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Association of *HSD17B1* Gene Polymorphisms with Male Infertility in the Khyber Pakhtunkhwa Population, Pakistan

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ABSTRACT

Male infertility is a complex disease recognized by the World Health Organization as a global health concern that affects men's reproductive health. This study investigated the association of the *HSD17B1* gene, a key regulator of the hormone testosterone, with male infertility. **Objectives:** To find out the genetic variation in the *HSD17B1* gene and the association of *HSD17B1* gene polymorphisms with male infertility. **Methods:** The study involved 106 male patients with infertility issues and 80 healthy controls. Hormonal profiles were evaluated using *ELISA*, and semen parameters such as sperm count, morphology, and motility were examined to identify any abnormalities. Target genomic sequencing was performed to identify three SNPs, rs605059, rs992310724, and rs2676530, in the *HSD17B1* gene that are associated with male infertility. **Results:** The findings indicated a significant association between rs992310724 variations and testosterone levels (*p-value*=0.041). However, rs605059 (*p-value*=0.783) and rs2676530 (*p-value*=0.381) were not significantly associated with male infertility. **Conclusions:** The findings suggest the potential for personalized diagnostic and therapeutic strategies, as well as the need for a multidisciplinary approach in male infertility research. Male reproductive health is influenced by genetic variations, with different SNPs emerging as potential contributors.

INTRODUCTION

Infertility is a reproductive system disease in which a woman fails to achieve pregnancy after regular unprotected sexual contact for one year or more [1]. It affects 8-12% of the world's population, with secondary infertility being more prevalent. The prevalence of infertility varies globally, with males experiencing it at a greater incidence than women [2, 3]. Factors such as low sperm counts, poor morphology, and other health issues, such as heart disease, type 2 diabetes, prostate tumors, and testicular cancer, can affect fertility [4, 5]. Pakistan has one of the highest rates globally, with 21.9%, 3.5% and 18.4% of married individuals having primary infertility and secondary infertility, respectively [6, 7]. Spermatogenesis and Steroidogenesis are both essential testicular functions. Spermatogenesis is a 74-day process occurring in the testes and involves mitotic cell division, meiotic cell division, and spermiogenesis [8, 9]. Sertoli cells provide structural and nutritional support to germ cells and

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maintain the blood testis barrier [10, 11]. Spermatogenesis is regulated by two major hormones, FSH and LH. LH stimulates testosterone production in testicular Leydig cells (Lcs), releasing androgens that maintain physical characteristics, support sexual organ development, and regulate androgen-dependent activities. Both gonadotropins have distinct functions and feedback loops. The hypothalamic-pituitary-gonadal (HPG) axis regulates this process, and maintaining hormonal balance is vital for male fertility [12, 13]. Figure 1 illustrates this normal physiological pathway of spermatogenesis, highlighting the interactions between Sertoli cells, Leydig cells, gonadotropins, and testosterone production, providing context for understanding the *HSD17B1* role (Figure 1).

