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Association Between *SPATA16* Gene (rs1515442) Polymorphisms and Oligozoospermia in Iraqi Men

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Abstract

Genetic factors contribute to impaired spermatogenesis and male infertility. Variants in spermatogenesis genes can increase susceptibility to defects in sperm production. Sperm-associated antigen 16 (*SPATA16*) plays a key role in Golgi-derived acrosome formation during spermiogenesis. This study investigated whether *SPATA16* gene (rs1515442 T/C) polymorphisms are associated with oligozoospermia in an Iraqi cohort. 125 infertile oligozoospermic men were compared to 125 normozoospermic fertile controls. Semen volume, sperm concentration, and motility were significantly reduced in the infertile men. The *SPATA16* polymorphism rs1515442 variant (T/C) was genotyped using the tetra-primer amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) method. This technique was employed to compare the infertile oligozoospermic men and fertile controls. Genotype and allele frequencies were compared between groups. The TC heterozygote and CC homozygote genotypes were significantly more prevalent in infertile than fertile men (TC: 15.2% vs 2.4%, p=0.0006; CC: 5.6% vs 0.8%, p=0.0339). The C allele frequency was also significantly higher in infertile men (13.2% vs 2%, p=0.0001). Both infertile oligozoospermic males and fertile controls were evaluated for the Hardy-Weinberg equilibrium (HWE) genotype frequencies for *SPATA16* (rs1515442). Both groups showed significant variations from HWE, suggesting possible underlying genetic or population-specific causes of the noted link between the *SPATA16* polymorphism and male infertility. This study found an association between *SPATA16* gene (rs1515442 T/C) variants and oligozoospermia, suggesting this polymorphism may confer susceptibility to impaired sperm production and male infertility. Additional studies are warranted to confirm the findings.

Keywords: *SPATA 16* gene, rs1515442, infertile oligozoospermic, normozoospermic fertile.

1. Introduction:

Infertility currently affects around 15% of couples globally, with male factor infertility accounting for 50% of cases [1]. In male infertility, many factors affect spermatogenesis and semen quality [2]. About 15%–30% of male infertility is inherited. Understanding the genes that cause poor sperm production and activity may help us comprehend infertility. Spermatogenesis involves mitosis, meiosis, and haploid spermatid differentiation into spermatozoa [3,4]. A complex testis-specific gene network controls this. Gene variants can induce spermatogenic failure oligozoospermia, asthenozoospermia, teratozoospermia, or

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azoospermia [5]. Oligospermia, a common male infertility cause, has sperm concentrations below 15 million per milliliter [5]. Spermiogenesis produces *SPATA16* in Golgi and proacrosomal vesicles. Oocyte binding and fertilization greatly affect acrosome biogenesis [6,7]. Globeozoospermia, spermatozoa without acrosomes and round heads, results from *SPATA16* homozygous mutations [6,8]. The spermatogenesis-associated (*SPATA16*) gene is responsible for encoding a protein related to globozoospermia; this protein is found in the Golgi apparatus and pro-acrosomic vesicles. In addition to playing a significant part in the development of the testis, this gene is also involved in the process of spermatogenesis and the generation of sperm, and research has shown that during puberty, the expression of the *SPATA16* gene is significantly increased in human testes. Within this gene, individuals who have non-syndromic monogenic male infertility have been shown to have a number of mutations and single nucleotide polymorphisms [9]. The exact effect of *SPATA16* variations on semen quality and oligozoospermia susceptibility is unknown. The present study aimed to evaluate the association between a SNP in *SPATA16* gene (rs 1515442 T/C) and oligozoospermia in Iraqi Men.

2. Material and methods

2.1 Samples analysis

This study on Iraqi men aged 18-45 years included 125 infertile oligozoospermic cases, and 125 fertile normozoospermic controls were collected from Kamal Al-Samarrai Hospital, Baghdad. The patient's consent and the hospital administration's consent were obtained according to the Helsinki Declaration, which is a set of ethical principles regarding medical and research experimentation approval number FM.SA 45, from January 2022 to December 2023. Cases had abnormal semen with <15 million sperm/ml, while controls had ≥15 million/ml. All participants provided medical history and underwent physical examination. Data were collected on age, smoking, alcohol use, medical conditions, and family infertility history. The exclusion criteria for this study included individuals with a history of chronic illness (e.g., diabetes, hypertension), prior surgeries related to infertility, exposure to radiation or toxic chemicals, current medication that could affect fertility, or genetic conditions. Participants with incomplete medical records or who failed to follow the abstinence period before semen collection were also excluded. After 2-5 days of abstinence, semen samples were obtained and analyzed for volume, concentration, and motility.

