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Single nucleotide polymorphisms of *CFAP43* and *TEX14* associated with idiopathic male infertility in a Vietnamese population

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Abstract

Male infertility is a multifactorial disease due to spermatogenesis impairment, with etiology remaining unknown for roughly one-third of infertile cases. Several studies have demonstrated that genetic variants are male infertility risk factors. *CFAP43* and *TEX14* are involved in the spermatogenesis process. The present study aimed to assess the association between single-nucleotide polymorphisms (SNPs) in *CFAP43* (rs17116635 and rs10883979) and *TEX14* (rs79813370 and rs34818467) and idiopathic male infertility in a Vietnamese population. A cohort of 206 infertile men and 195 controls were recruited for the study. *CFAP43* and *TEX14* SNPs were genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Genotypes of randomly selected samples, accounting for 10% of the total, were confirmed using Sanger sequencing. The obtained data were analyzed using statistical methods. The results showed that 4 SNPs (rs17116635, rs10883979, rs79813370, and rs34818467) were in accordance with Hardy-Weinberg Equilibrium (HWE; $P > .05$). *CFAP43* rs10883979 and *TEX14* rs79813370 were associated with male infertility. For *CFAP43* rs10883979, in the recessive model, the combination AA + AG was associated with male infertility when compared to the GG genotype (OR = 0.26; 95% CI: 0.06–0.85; $P = .02$). For *TEX14* rs79813370, a protective effect against infertility risk was identified in the presence of the T allele of rs79813370 when compared to the G allele (OR = 0.48; 95% CI: 0.32–0.72; $P < .001$). Our results suggest that *CFAP43* rs10883979 and *TEX14* rs79813370 are likely associated with male infertility in the Vietnamese population, in which the G allele of rs79813370 may be a risk factor for male infertility.

Abbreviations: 95% CI = 95% confidence interval, CFAP43 = cilia- and flagella-associated proteins 43, DNA = deoxyribonucleic acid, HWE = Hardy–Weinberg equilibrium, MMAF = multiple morphological abnormalities of sperm flagella, OR = odds ratio, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, SNPs = single nucleotide polymorphisms, TEX14 = testis-expressed 14.

Keywords: *CFAP43*, infertility, polymorphism, *TEX14*, Vietnamese

1. Introduction

Infertility is defined as a reproductive disease featured by the failure to initiate a clinical pregnancy after at least 1 year of regular, unprotected sexual intercourse.[1] Male factors were responsible for roughly half of the infertile cases,[2] with about 7% of the global male population being affected.[3,4] The prevalence of male infertility varies between regions, highest in Northern and Central Europe at 8% to 12% and lowest in North America at 4.5% to 6%.[5] Meanwhile, the rate in Asia, the most populous region in the world, is virtually unknown. In Vietnam, this disease is on the rise, with the age-standardized prevalence rate of male infertility increasing by 0.55% from 1990 to 2017.[6] The disease manifested through multiple semen phenotypes, including complete lack of sperm (azoospermia), reduced sperm count (oligozoospermia), decreased sperm motility (asthenozoospermia), abnormal sperm morphology (teratozoospermia), or the combination of quantitative and qualitative defects (oligoasthenoteratozoospermia).[7] Over the last 2 decades, many studies have identified various genes involved in spermatogenesis related

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to male infertility,[8,9] including cilia- and flagella-associated proteins 43 (CFAP43) and testis-expressed 14 (TEX14).

CFAP43, also known as *WDR96*, is located on chromosome 10q25.1, contains 38 exons, and encodes a WD-repeat-domain (WDR) protein expressed explicitly or preferentially in the testis.[10] This protein is essential for sperm flagella production and proper sperm motility, and its absence is detrimental to sperm axoneme assembly, resulting in aborted sperm flagella and male infertility.[11] The knockout mouse models of the *CFAP43* ortholog gene resulted in male mice with multiple morphological abnormalities of sperm flagella (MMAF) phenotype, infertility, complete sperm immobility, and axonal malformations. In addition, depletion of *CFAP43* also resulted in sperm head abnormalities and oligozoospermia, demonstrating that, in mice, CFAP43-mediated intra-manchette transport is crucial for sperm head shaping and sperm flagella formation.[12] Multiple mutations in *CFAP43* have been found in MMAF patients, and in the studied MMAF cohorts, biallelic mutations of *CFAP43* have been estimated to make up about 4% to 31% of cases.[10,13–20]

