and rs726546) might have an implication on male infertility among this population, but they do not seem to be the cause of lowered serum testosterone. More research with an increased sample size and functional studies needs to be done to elucidate the functions of these variants. Additional studies on the genetic role of oestrogen metabolism in the occurrence of male infertility need larger samples and other functional variants of *CYP19A1*.

INTRODUCTION

Fertility refers to the ability to conceive and bear children, whereas infertility, as defined by the World Health Organization as the failure to conceive after 12 months of unprotected sexual contact [1, 2]. Infertility affects approximately 8-12% of couples worldwide, corresponding to nearly 80 million couples, with a higher burden in low and middle-income countries [3, 4]. In industrialized nations, infertility affects approximately 10-15% of reproductive-age couples due to abnormalities in gamete production, fertilization, and inadequate embryo development [5]. In Pakistan, infertility prevalence has been reported to be as high as 21.9%, affecting more than one-fifth of the married population [6, 7]. Male infertility is commonly associated with sperm abnormalities, low sperm count, impaired motility, morphological defects, and azoospermia [8]. Various factors such as genetic abnormalities, lifestyle factors, infections, endocrine disorders, and testicular pathologies contribute to male Infertility [9, 10].

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Spermatogenesis is regulated by the hypothalamic pituitary gonadal axis, in which gonadotropin-releasing hormone stimulates the secretion of LH and FSH. LH acts on Leydig cells to promote testosterone synthesis, while FSH supports Sertoli cell function and spermatogenesis [11, 12]. Leydig cells (LCs), located between seminiferous tubules, are responsible for testosterone production through Steroidogenesis, a process that converts cholesterol into biologically active steroid hormones. Testosterone and estrogen play an essential role in male reproductive development and adult spermatogenesis [13]. Aromatase, encoded by the *CYP19A1* gene, exists in multiple transcriptional variants and has been linked to altering enzymatic activity due to certain genetic polymorphisms [14, 15]. The *CYP19A1* gene encodes aromatase, a member of the Cytochrome P450 family, which catalyzes the conversion of androgens such as testosterone and androstenedione into estrogens [16]. Mutations can inhibit or stimulate the expression of the enzyme aromatase, and this enzyme is expressed in both sexes' gonads. The *CYP19A1* gene is located on Chromosome 15q21.2 and consists of 18 exons [17].

Male infertility is a multifactorial condition with growing evidence suggesting that genetic variations, particularly in steroidogenesis-related genes such as CYP19A1, may influence reproductive function; however, data from the Khyber Pakhtunkhwa population remain scarce. Most existing studies focus on other ethnic groups, creating a research gap in understanding the role of *CYP19A1* polymorphisms within this genetically diverse region. Therefore, the present study aimed to investigate the association between selected *CYP19A1* gene polymorphisms (rs17703883, rs726546, and rs10046) and male infertility, as well as their relationship with hormonal profiles and semen parameters. Addressing this gap may improve the understanding of genetic susceptibility to male infertility and support population-specific diagnostic strategies.

METHODS

A case-control study was carried out from 5 September 2023 to 5 September 2024 at an infertility centre at Imperial Polyclinic, Peshawar, Pakistan. The study included 106 infertile males (cases) and 80 matched healthy fertile males (controls). All participants were residents of the Khyber Pakhtunkhwa province. While the province is ethnically diverse, recruitment was not stratified by specific ethnic subgroups. This potential source of population stratification is considered a limitation of the study design. Cases were recruited consecutively from men presenting for infertility evaluation at the clinic during the study period who met the inclusion criteria. Controls were recruited via convenience sampling from men accompanying patients to general outpatient departments, after verification of their fertility status. Demographic and clinical data were collected through interviews using a semi-structured questionnaire. Ethical approval was obtained from the institutional review board of Khyber Medical University, Peshawar (Ref. No. KMU/IBMS/IRBE/7th meeting/2023/209-4). All participants were provided with informed consent, which was written. Interviews using a semi-structured questionnaire were used to gather demographic and clinical data. Semen samples were collected through masturbation after a period of abstinence in accordance with conventional guidelines. Physical parameters were also examined; volume, viscosity, and pH of samples were found after proper dilution with the help of the counting chamber under light microscopic study. The assessment of the sperm motility and morphology was based on the standard laboratory procedures. The fructose test was used to determine the levels of seminal fructose to measure the functionality of the seminal vesicles. The G + Power software (version 3.1.9.7) was used to calculate a priori sample size. The calculation was done based on finding a relationship between an SNP and male infertility through a chi-square test of independence. Using an assumed odds ratio (OR) of 2.5, a minor allele frequency (MAF) of 0.15 in the control group, alpha (0.05) error probability, and power (1-β) of 0.80, the required sample size was 88 participants per group. This requirement is met by our study sample of 106 cases and 80 controls, which would have sufficient statistical power to perform the main genetic association test. The DNA sequences of genes were retrieved through the NCBI database, and the primers of each SNP were written with the Primer 3 plus programme. The phenol-chloroform method of DNA extraction was used. Amplification of extracted genomic DNA was done using polymerase chain reaction (PCR). A TCY48 thermocycler was used in PCR amplification. The Sanger sequencing was done to determine specific single nucleotide polymorphism (SNPs) of the *CYP19A1* gene. The commercial ELISA and chemiluminescence kits were used to measure testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH in the serum, according to the protocols of the manufacturers. DNA sequences of genes were obtained from the NCBI database, and primers of each SNP were designed using the Primer 3 plus program (https://www.primer3plus.com)(Table 1).