2.2 The extraction and genotyping of DNA

Genomic DNA was extracted from fresh peripheral blood samples (5 ml) of cases and controls using the Qiagen DNeasy Blood & Tissue Kit (Qiagen, Germany, Cat. No. / ID: 69506) according to the manufacturer's protocol. The samples were processed immediately after collection to ensure high-quality DNA for genotyping. Genotyping of the *SPATA16* polymorphism was done by tetra-primer amplification refractory mutation system PCR (tetra-ARMS-PCR) [10]. This method uses two external and two internal sequence-specific primers to amplify mutant and wild-type alleles in a single PCR reaction. The primers were designed and validated using the Primer-BLAST tool from the National Center for Biotechnology Information (NCBI) database to ensure specificity and accuracy in targeting the *SPATA16* rs1515442 T/C polymorphism. The primers were used to identify the mutation (T/C) rs1515442, which is shown in Table 1.

Table 1: Primers used to identify the mutation (T/C) rs1515442.

Typs	Primers 5'- 3'	bp
External forward	TAACATCCTGGAAATGTCACAAGAG	515
External reverse	TTCTTTAATCCCATACCTCAAGTGC	
Internal forward, T allele	ATGAAGTTGGTCTACATTGATGAAA	256
Internal reverse, C allele	CTACAAACTCATAGCGAACACCCAC	308

The ARMS-PCR was performed in a 25µl volume containing 50 ng template DNA, 2 pmol of each external primer, 2 pmol of each internal primer, 12.5 µl master (Thermo Scientific), and nuclease-free water. 2U of SD polymerase and four primers with outer to inner primer ratio of 2:1 in a final reaction volume of 25 µl. The reaction condition consisted of pre-heating at 92 °C for 2 min followed by 25 cycles of denaturation at 92 °C for 40 sec, annealing at 60 °C for 45 sec, extension at 68 °C for 35 sec, and a final extension at 68 °C for 5 min. Scoring was done by running the PCR products on a 1.5% agarose gel electrophoresis at 3–5 volts/cm for 40 min. The ARMS-PCR products were visualized on a 2% agarose gel stained with ethidium bromide. The wild-type T allele resulted in a 256 bp band, while the mutant C allele resulted in a 308 bp band (Figures 1 and 2).

Figure 1: Homo sapiens spermatogenesis associated 16 (*SPATA16*), RefSeqGene on chromosome 3, NCBI Reference Sequence: NG_021422.1:28651-29165.

2.3 Hardy-Weinberg Equilibrium Analysis

Genotype frequencies (TT, TC, CC) were derived for infertile cases and fertile controls; Hardy-Weinberg equilibrium (HWE) was assessed to ascertain whether the genotype frequencies of the *SPATA16* (rs1515442 T/C) polymorphism conformed to expected proportions under random mating conditions. Allele frequencies were computed as follows:

p=2×TT count+TC count\ 2×total individuals, $q=1-p$

Expected genotype frequencies were calculated using the formulas:

Expected TT=p^2×total individuals

Expected TC=2pq×total individuals

Expected CC=q^2×total individuals

A chi-square goodness-of-fit test was applied to compare observed and expected genotype frequencies for each group. Statistical significance was determined at $p \leq 0.05$.

2.3 Statistical Analysis

The Statistical Analysis System- SAS program was used to detect the effect of different factors on study parameters. A T-test was used to compare between means significantly. The

chi-square test was used to significantly compare between percentages (0.05 and 0.01 probability). Estimate of Odd ratio and CI in this study [11].

men (controls). Table 1 shows the clinical characteristics of the infertile and fertile groups in the *SPATA16* gene study. Semen volume was significantly lower in infertile men (3.80 ± 0.15 ml) than in fertile men (4.58 ± 0.19 ml). Sperm concentration was significantly higher in infertile men (3.57 ± 0.58 million/ml) than in fertile men (102.76 ± 5.45 million/ml). Sperm motility was significantly higher in infertile men (22.32 ± 5.37%) than in fertile men (72.9 ± 4.78%). All seminal parameters (volume, concentration, motility) were significantly impaired in the infertile group compared to the fertile controls. In summary, this table highlights the reduced semen quality in infertile oligozoospermic men compared to fertile normozoospermic men enrolled in the *SPATA16* gene study. The differences were statistically significant.