TEX14, located on chromosome 17q22, encodes a 1497 amino acid protein exclusively expressed in the testis during meiosis.[21] The loss of this protein, whose function is to form the germ-cell intracellular bridges in vertebrates, might disrupt spermatogenesis and cause infertility.[22–24] *TEX14* gene mutations with an autosomal recessive pattern were identified in infertile men with spermatogenic failure.[25–28] In addition, genetic variants in this gene were associated with the development of testicular germ cell cancer[29] and a higher risk of breast cancer.[30]

The 2 genes *TEX14* and *CFAP43* participate in spermatogenesis at different cellular stages[31] and are highly expressed in the testis, especially in primary and secondary spermatocytes.[32] While the role of genetic variants of *CFAP43* and *TEX14* in the pathogenesis of male infertility has been reported, there likely exist undescribed polymorphisms within *CFAP43* and *TEX14* associated with male infertility. Four polymorphisms, *CFAP43* rs17116635, *CFAP43* rs10883979, *TEX14* rs79813370, and *TEX14* rs34818467, have been found in the 1000 Genomes Project for Vietnamese population with minor allele frequencies of 0.07; 0.18; 0.11 and 0.13, respectively. The 3 SNPs, *CFAP43* rs17116635, *CFAP43* rs10883979, and *TEX14* rs79813370, are missense variants, while the remaining SNP is a splice-site one. In addition, all 4 SNPs have high Remap densities in the ReMap Atlas of Regulatory Regions (http://www.genome.ucsc.edu), indicating that these SNPs can affect the binding of multiple transcription factors and potentially alter gene expression.[33] Given the increasing frequency of male infertility and the importance of genetic contributors, we conducted this study to investigate the correlation of *CFAP43* (rs17116635, rs10883979) and *TEX14* (rs79813370, rs34818467) with idiopathic male infertility in a Vietnamese population.

2. Materials and methods

2.1. Study subjects

A total of 206 men with idiopathic infertility in the age range of 25 to 45 were recruited from Hanoi Medical University Hospital. Infertile men with chromosomal abnormalities, Y chromosomal macro- or microdeletions, obstructive azoospermia, and a history of diseases affecting fertility were all excluded from the study. The control group included 195 healthy men in the same age group who had fathered at least 1 child without seeking assisted reproductive technology. All subjects were of Vietnamese ethnicity and gave written informed consent to donate their blood. Semen data for all the subjects were recorded by the physicians, including age, pH, ejaculate volume, total sperm, sperm count, motility, vitality, and normal morphology (Table 1). The study was approved by the Institutional Review Board of the Institute of Genome Research, Vietnam Academy of Science and Technology (No: 9-2019/NCHG-HĐĐĐ), and all experimental protocols on human subjects were in accordance with the Helsinki Declaration of 1975, as revised in 2013.

2.2. SNP genotyping

Genomic DNA was extracted from the blood samples of participants using GeneJET Whole Blood Genomic DNA Purification Mini Kit (ThermoFisher, Waltham). To genotype the polymorphisms of *CFAP43* (rs17116635 and rs10883979) and *TEX14* (rs79813370 and rs34818467), polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used. Specific pairs of primers for amplification of the DNA region containing the polymorphisms are listed in Table 2. If the polymorphism is not present at a recognition site of a restriction enzyme, nucleotides near the 3′ end of the primer forward/reverse might be mutated to create a restriction site. After that, the PCR products of rs17116635, rs10883979, rs79813370, and rs34818467 were digested with restriction enzymes *Rsa*I, *Mun*I, *Eco*130I, and *Nde*I, respectively. To validate PCR-RFLP results, 10% of the samples were randomly selected to be purified by PCR purification kit (ThermoFisher, Waltham) and subsequently sequenced using ABI PRISM 3500 genetic analyzer (Applied Bio-systems, Carlsbad). The obtained sequences were then compared with reference sequences of *CFAP43* (NM_025145.7) and *TEX14* (NM_001201457.2) published in GenBank. The Sanger sequencing results indicated 100% concordance with genotypes obtained from PCR-RFLP.