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Table 1: Primers for gene amplification

SNP	Primer	Length	Tm	GC	ANY	Product Size
rs17703883, rs726546	AAAGAGCTGACAGTCTTGCT (F)	20	57.1 C	45.0	17	531 bp
	AGAGATGGGGAGTCAGGCAA (R)	20	60.3 C	55.0	0.0	
rs10046 SNP	AGCCATCCTCGTTACACTTCTG (F)	22	60.1 C	50.0	0.0	402 bp
	TCTCCCTCAAACTCTTGGCC (R)	20	59.3 C	55.0	0.0	

Statistical analyses were performed using SPSS version 25. Genotype and allele frequencies were calculated, and the Hardy-Weinberg equilibrium was assessed in the control group. Associations between SNPs and male infertility were evaluated using the chi-square test and odds ratios with 95% confidence intervals. The distribution of continuous variables was examined using the Shapiro–Wilk test, and equality of variances was assessed using Levene's test. For all continuous variables compared (e.g., age, weight, hormone levels), the assumptions of normality and homogeneity of variances were satisfied ($p>0.05$ for both Shapiro–Wilk and Levene's tests), allowing for the use of parametric tests. Comparisons between cases and controls were therefore performed using independent-samples t-tests. Comparisons of continuous variables were performed using independent-samples t-tests when statistical assumptions were satisfied. Associations between genetic polymorphism and hormone concentrations were analyzed using Pearson's correlation coefficient. Statistical significance was defined as a two-sided p-value of less than *0.05*.

RESULTS

This study was performed on 106 infertile men and 80 healthy controls with known demographic data in KPK province of Pakistan. The results obtained in this study concluded that out of 106 infertile males, 77 (72.64%) had primary infertility and 29 (27.35%) had secondary infertility. Various factors were studied include age, weight, hormonal profiles, different semen parameters, and single-nucleotide polymorphism, to know the association of these factors with infertility. Characteristics of the study population were compared by case-control status. The Mean ages of infertile males were 31.87 ± 6.07 years (Table 2).

Table 2: Age Distribution of Infertility Type

Sr. No.	Age (Years)	Primary Infertility, n (%)	Secondary Infertility, n (%)	Total, n (%)
1	21-30	43 (40.56%)	10 (9.43%)	53 (50%)
2	31-40	30 (28.30%)	15 (14.15%)	45 (42.45%)
3	41-50	4 (3.77%)	4 (3.77%)	8 (7.54%)
Total	21-50	77 (72.64%)	29 (27.35%)	106 (100%)

Furthermore, the study examined infertility distribution across different body weights. The mean weight of the participant was 72.4 ± 8.47kg (Table 3).

Table 3: Weight Distribution of Infertility Types

Sr. No.	Age (Years)	Primary Infertility, n (%)	Secondary Infertility, n (%)	Total, n (%)
1	60-80	68 (64.15%)	24 (22.64%)	92 (86.79%)
2	81-100	9 (8.49%)	3 (2.83%)	12 (11.32%)
3	101-118	0 (0%)	2 (1.88%)	2 (1.88%)
Total	60-118	77 (72.64%)	29 (27.35%)	106 (100%)

The study revealed and analyzed infertile patients with sperm pathologies. This study found that 39% asthenospermic, 27% azoospermic, 18% normal, 13% teratospermic, and 3% oligospermic. Out of 106 infertile men, 27 had azoospermia, 13 had teratospermia, 3 had oligospermia, and 39 had asthenospermia (Figure 1).