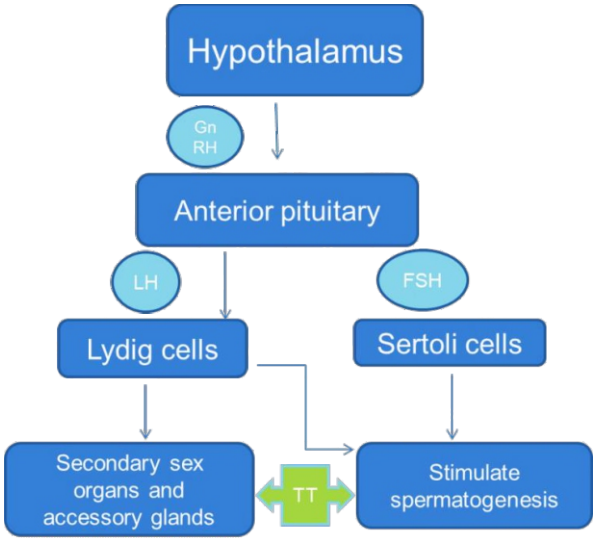

Figure 1: Normal Physiological Pathway of Spermatogenesis

Steroidogenesis is the process of converting cholesterol, primarily in Leydig cells, into androgens such as testosterone. Androgens support various developmental processes, including secondary sexual traits and spermatogenesis [14, 15]. In lateral lobes (LCs), male gonads produce steroid hormones, which are important for reproductive health. [16]. Testosterone is the primary hormone produced by LCs and affects fetal growth and secondary sexual function [17]. The enzyme *HSD17B* is essential for the conversion of hormones to more potent forms. Fourteen distinct *HSD17B* enzymes are present in various tissues and organs, regulating hormone activities and potentially causing hormone-related disorders such as breast cancer and endometriosis. Therefore, targeting *HSD17Bs* could be a promising therapeutic approach. *HSD17B1* is responsible for testosterone production in the gonads [18]. Hydroxysteroid (17b) dehydrogenase type 1 "*HSD17B1*" is an enzyme that plays a role in the synthesis of steroids in humans and other animals. This enzyme belongs to the enzyme family known as hydroxysteroid (17b) dehydrogenases (*HSD17Bs)*, which convert low-potency 17-ketosteroids to high-potency 17b-hydroxysteroids. *HSD17B1* is highly expressed in tissues known for their ability to produce estradiol, such as rat and human ovaries, as well as in the human placenta [19]. On chromosome 17q21, near BRCA1, the *HSD17B1* gene encodes 17b-hydroxysteroid dehydrogenase 1 (17b-HSD-1). 17b-HSD-1 is required for the production of oestrogens and testosterone. The principal site of testosterone production, the testis, is where 17b-HSD-1 is mostly expressed [20, 21]. Three SNPs in the *HSD17B1* gene (rs605059, rs992310724, and rs2676530) were selected based on their reported functional consequences and potential impact on steroid metabolism and testosterone production, making them strong candidates for evaluating genetic susceptibility to male infertility. Three SNPs in the *HSD17B1* gene were selected based on their functional consequences.

Male infertility is a multifactorial condition in which genetic determinants, particularly polymorphisms in steroidogenic genes such as *HSD17B1*, remain insufficiently characterized in the Pakistani population. Limited regional data regarding the association of specific SNPs (rs605059, rs992310724, and rs2676530) with hormonal profiles and infertility risk creates uncertainty in understanding their clinical relevance. There is limited population-specific evidence from Pakistan examining the association between *HSD17B1* gene polymorphisms (rs605059, rs992310724, rs2676530) and male infertility, particularly in relation to hormonal profiles such as serum testosterone. Moreover, the functional and clinical relevance of these SNPs in the local ethnic context remains insufficiently characterized, necessitating targeted genetic studies. Therefore, this study aimed to evaluate the association between selected *HSD17B1* gene polymorphisms and male infertility, as well as their relationship with serum testosterone levels.

METHODS

This case-control study was conducted between January 2023 to January 2024 at the Imperial Poly Clinic in Dabgari Garden, Peshawar, Pakistan, and involved 186 participants. The study was approved by the Khyber Medical University Ethical Research Committee (ASRB Reference No. KMU/IBMS/IRBE/7th meeting/2023/1209-3). Cases and controls were matched by age and weight to minimize confounding effects. The mean age and weight of both groups were compared using independent samples t-tests to confirm successful matching. Participants were included if, according to WHO criteria, they failed to achieve pregnancy with their partners after at least one year of regular unprotected sexual intercourse. The control group included men who were currently having children with their partners. Demographic data were carefully recorded, and