2.3. Statistical analysis

Acquired data were statistically processed using Microsoft Excel (Microsoft Corp., Washington) and R version 4.2.2.[34] The function "HWExact" from "HardyWeinberg" package[35–37] was used to calculate the Hardy-Weinberg equilibrium (HWE) of the population. The function "oddsratio" from package "epitools"[38] was used to evaluate the association between the studied polymorphisms and male infertility in allele form and 3 test models (additive, dominant, and recessive). Differences in demographic and semen parameters between the patient and control groups were evaluated using an independent *t* test. Fisher's exact test was selected for SNPs with expected sample sizes less than 5 and the Chi-squared test was used for those with larger expected sample sizes. An odds ratio with a confidence interval of 95% was used to estimate the association. All statistical tests were 2-sided. Calculation results were considered statistically significant if the *P* value < .05.

Table 1

Semen characteristics of the studied participants.

Characteristics	Controls	Cases	*P* value
Age	34.17 ± 6.13	33.13 ± 5.78	.07
pH	7.51 ± 0.05	7.24 ± 0.40	.13
Ejaculate volume (mL)	2.82 ± 0.86	2.83 ± 0.57	.99
Total sperm/ ejaculate (10^6)	62.56 ± 31.65	1.81 ± 1.83	<.001
Sperm count (10^6/mL)	174.75 ± 97.13	5.05 ± 5.52	<.001
Motility			<.001
Progressive motility, PR (%)	45.02 ± 12.74	13.02 ± 11.32	<.001
Fast progressive (%)	14.49 ± 7.42	3.02 ± 4.05	<.001
Slow progressive (%)	30.24 ± 8.14	10.00 ± 8.69	<.001
Non-progressive, NP (%)	29.26 ± 10.18	6.93 ± 7.03	<.001
Motile (PR + NP) (%)	74.35 ± 15.20	23.28 ± 20.89	<.001
Immotile, IM (%)	25.72 ± 15.23	51.72 ± 34.81	.03
Vitality (%)	79.13 ± 13.76	26.92 ± 23.60	<.001
Normal morphology (%)	4.87 ± 0.73	0.82 ± 0.75	<.001

Data are presented as mean ± standard deviations.

IM = immotile, n = number, NP = non-progressive, PR = progressive motility.

P values calculated by independent *t* test.

P < .05 indicates statistical significance.

3. Results

3.1. Comparison of demographic and clinical characteristics between patient and control groups

Demographic and clinical data of a total of 401 subjects, including 206 infertile patients and 195 controls, are described in Table 1. Statistical analysis demonstrated significant differences between patient and control groups in total sperm, sperm count, motility, and normal morphology ($P < .001$), whereas there was no significant association in terms of age, pH, and ejaculate volume ($P > .05$; Table 1).

3.2. Genetic analysis of CFAP43 and TEX14 polymorphisms

Single nucleotide polymorphisms *CFAP43* (rs17116635 and rs10883979) and *TEX14* (rs79813370 and rs34818467) were genotyped for all studied subjects. Statistical results showed that all 4 SNPs followed Hardy-Weinberg equilibrium (HWE; $P > .05$; Table 3).

Statistical analyses were performed on allele form and 3 test models of the minor allele (additive, dominant, and recessive; Table 4). For *CFAP43* rs10883979, both patient and control groups showed high frequencies of AA genotype at 66.5% and 65.64%, respectively. In comparison to the AA genotype, the frequency of the GG genotype was significantly different between the 2 groups and associated with a protective effect against male infertility risk (OR = 0.27; 95% CI: 0.06–0.89; $P = .03$). No significant difference in the AG genotype between the 2 groups was obtained compared to the AA genotype ($P = .66$). Similarly, in the recessive model, the GG genotype was associated with a reduced infertility risk compared to the AA + AG genotype group (OR = 0.26; 95% CI: 0.06–0.85; $P = .02$). For *TEX14* rs79813370, a significant difference in genotypes was obtained in the additive model ($P = .001$). The frequency of the GT genotype differed significantly between the infertile and control groups (17.96% and 32.82%, respectively). This genotype was associated with a protective effect against male infertility (OR = 0.44; 95% CI: 0.27–0.69; $P < .001$) compared to the GG genotype. No significant correlation of the TT genotype between the 2 groups was obtained in comparison to the GG genotype ($P = .19$). In the dominant model, the combination of the GT and TT genotype groups reduced susceptibility to infertility in men compared to the GG genotype (OR = 0.43; 95% CI: 0.27–0.69; $P < .001$); the T allele lowered the risk of male infertility (OR = 0.48; 95% CI: 0.32–0.72; $P < .001$) in comparison to the G allele.