Overall, Table 2 demonstrates that the infertile oligozoospermic men had statistically significant impairments in all seminal parameters (volume, concentration, and motility) compared to the fertile normozoospermic control men. These results highlight the reduced semen quality in infertile men enrolled in this study investigating the *SPATA16* gene.

Table 2: Clinical characteristics of the *SPATA16* gene of the study group.

Sections	Cases infertile Oligozoospermic N=125	Controls fertile Normozoospermic N=125	T-test	*P*- value
The average age in years	29.96 ± 0.53	32.72 ± 0.58	4.607	0.0923 NS
Volume of semen (ml)	3.80 ± 0.15	4.58 ± 0.19	0.419	0.0388 *
Concentration of sperm ($\times 10^6$/mL)	3.57 ± 0.58	102.76 ± 5.45	3.481	0.0001 **
The Motility of sperm (%)	22.32 ± 5.37	72.9 ± 4.78	7.902	0.0001**
* ($P \leq 0.05$), ** ($P \leq 0.01$), NS: Non-Significant.				

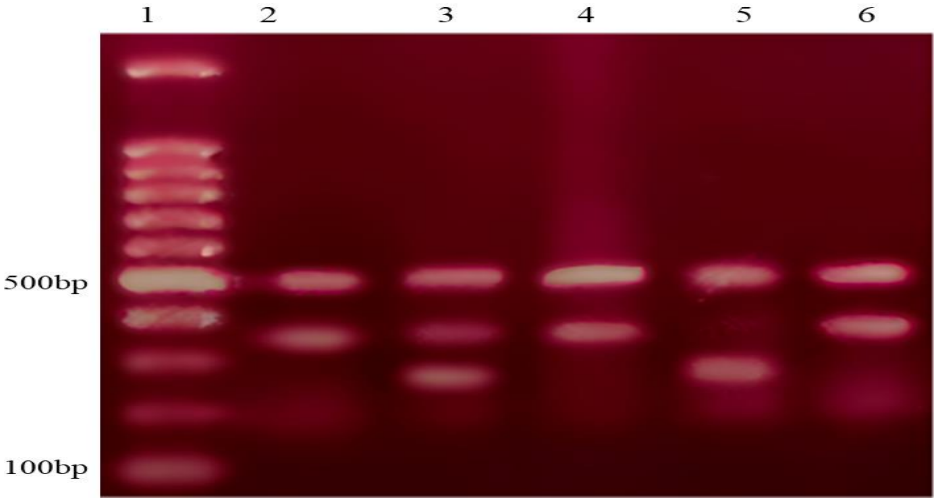

Figure 2: Tetra Primer ARMS-PCR amplification of DNA samples. Lane 1: DNA ladder (100 bp), Lanes 2, 4, and 6: CC mutation homozygous genotype two band 515bp and 308bp; lane 3: TC heterozygous mutation genotype three band 515bp, 256bp and 308bp; lane 5: TT homozygous genotype wild type two band 515bp, 256bp.

The results in Table 3 showed the genotype frequencies of the *SPATA16* rs1515442 T/C polymorphism. For the wild-type TT genotype, the frequency was 79.2% in infertile men compared to 96.8% in fertile controls, with the difference not being statistically significant according to the chi-square test (p = 0.138). The frequency of the mutant heterozygous TC

genotype was 15.2% in infertile men versus 2.4% in fertile controls, a statistically significant difference ($p = 0.0006$). For the mutant homozygous CC genotype, the frequency was 5.6% in infertile men compared to 0.8% in controls, also showing statistical significance ($p = 0.0339$).

In the allelic model, the frequency of the mutant C allele was significantly higher in infertile men (13.2%) compared to fertile controls (2.0%) ($p = 0.0001$). In the codominant model, the frequencies of the genotypes TT, TC, and CC were 79.2%, 15.2%, and 5.6% in the infertile group, respectively, compared to 96.8%, 2.4%, and 0.8% in the control group, with the heterozygous TC and homozygous CC genotypes significantly associated with infertility ($p = 0.0006$ for TC and $p = 0.0339$ for CC).