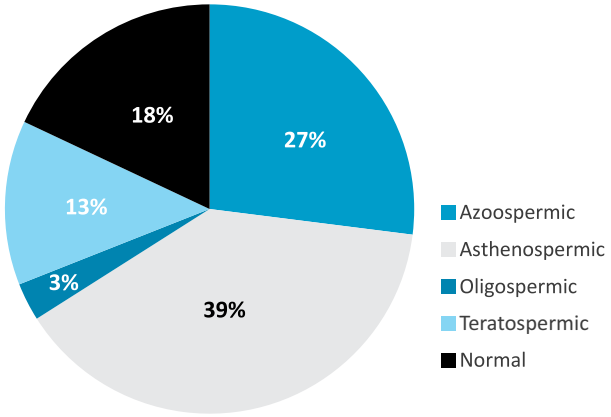

Figure 1: The Percentage of Infertile Patients Having Different Sperm Abnormalities

Chromatogram results were analyzed by Finch TV and Bio-Edit, and Well-defined peaks indicate a successful sequencing reaction. SNPs 726546 showing a C>T variation with peaks for both C and T, and rs17703883 displaying an A>G variation with distinct peaks for both alleles A and G. The presence of peaks for alleles at each SNP Position Suggests genetic variation within the sample. The study examined the genotypes and allelic frequencies for the selected SNPs, rs17703883, rs726546, and rs10046. The analysis showed the AG and AG+GG genotypes and the G allele were more frequent in cases than in controls. Similarly, rs726546 demonstrated the TC and TC+TT genotypes, and the T allele was significantly enriched among infertile men. In contrast, rs10046 showed no significant differences in genotype or allele distributions between cases and controls (Table 4).

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Table 4: Shows the Frequencies of Genotypes and Alleles in Three Selected Snaps of the *CYP19A1* Gene

Sr. No.	SNP Name	Genotype	Cases	Controls	OR (95%)	p-value
1	SNP rs17703883	AG	27 (25.47%)	8 (10%)	3.0721 (1.3105 - 7.2018)	0.009
		GG	1 (0.94%)	1 (1.25%)	0.9103 (0.0559 - 14.8264)	0.947
		AG+GG	28 (26.41%)	9 (11.25%)	2.8319 (1.2511 - 6.4102)	0.012
		Alleles				
		A	183 (86.32%)	150 (93.75%)	1	–
		G	29 (13.67%)	10 (6.25%)	2.3770 (1.1223 - 5.0347)	0.023
		AG	27 (25.47%)	8 (10%)	3.0721 (1.3105 - 7.2018)	0.009
2	SNP rs726546	CC	92 (86.8%)	79 (98.75%)	1	–
		TC	13 (12.26%)	0 (0%)	23.2054 (1.3577 - 396.6202)	0.029
		TT	1 (0.94%)	1 (.25%)	0.8587 (0.0528 - 13.9541)	0.914
		TC+TT	14 (13.20%)	1 (1.25%)	12.0217 (1.5462 - 93.4722)	0.017
		Alleles				
		C	197 (92.92%)	158 (98.75%)	1	–
		T	15 (7.8%)	2 (1.25%)	6.0152 (1.3554 - 26.6957)	0.018
3	SNP rs10046	AA	103 (97%)	77 (96.3%)	1	–
		AG	2 (1.9%)	2 (2.5%)	0.7476 (0.1030 - 5.4260)	0.773
		GG	1 (0.94%)	1 (1.25%)	0.7476 (0.0460 - 12.1414)	0.837
		AG+GG	3 (2.83%)	3 (3.75%)	0.7476 (0.1469 - 3.8054)	0.726
		Alleles				
		A	207 (97.64%)	155 (96.87%)	1	–
		G	4 (1.89%)	4 (5%)	0.7488 (0.1844 - 3.0410)	0.685

The relationships between the three *CYP19A1* SNPs (rs17703883, rs726546, and rs10046) and serum testosterone levels were analysed using Pearson's correlation, as specified in the methods. Testosterone levels were treated as a continuous variable, and genotypes were coded additively (e.g., 0, 1, 2 for the number of minor alleles). The analysis revealed no significant linear correlations: for rs17703883 (r = -0.045, p=0.649), for rs726546 (r = -0.087, p=0.374), and for rs10046 (r=0.019, p=0.847). These results indicate no statistically significant association between any of the studied SNPs and serum testosterone levels in the study population (Table 5).