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biochemical information, including blood components, hormone levels, and semen analysis, was collected. Semen samples were obtained by masturbation into a sterile plastic cup, and sperm morphology was manually assessed. The overall motile sperm count was calculated as (Concentration × ejaculate volume × % overall motility). The total normal count was calculated as (Concentration × ejaculate volume × % morphologically normal). Sperm parameters were classified according to the WHO lower reference limits: total sperm count 39 million per ejaculate, sperm concentration 15 million per mL, total sperm motility 40%, progressive motility 32%, morphologically normal sperm 4%, and ejaculate volume 1.5 mL. Serum hormone assays were performed to measure testosterone, LH, and FSH levels. Testosterone was measured using a chemiluminescence kit (Siemens, Germany, Lot No. CIA37K3K2) with a detection threshold of 0.2 ng/mL. Serum levels of FSH and LH were assessed using ELISA kits (Lot No. 4K11x 13 and CIA-6K1B2, respectively). Genomic DNA was extracted from blood samples using the phenol–chloroform method. SNPs (rs605059, rs992310724, and rs2676530) were genotyped using PCR according to standard protocols. PCR amplification was performed in a Conversion TCY48 thermocycler under standard cycling conditions, and selected PCR products were confirmed by Sanger sequencing. Sequencing outputs were obtained in ABI and SEQ formats and analyzed using FinchTV and BioEdit software for accuracy and precision. Age and weight distributions were analyzed using Microsoft Excel. SPSS version 25 was used to evaluate associations between SNPs and clinical parameters, including testosterone levels, sperm count, hormone profiles, and sperm morphology/motility. The normality of testosterone level distribution and homogeneity of variances were assessed using Shapiro–Wilk and Levene's tests, respectively. When assumptions were met, t-tests and Pearson correlation were applied; otherwise, non-parametric alternatives such as the Mann–Whitney U test or Spearman's correlation were employed. Chi-square tests were used for categorical comparisons (e.g., genotype frequencies), independent samples t-tests for continuous variables (e.g., testosterone levels between groups), and Pearson correlation to assess relationships between genetic variants and hormone levels. Logistic regression was applied for association analyses under additive genetic models, and the Bonferroni method was used to correct for multiple comparisons. Allelic distributions were tested for Hardy–Weinberg equilibrium in the control group. A p-value <0.05 was considered statistically significant.

RESULTS

The study involved 186 male individuals, including 106 infertile patients (cases) and 80 healthy controls. The mean age of the patients was 31.87 ± 6.07 years, while the mean age of the controls was 30.16 ± 4.75 years. Our research data categorized the cases into two groups: primary infertility (77 patients; 72.64%) and secondary infertility (29 patients; 27.35%), each presenting unique issues within the context of reproductive health. The mean age of the participants was 31.87±6.07 years. The minimum age of the participants was 21 years, and the maximum age was 50 years (Figure 2).

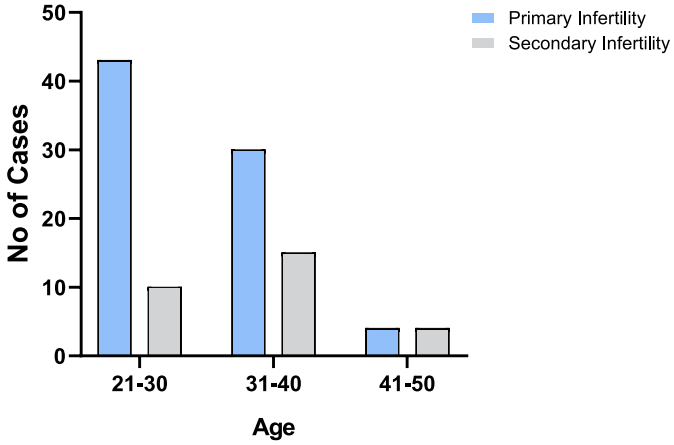

Figure 2: Age Distribution of Participants with Primary and Secondary Infertility

The mean weight of the participants was 72.4±8.74 kg. The minimum weight of the participants was 60 kg, and the maximum weight was 118 kg (Figure 3).