4. Discussion

Male infertility is caused by deterioration in spermatogenesis, a critical process in the male reproduction system regulated by a multitude of genes.[3,31] Over the last decades, thousands of genes involved in the spermatogenic process have been discovered to be related to male infertility.[31] However, in approximately 30% of cases, the causes of infertility are still unknown,[2] suggesting that novel genes or SNPs may be linked with male infertility. In this study, blood samples from 206 men with idiopathic infertility and 195 healthy controls from the Vietnamese population were collected and analyzed to assess the association of the polymorphisms of *CFAP43* (rs17116635 and rs10883979) and *TEX14* (rs79813370 and rs34818467) with the risk of male infertility.

CFAP43 encodes a protein located between doublet microtubules 5 and 6 and para-flagellar rods in the flagella axonemes of many animals.[10,13] Its absence may make the entire complex unstable, resulting in both peri-axonemal and axonemal defects.[39] The most well-known disease linked to the defects of *CFAP43* is MMAF, a severe form of asthenoteratozoospermia characterized by morphological abnormalities of the flagellum, such as absent, short, curled, or abnormal size, thereby impairing sperm motility. In 2017, Tang et al[10] first identified the loss of a bi-allelic function mutation in the *CFAP43* gene in 3 out of 30 Han patients with MMAF and also showed that male mice lacking *Cfap43* had the MMAF phenotype. In a later study, Coutton et al[13] identified *CFAP43* mutations accounting for 12.8% of the analyzed MMAF patients (10/78) originating from North Africa, Europe, and the Middle East, and these mutations convincingly showed that loss of function of CFAP43 had been linked to azoospermia and abnormalities of the flagellum in humans. In subsequent studies on different cohorts, including Chinese,[16,18] Pakistani,[15] Argentinian,[20]

Table 2

Primer information.

Gene/SNP	Location	Primer (5′-3′)	Amplicon size (bp)	Tm, *T* (°C)
CFAP43/ rs17116635	10q25.1	F: ACTTCCAATGGCAAGCAAGG R: GCAGAGGCTTGGAGGTAGGA	681	62
CFAP43/ rs10883979	10q25.1	F: GAGCTTGGGTGGTGAAAACC R: CTGTTTCCACATAGAGCCTTGG	518	61
TEX14/ rs79813370	17q22	F: GCCCAGTGCATAGGGGTATTC R: AGGTGTTCCCTGTGTTTGAGT	372	60
TEX14/ rs34818467	17q22	F: TACATGGCTCTGTACATGGAGCT R: AAGTGATGGAGGAGGCACTGCATA	270	57

SNP = single nucleotide polymorphism, Tm = annealing temperature.

Table 3

General information on the studied single nucleotide polymorphisms (SNPs).

Gene/SNP	Position	Type of variant	Allele	MAF in case	HWE in case	MAF in control	HWE in control	HWE in all population
CFAP43/rs17116635	10:104186084	Missense	C > T	0.09	+	0.09	+	+
CFAP43/rs10883979	10:104197956	Missense	A > G	0.18	+	0.20	+	+
TEX14/rs79813370	17:58616316	Missense	G > T	0.10	+	0.20	+	+
TEX14/rs34818467	17:58565748	Splice site	A > G	0.15	+	0.12	+	+

Note: Position refers to the GRCh38.p14 assembly.

MAF = Minor allele frequency, HWE = Hardy–Weinberg equilibrium was checked by Chi-squared test.

Table 4

Association of *CFAP43* and *TEX14* SNPs with male infertility.