The dominant model (TC + CC vs TT) revealed a combined frequency of the mutant genotypes (TC + CC) of 20.8% in infertile men compared to 3.2% in fertile controls, with a statistically significant association with infertility ($p = 0.0001$). In the recessive model (CC vs TC + TT), the frequency of the homozygous mutant CC genotype was 5.6% in infertile men compared to 0.8% in controls, but this difference was not statistically significant ($p = 0.699$). Finally, in the overdominant model (TC vs CC + TT), the heterozygous TC genotype was significantly more frequent in infertile men (15.2%) compared to controls (2.4%) ($p = 0.0006$), suggesting that the heterozygous state may contribute to increased infertility risk.

Overall, the genotype frequency analysis shows that the TC heterozygote and CC homozygote genotypes were significantly more prevalent in infertile than fertile men. This suggests these genotypes may be associated with impaired fertility.

In summary, the genotype and allele frequency analyses consistently show the heterozygous (TC) and homozygous mutant (CC) genotypes and mutant C allele were significantly more prevalent among infertile than fertile men for this *SPATA16* polymorphism. This provides evidence these genetic variants may contribute to infertility risk. Additional studies are needed to confirm the association.

Table 3: Genotype and allele frequencies of the *SPATA16* gene polymorphisms in patients and healthy control

Genotype	Oligozoospermic men; N=125 (%)		Oligozoospermic men; N=125 (%)		Chi-square	*P*-value	Odds ratio Confidence interval (95% CI)
Codominant							
	Observed No (%)	Expected No. (%)	Observed No (%)	Expected No. (%)			
TT	99 (79.2%)	94.61 (75.69%)	121 (96.8%)	120.05 (96.04%)	2.20 NS	0.138	Ref.
TC	19 (15.2%)	28.28 (22.62%)	3 (2.4%)	4.90 (3.92%)	11.63 **	0.0006	1.084 (0.79-2.16)
CC	7 (5.6%)	2.11 (1.69%)	1 (0.8%)	0.05 (0.04)	4.50 *	0.0339	0.877 (0.52-1.67)
Dominant							
TT	99 (79.2%)		121 (96.8%)		2.20 NS	0.138	Ref.
TC+CC	26 (20.8%)		4 (3.2%)		16.13 **	0.0001	1.253 (0.01-2.85)
Recessive							
CC	7 (0.06)		1 (0.8%)		4.50 *	0.0339	Ref.
TC+TT	118 (0.94)		124 (9)		0.148 NS	0.699	0.458 (0.23-1.19)
Over dominant							
TC	19 (0.15)		3 (0.02%)		11.63 **	0.0006	Ref.
CC+TT	106 (0.85)		122 (0.98%)		1.123 NS	0.289	0.572 (0.34-1.26)
Allele frequency							
Wild T	217 (0.87)		245 (0.98)		1.697 NS	0.192	0.317 (0.18-0.79)
Mutant C	33 (0.13)		5 (0.02)		20.63 **	0.0001	1.863 (0.92-3.07)
* ($P \leq 0.05$), ** ($P \leq 0.01$), NS: Non-Significant.							

Hardy-Weinberg Equilibrium

The observed and expected genotype frequencies for the *SPATA16* (rs1515442) polymorphism are presented in Table 3. For infertile cases, the observed genotype frequencies deviated significantly from HWE (χ^2=14.17,p<0.05), with a higher than expected prevalence of the heterozygous TC genotype and homozygous mutant CC genotype. Likewise, fertile controls also showed significant deviation from HWE (χ^2=18.79,p<0.05), attributed to an overrepresentation of the wild-type TT genotype and underrepresentation of the TC and CC genotypes. These variations from HWE suggest that non-random mating, population stratification, or other genetic factors may affect the distribution of genotypes in the researched population.

3. Discussion

The *SPATA16* genotype and allele frequency results from this study showed the heterozygous TC and homozygous mutant CC genotypes were significantly more prevalent in infertile compared to fertile men (TC: 15.2% vs 2.4%, *p*=0.0006; CC: 5.6% vs 0.8%, *p*=0.0339). When combined under a dominant model, the TC+CC frequency was also significantly higher in infertile men (20.8% vs 3.2%, *p*=0.0001). This finding of increased mutant genotypes aligns with previous studies showing variants in spermatogenesis genes like CATSPER1 [12], PRMT6 [13], P2RX2 [14], and MTHFR [15] are associated with infertility risk. The high prevalence of TC and CC genotypes in infertile men suggests the *SPATA16* polymorphism may disrupt normal sperm production and function, thereby impairing fertility. *SPATA16* plays a key role in Golgi-derived acrosome development during spermiogenesis [16]. Mutations in this gene have been linked to globozoospermia. The mutant genotypes could reduce *SPATA16* expression or activity, interfering with acrosome formation and sperm head development [17,18].