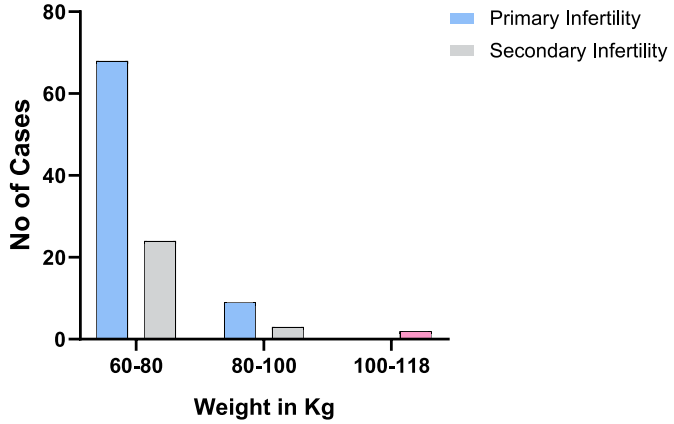

Figure 3: Weight Distributions of Participants with Primary and Secondary Infertility

Semen samples were collected from participants following WHO guidelines; their ejaculation time was recorded, and ejaculation was avoided for at least three days. The sperm morphology was manually examined using high-resolution oil-immersion microscope optics. The samples were categorized into five groups: azoospermic (29), oligospermic (3), asthenospermic (41), teratospermic (14),

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and normal (19) individuals. The data presented in Figure IV are based on the sperm count. Numbers indicate the sample size for each group: azoospermic (n=29), oligospermic (n=3), asthenospermic (n=41), teratospermic (n=14), and normal (n=19)

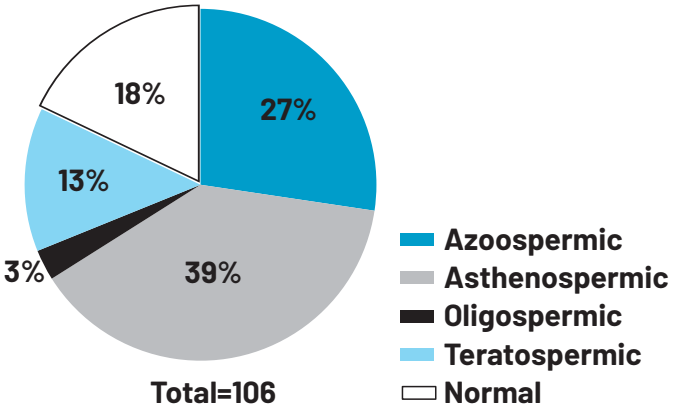

Figure 4: Distribution of Sperm Count Categories Among Infertile Participants

The genetic variations in selected SNPs were analysed using Sanger sequencing, ensuring quality and mutation detection. Using the specialized software Finch TV and BioEdit, the sequencing data were analysed for reliability and precision. Each chromatogram displays nucleotide composition and quality for the indicated SNP in infertile and control samples (sample sizes: n=106 cases, n=80 controls)(Figure 5).

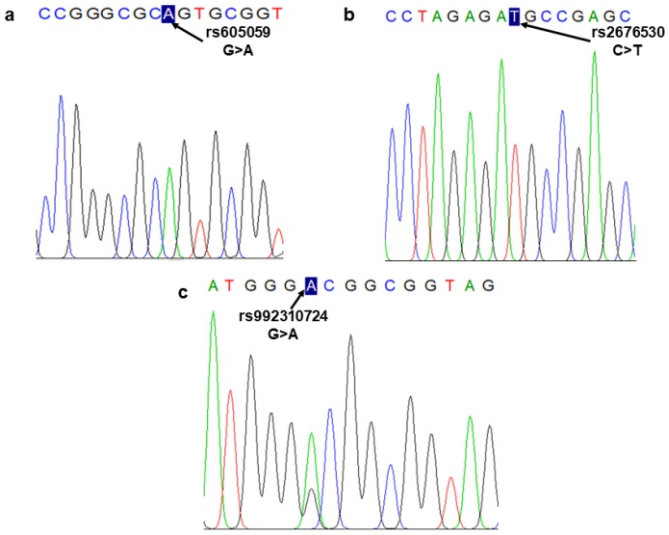

Figure 5: Representative Sanger Sequencing Chromatograms for Selected SNPs: (a) rs605059, (b) rs2676530, and (c) rs992310724