SNP	Genotype	Control (n = 195)	Case (n = 206)	OR	95% CI	*P* value
CFAP43	Additive					.84*
rs17116635	CC	160 (82.05%)	171 (83.01%)	1.00		
	CT	34 (17.44%)	35 (16.99%)	0.96	0.57–1.63	.89**
	TT	1 (0.51%)	0 (0.00%)	0.00	0.00–36.72	.49*
	Recessive					
	CC + CT	194 (99.49%)	206 (100.00%)	1.00		
	TT	1 (0.51%)	0 (0.00%)	0.00	0.00–36.92	.49*
	Dominant					
	CC	160 (82.05%)	171 (83.01%)	1.00		
	CT + TT	35 (17.95%)	35 (16.99%)	0.94	0.54–1.62	.90**
	Allele					
	C	354 (90.77%)	377 (91.50%)	1.00		
	T	36 (9.23%)	35 (8.50%)	0.91	0.56–1.49	.71**
CFAP43	Additive					.07**
rs10883979	AA	128 (65.64%)	137 (66.50%)	1.00		
	AG	56 (28.72%)	66 (32.04%)	1.10	0.72–1.70	.66**
	GG	11 (5.64%)	3 (1.46%)	0.27	0.06–0.89	**.03****
	Recessive					
	AA + AG	184 (94.36%)	203 (98.54%)	1.00		
	GG	11 (5.64%)	3 (1.46%)	0.26	0.06–0.85	**.02****
	Dominant					
	AA	128 (65.64%)	137 (66.50%)	1.00		
	AG + GG	67 (34.36%)	69 (33.50%)	0.96	0.62–1.49	.92**
	Allele					
	A	312 (80.00%)	340 (82.52%)	1.00		
	G	78 (20.00%)	72 (17.48%)	0.85	0.59–1.21	.36**
TEX14	Additive					**.001***
rs79813370	GG	125 (64.10%)	166 (80.58%)	1.00		
	GT	64 (32.82%)	37 (17.96%)	0.44	0.27–0.69	**<.001****
	TT	6 (3.08%)	3 (1.46%)	0.38	0.06–1.81	.19*
	Recessive					
	GG + GT	189 (96.92%)	203 (98.54%)	1.00		
	TT	6 (3.08%)	3 (1.46%)	0.47	0.07–2.22	.33*
	Dominant					
	GG	125 (64.10%)	166 (80.58%)	1.00		
	GT + TT	70 (35.90%)	40 (19.42%)	0.43	0.27–0.69	**<.001****
	Allele					
	G	314 (80.51%)	369 (89.56%)	1.00		
	T	76 (19.49%)	43 (10.44%)	0.48	0.32–0.72	**<.001****
TEX14	Additive					.19*
rs34818467	AA	151 (77.44%)	147 (71.36%)	1.00		
	AG	41 (21.03%)	58 (28.16%)	1.45	0.92–2.31	.11**
	GG	3 (1.54%)	1 (0.49%)	0.34	0.01–4.33	.62*
	Recessive					
	AA + AG	192 (98.46%)	205 (99.51%)	1.00		
	GG	3 (1.54%)	1 (0.49%)	0.31	0.01–3.94	.36*
	Dominant					
	AA	151 (77.44%)	147 (71.36%)	1.00		
	AG + GG	44 (22.56%)	59 (28.64%)	1.38	0.86–2.22	.17**
	Allele					
	A	343 (87.95%)	352 (85.44%)	1.00		
	G	47 (12.05%)	60 (14.56%)	1.24	0.83–1.88	.30**

95% CI = 95% confidence interval, n = number, OR = odds ratio, SNP = single nucleotide polymorphism.

P < .05 (in bold) indicates statistical significance.

* *P* values calculated by Fisher's exact test.

** *P* values calculated by Chi-squared test.

and French[19] individuals with severe sperm motility disorders, mutations in *CFAP43* were also identified. Given the important role that *CFAP43* plays in sperm morphology, this research is the first-ever case-control study of polymorphisms in this gene with results showing an association between the polymorphism rs10883979 and male infertility in the Vietnamese population.

TEX14 is highly expressed in germ cells and participates in spermatocyte meiotic divisions in spermatogenesis. It promotes the conversion of midbodies into intact intercellular bridges (ICBs), which are required for chromosome segregation to occur after crossing over has been completed.[22] However, the precise role of intact intercellular bridges has not been determined and is only predicted to be involved in the communication and synchronization of germ cells within a syncytium.[24] Previous studies have suggested that mutations on *TEX14*, especially missense and splice site variants, were frequently found in patients with azoospermia and oligospermia.[25,26,40] However, few studies on the role of the *TEX14* gene in susceptibility to infertility have been conducted. A follow-up genome-wide association study assessed the role of *TEX14* SNPs (rs389389, rs7220834, rs35927726, rs35195402, rs35081269, rs34960869) in male infertility in a Caucasian population, showing no correlation

between this gene and male infertility.[41] In the present study, an association of the polymorphism *TEX14* rs79813370 with male infertility was found. To the best of our knowledge, the current case-control study is the first report of an association between *TEX14* rs7913370 and male infertility worldwide.