Table 5: Associations of SNPs with Testosterone Level

Sr. No.	SNP	Allele (n)	Mean testosterone level (ng/mL)	p-value
1	rs17703883	G 27 (25.2%)	2.230-6.420	0.406
		A 78 (72.9%)	1.140-7.850	
2	rs726546	T 14 (13.2%)	1.950-5.550	0.710
		A 93 (87.7%)	1.140-7.850	

The study displays a detailed chromatogram obtained from sequencing, which includes (a) the rs726546 and (b) the rs17703883 SNPs. Each segment of the chromatogram provides insight into the nucleotide composition and quality of the sequencing data for these specific genetic regions (Figure 2).

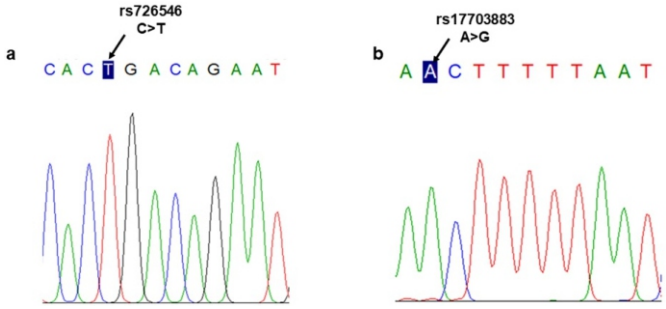

Figure 2: A Detailed Chromatogram Obtained from Sequencing

DISCUSSION

The genetic factor of male infertility is very high, and the single-nucleotide polymorphisms (SNPs) have an important role in the spermatogenic failure and the reproductive dysfunction. The current research assessed the relationship between polymorphisms of the *CYP19A1* gene (rs17703883, rs726546, and rs10046) and male infertility in one of the least studied ethnic groups, Khyber Pakhtunkhwa (KPK), Pakistan, and offers innovative data on the genetic foundation of infertility in the group. The *CYP19A1* gene codes for the aromatase enzyme, a cytochrome P450 family enzyme, which converts androgens (testosterone) into estrogens (estradiol and estrone). Despite being regarded as female hormones, estrogens are synthesized in the male reproductive tissue through aromatization and have been found to play major roles in male fertility. Estrogens have now been identified as obligatory regulators of male fertility and participating in