The study investigated the allelic distribution of selected SNPs in male infertility patients. Allelic distributions for the three SNPs are summarized in Table I. Briefly, rs605059 showed a higher frequency of allele A (69.8% in cases) compared to allele G (30.8%). For rs2676530, allele C was most frequent (89.6% in cases), whereas allele T was rare (5.7%). In rs992310724, allele G predominated (96.2%), with allele A being uncommon (3.77%) (Table 1).

Table 1: Genotype and Allelic Distribution for Selected SNPs in Male Infertility Patients

SNP	Genotype / Allele	Cases (N, %)	Controls (N, %)	OR (95% CI)	*p-Value*	Reference
rs605059	GG	73 (69.8%)	75 (93.75%)	1	–	G
	GA	32 (30.8%)	4 (5.0%)	8.22 (2.77–24.40)	0.001	–
	AA	1 (0.94%)	1 (1.25%)	1.03 (0.06–16.74)	0.984	–
	GA + AA	74 (69.81%)	5 (6.25%)	15.21 (5.81–39.76)	<0.001	–
	Alleles					
	G	147 (69.3%)	154 (96.3%)	1	–	G
	A	34 (16.03%)	6 (3.7%)	5.94 (2.42–14.56)	0.001	–
rs2676530	CC	95 (89.6%)	40 (50.0%)	1	–	C
	CT	10 (9.43%)	39 (48.75%)	0.11 (0.05–0.24)	<0.001	–
	TT	1 (0.94%)	1 (2.27%)	0.42 (0.03–6.90)	0.544	–
	CT + TT	11 (10.37%)	40 (50.0%)	0.12 (0.05–0.25)	<0.001	–
	Alleles					
	C	191 (90.0%)	81 (50.62%)	1	–	C
	T	12 (5.7%)	41 (25.62%)	0.12 (0.06–0.25)	<0.001	–
rs992310724	GG	99 (93.39%)	79 (98.8%)	1	–	G
	GA	6 (5.6%)	0 (0%)	10.39 (0.58–187.19)	0.112	–
	AA	1 (0.94%)	1 (1.25%)	0.80 (0.05–12.96)	0.873	–
	GA + AA	7 (6.67%)	1 (1.25%)	5.59 (0.67–46.35)	0.111	–
	Alleles					
	G	204 (96.2%)	159 (99.4%)	1	–	G
	A	8 (3.77%)	2 (1.25%)	3.12 (0.65–14.89)	0.154	–

In addition, the potential associations between particular single-nucleotide polymorphisms (SNPs)(rs605059, rs992310724,

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and 2676530) and testosterone levels in men were investigated. Analysis of the Independent sample t-test showed no significant association between the SNP rs605059 and testosterone levels in male participants, with a *p-value* of 0.783. There was a weak positive correlation with the SNP rs992310724, with a *p-value* of 0.041. Further analysis by using Pearson correlation showed a correlation coefficient of 0.1, indicating a very weak positive correlation. SNP 2676530 had no significant association with testosterone levels, with a *p-value* of 0.318. These findings suggest that polymorphisms in these SNPs do not affect testosterone function (Table 2).