The recessive model (CC vs TC+TT) compared the homozygous mutant CC genotype versus the combined TC heterozygous and TT wild-type genotypes. The CC genotype frequency was 5.6% in infertile men compared to 0.8% in fertile controls. However, this difference was not statistically significant (*p*=0.699). A lack of significance under the recessive model suggests the CC genotype alone may not impart substantial susceptibility to infertility. Other studies have found recessive models were not significant for some polymorphisms like MTHFR C677T despite increased infertility risk with the TT genotype [19]. The low frequency of the homozygous CC genotype, even among infertile men, suggests that this genotype alone may not fully explain infertility. It is possible that other genetic factors or interactions with different genes contribute to the overall effect on infertility rather than the CC genotype being the sole cause [20].

The overdominant model (TC vs CC+TT) compared heterozygous TC versus the combined CC and TT homozygous genotypes. The TC genotype was significantly more frequent in infertile than fertile men (15.2% vs 2.4%, *p*=0.0006). This suggests the heterozygous state specifically may increase susceptibility to impaired fertility. While the mechanisms are unclear, overdominance has been reported for MHC variants associated with disease risk [21]. One hypothesis is the TC genotype results in a protein product with altered function compared to wild-type and homozygous mutant genotypes. Further studies on *SPATA16* protein expression and activity based on genotype could provide insights into over dominant effects on fertility [22].

This research has shown that allele frequency analysis found the mutant C allele was significantly more common in infertile versus fertile men (13.2% vs 2%, *p*=0.0001). This confirms results from an earlier study by Zhu *et al*. that found the C allele frequency was higher in Chinese infertile males, though not significantly (4.3% vs 1.7%, *p*=0.17). The C

allele may confer susceptibility to impaired sperm production or function [23]. Population-specific factors may influence the phenotypic expression of this allele. Allele frequency differences have been reported for variants in other sperm-related genes, including CATSPER1, PRM1, and P2RX2, between fertile and infertile men [12]. The high C allele frequency here suggests it is a risk factor for infertility in this population. Genome-wide association studies have identified multiple variants in spermatogenesis genes associated with seminal parameters [24]. This research has demonstrated the functionality of this *SPATA16* polymorphism, and the mechanism by which it may impair fertility remains to be determined. Additional genetic and environmental factors likely contribute to the phenotype. However, the significantly higher prevalence of the TC, CC, and C alleles among infertile men provides evidence this *SPATA16* variant may increase susceptibility to impaired sperm production and fertility. Recent research has shown that the *SPATA16* gene has a role in the generation of sperm and has the potential to induce globozoospermia, testicular disorders, spermatogenesis arrest, and sperm aneuploidy in humans [21, 25]. The number of research that has been published on the relationship between *SPATA16* gene variants and male infertility is quite limited. Because of this, the precise function of the *SPATA16* gene polymorphisms in the molecular etiology of male infertility is not well understood.

Analysis of the Hardy-Weinberg equilibrium found significant differences in genotype frequencies between fertile controls and infertile cases. Among infertile males, the observed higher-than-expected frequencies of the TC and CC genotypes fit the theory that the mutant C allele increases sensitivity to reduced spermatogenesis. The overrepresentation of the wild-type TT genotype implies either population-specific mechanisms preserving this genotype or possible selection pressure for fertile controls. Small sample size, genotyping mistakes, demographic stratification, or selection bias are among the many reasons one could deviate from HWE. The notable variation in both groups in this research emphasizes the possible impact of non-genetic as well as genetic elements on the *SPATA16* genotype distribution [9]. More research is required to grasp how these variances support the function of *SPATA16* polymorphisms in population dynamics and male infertility.

4. Conclusion

Semen volume, sperm concentration, and motility were significantly lower in the infertile group compared to fertile controls. The frequencies of the TC and CC genotypes, as well as the C allele, were significantly higher in infertile men, suggesting an association between the *SPATA16* rs1515442 T/C polymorphism and an increased risk of oligozoospermia in this Iraqi cohort. Genotype frequencies for the *SPATA16* (rs1515442) polymorphism showed significant variations in both infertile oligozoospermic males and fertile controls according to the Hardy-Weinberg Equilibrium (HWE) study. These results imply that the distribution of genotypes could be influenced by genetic or population-specific elements such as stratification or selection pressure. Further studies are required to confirm these findings and clarify the role of this genetic variant in male infertility.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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