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spermatogenesis, sperm maturation as well as regulation of the hypothalamic-pituitary-gonadal axis [18, 19]. *CYP19A1* genetic variations can alter the aromatase activity, disrupt the androgen-estrogen balance, and, thus, cause hampered sperm production and functionality. Genetic studies were conducted in this paper where the mean age of a participant was 31.87 ± 6.07 years, and the mean weight was 72.4 ± 8.47kg. Past literature has indicated the correlation between *CYP19A1* polymorphisms and the absence of normal spermatogenesis, defective semen metrics, and disturbed metabolism [20]. The fact that genetic variations in *CYP19A1* are observed to correlate with what is hypothesized in this study is that the variation in *CYP19A1* could influence the production of estrogen in the local area of the testes, and could not be due to a complete deficiency of the hormone. Infertile men might also have a high rate of asthenospermia and azoospermia in this study, which can be partially attributed to extreme cases of genetic influence. According to the functional research, destabilized estrogen activity in the testis, the result of alterations in aromatase encoded by the *CYP19A1* gene, is associated with impairments in spermatogenesis and abnormalities in sperm maturation and motility. Male aromatase-deficient mice were developed progressive spermatogenic arrest and infertility as a result of suppressed estrogen production during germ cells development [21], and the *CYP19A1* knockout rabbits had reduced numbers of sperm, impaired spermatogenesis, and lower levels of sperm motility with defective flagellar structure [22]. These hereditary effects can be independent of the sperm count, and this is why the role of molecular mechanisms in infertility in males is also important. As the current research showed no statistically significant relationship between serum testosterone and the SNP polymorphisms: rs17703883, rs726546, and rs10046, it can be assumed that the SNP polymorphisms do not affect the levels of circulating testosterone in our population (Table 4). This lack of association is aligned with other past genetic studies that have been conducted to determine *CYP19A1* polymorphisms with respect to hormones. In a study that examined whole gene sequencing of aromatase gene variants in a large cohort of males, it was also found that whilst some *CYP19A1* haplotypes were linked with the variations in estradiol and luteinizing hormone, these haplotypes did not have a significant impact on the levels of circulating testosterone, complex interactions between aromatase variants and steroid hormone-regulating activities instead of a direct effect on testosterone concentration itself [23]. On the same note, some studies have found no apparent or consistent relationship between the prevalent *CYP19A1* SNP and blood levels of sex hormones. The research conducted on 19 polymorphisms of *CYP19A1* in women in China discovered the association with estrogen metabolites, but no distinct association of the other genetic polymorphisms assessed in the study, such as testosterone levels [24]. The association between some *CYP19A1* haplotypes and SNPs with serum testosterone and other sex hormones in some sub-groups has also been observed in another study in postmenopausal Japanese women, and demonstrates that the effect that aromatase gene variation has on hormones may be population- and context-specific. Research findings are opposite to the past findings [25]. The polymorphism rs10046 has been commonly researched on various occasions. Even though other researchers explain its correlation to estrogen-related conditions or disease phenotype (e.g., cardiovascular risks in postmenopausal women or hormone-related cancers), they seem to be context- and tissue-specific and are not always represented in systemic concentrations of testosterone [26]. In addition, meta-analysis of *CYP19A1* variants has provided substantial risk factors to the disease like Alzheimer's under certain genetic models, but also did not indicate a direct relationship to the varied testosterone levels in males [27]. Although *CYP19A1* polymorphisms other than those studied in the current study (e.g., rs749292 or rs2414096) have been linked to hormone levels and sperm parameters in specific subgroups of the population (e.g., obese male), they do not apply to the SNPs under study. The total genetic effect on hormone levels of *CYP19A1* variants is likely a result of interactions between genes and the environment, rather than a single SNP effect. Also, polymorphism in *CYP19A1*, like rs749292 and rs2414096 were found to be associated with the change in reproductive hormone profile, which included reduced circulating testosterone and increased estrogen levels in obese males with idiopathic infertility, indicating that certain *CYP19A1* variants may modulate hormone homeostasis in specific physiological contexts [28]. These investigations indicate that although rs17703883, rs726546, and rs10046 did not significantly correlate with testosterone in the current sample, other *CYP19A1* gene variants are capable of relating to the alteration of sex steroid levels in various groups and in different clinical conditions. The lack of correlation in the existing data can also indicate the multifaceted aspect of testosterone regulation by various enzymes and receptors, as well as aromatase, 5alpha-reductase, luteinizing hormone receptor pathways, and androgen binding proteins, which have proven to play a vital role in testosterone metabolism and reproductive endocrinology. Overall, the absence of correlation between the rs17703883, rs726546, and rs10046 with the testosterone level in this study is consistent with the previous studies, indicating that the genetic variations of *CYP19A1* do not directly predict the level of systemic testosterone in adults.

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Instead, the consequences of these polymorphisms can be delicate, tissue-specific, or controlled by an estrogen biosynthesis pathway that needs further functional studies. The general analysis failed to present strong evidence of the direct correlation that exists between the *CYP19A1* polymorphism and male infertility. This implies that these variants might not significantly contribute to infertility vulnerability in the population under study, and it might be other genetic, environmental, or epigenetic influences.

This study is limited by its modest sample size, potential population stratification within the ethnically diverse Khyber Pakhtunkhwa region, and the use of convenience sampling for controls, which may affect generalizability. The lack of association between the studied SNPs and serum testosterone suggests that other *CYP19A1* variants, gene-gene interactions, or local testicular estrogen dynamics may be more relevant. Future studies should employ larger, multi-center cohorts with ethnic stratification, include functional assays to assess aromatase activity, and explore a broader panel of *CYP19A1* variants alongside environmental and epigenetic factors to fully elucidate the genetic architecture of male infertility.

CONCLUSIONS

This study found no statistically significant association between the *CYP19A1* gene polymorphisms rs17703883, rs726546, and rs10046 and male infertility in the Khyber Pakhtunkhwa population. Additionally, none of the studied SNPs showed a significant relationship with serum testosterone levels. Further investigations involving larger sample sizes and additional functional variants of *CYP19A1* are required to clarify the potential genetic contribution of estrogen metabolism to male infertility.

Authors Contribution

Conceptualization: MA, HM
Methodology: MFK, FUR, SK
Formal analysis: MI, IA,
Writing and Drafting: MA, MFK, HM
Review and Editing: MA, MI, IA, MFK, FUR, SK, HM

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

The authors declare no conflict of interest.

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