Table 2: Association of Selected SNPs with Serum Testosterone Levels

SNP	Allele (n)	Mean Testosterone (ng/mL)	*p-Value*	Pearson Correlation (r)
rs605059	G 147 (69.3%)	1.140–7.850	0.783	Not applicable*
	A 34 (16.03%)			
rs992310724	G 204 (96.02%)	1.140–7.850	0.041	0.1
	A 8 (3.77%)			
rs2676530	C 191 (90.0%)	1.140–7.850	0.318	Not applicable*
	T 12 (5.7%)			

DISCUSSION

Frequency analysis of SNPs in the *HSD17B1* gene in male infertility is essential for understanding genetic factors influencing reproductive health. Variants in this gene are linked with changes in sex steroid hormone metabolism and potentially impair male fertility. Previous study reported that the *HSD17B1* gene is expressed in the testis, contributes to the synthesis of steroids, and is essential for male fertility. This study demonstrates that the *HSD17B1* gene may cause disturbances in the metabolism of sex steroid hormones, thereby affecting the health of male reproduction [19]. The ultimate goal of this study is to find new diagnostic and treatment strategies by expanding our understanding of these genetic factors. We analyzed data from participants with a mean age of 31.87±6.07 years (range 21–50 years) and a mean weight of 72.4±8.74 kg (range 60–118 kg). At rs605059, allele A was dominant (69.8%) and allele G was less common (30.8%), aligning with previous studies on *HSD17B1* in hormone metabolism and male reproductive health [20, 22]. Prior research has also investigated the rs605059 polymorphism in estrogen-dependent diseases (e.g., endometriosis, breast, prostate, endometrial, and uterine cancers), suggesting a potential link with increased enzyme activity. Previous studies indicated that this variant may not affect enzyme function in infertility or other contexts [23-29]. Following the rs605059 analysis, we examined rs2676530. Allele C predominated, found in 95 participants (89.6%), while allele T was observed in only 10 participants (9.43%), revealing notable allelic distribution changes in male infertility. Previous studies found no association of this SNP with endometriosis across different ethnic groups and no effect on Alzheimer's disease [30, 31]. These inconsistent results highlight the disease-specific nature of genetic variants and the need for further investigations to clarify the role of rs2676530 in male infertility [32]. Additionally, we identified rs992310724 as a novel SNP in the context of male infertility. Analysis revealed that 99 participants (93.39%) carried the dominant allele G, while only 6 participants (5.6%) carried allele A. These results demonstrate the unique and significant allelic distribution of rs992310724 and provide a new direction for exploring the genetic causes of male infertility. We examined the correlation between SNPs and testosterone levels. Rs605059 (p=0.783) and rs2676530 (p=0.318) showed no statistically significant association, whereas rs992310724 (p=0.041) showed a weak positive correlation. Similar findings were reported by previous studies, concluding that *HSD17B1* polymorphisms do not significantly impact testosterone levels [20, 33, 34]. These data, along with our findings, illustrate the intricate nature of genetic contributions to male infertility and suggest that sample size and environmental factors may influence outcomes. The study had a modest sample size and an ethnically homogeneous population, limiting generalizability. Environmental and lifestyle factors were not fully controlled, and the borderline significance of rs992310724 requires cautious interpretation and further validation.

This study was limited by its modest sample size, single-center design, and ethnically homogeneous population, which may restrict generalizability of the findings. Additionally, environmental, lifestyle, and epigenetic factors influencing infertility were not comprehensively assessed, and the borderline significance observed for rs992310724 warrants cautious interpretation. Future studies should incorporate larger, multi-center populations, detailed exposure assessments, and functional molecular investigations to better clarify the biological mechanisms linking *HSD17B1* polymorphisms with male infertility.

CONCLUSIONS

In conclusion, the SNP rs992310724 showed a suggestive association with male infertility and testosterone levels; further research studies are needed due to its borderline p-value, and this SNP may be a potent target for precision or targeted medicine. However, neither SNP rs605059 nor SNP rs2676530 showed any significant relationship with testosterone levels. These findings emphasize the complexities of male infertility, highlighting the importance of ongoing research to fully comprehend the genetic and hormonal components that contribute to this condition.

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Authors' Contribution

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

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

Conflicts of Interest

The authors declare no conflict of interest.

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