This study was the first report to investigate the genotype distributions and the effects of *CFAP43* (rs17116635 and rs10883979) and *TEX14* (rs79813370 and rs34818467) on male infertility worldwide. Additionally, only *CFAP43* rs10883979 has so far been studied in case-control research on Late-onset Alzheimer's Disease.[42] Since the findings of this study were novel, several limitations should be considered. First, all participants (both case and control groups) were recruited from the same hospital, potentially introducing selection bias. Second, more extensive studies with participants collected from different sampling sites and different ethnic populations should be conducted to further validate the findings here. We can also perform quantitative RT-PCR or RNA sequencing to determine whether the studied SNPs are associated with differential expression of the studied genes or of other genes, respectively.

5. Conclusion

Our study suggested that *CFAP43* rs10883979 and *TEX14* rs79813370 were significantly associated with the risk of idiopathic male infertility in the Vietnamese population. Additionally, the G allele of rs79813370 may be a risk factor for male infertility. To obtain more insights into the association of the 2 genes *CFAP43* and *TEX14* and male infertility, further investigation on the 4 studied SNPs and others on these genes should be implemented in different populations.

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References

[1] Zegers-Hochschild F, Adamson GD, Dyer S, et al. The international glossary on infertility and fertility care, 2017. Fertil Steril. 2017;108:393–406.
[2] Fainberg J, Kashanian JA. Recent advances in understanding and managing male infertility. F1000Res. 2019;8:F1000 Faculty Rev–670.
[3] Krausz C, Escamilla AR, Chianese C. Genetics of male infertility: from research to clinic. Reproduction. 2015;150:R159–74.
[4] Krausz C, Riera-Escamilla A. Genetics of male infertility. Nat Rev Urol. 2018;15:369–84.
[5] Agarwal A, Mulgund A, Hamada A, Chyatte MR. A unique view on male infertility around the globe. Reprod Biol Endocrinol. 2015;13:37.
[6] Sun H, Gong TT, Jiang YT, Zhang S, Zhao YH, Wu QJ. Global, regional, and national prevalence and disability-adjusted life-years for infertility in 195 countries and territories, 1990-2017: results from a global burden of disease study, 2017. Aging (Albany NY). 2019;11:10952–91.
[7] Pereira R, Sousa M. Morphological and molecular bases of male infertility: a closer look at sperm flagellum. Genes (Basel). 2023;14:383.
[8] Cioppi F, Rosta V, Krausz C. Genetics of azoospermia. Int J Mol Sci. 2021;22:3264.
[9] Cannarella R, Condorelli RA, Mongioi LM, La Vignera S, Calogero AE. Molecular biology of spermatogenesis: novel targets of apparently idiopathic male infertility. Int J Mol Sci. 2020;21:1728.
[10] Tang S, Wang X, Li W, et al. Biallelic mutations in CFAP43 and CFAP44 cause male infertility with multiple morphological abnormalities of the sperm flagella. Am J Hum Genet. 2017;100:854–64.
[11] Toure A, Martinez G, Kherraf ZE, et al. The genetic architecture of morphological abnormalities of the sperm tail. Hum Genet. 2021;140:21–42.
[12] Yu Y, Wang J, Zhou L, Li H, Zheng B, Yang S. CFAP43-mediated intra-manchette transport is required for sperm head shaping and flagella formation. Zygote. 2021;29:75–81.
[13] Coutton C, Vargas AS, Amiri-Yekta A, et al. Mutations in CFAP43 and CFAP44 cause male infertility and flagellum defects in Trypanosoma and human. Nat Commun. 2018;9:686.
[14] Morimoto Y, Yoshida S, Kinoshita A, et al. Nonsense mutation in CFAP43 causes normal-pressure hydrocephalus with ciliary abnormalities. Neurology. 2019;92:e2364–74.
[15] Khan I, Shah B, Dil S, et al. Novel biallelic loss-of-function mutations in CFAP43 cause multiple morphological abnormalities of the sperm flagellum in Pakistani families. Asian J Androl. 2021;23:627–32.
[16] Sha YW, Wang X, Su ZY, et al. Patients with multiple morphological abnormalities of the sperm flagella harbouring CFAP44 or CFAP43 mutations have a good pregnancy outcome following intracytoplasmic sperm injection. Andrologia. 2019;51:e13151.
[17] Sha YW, Wang X, Xu X, et al. Novel Mutations in CFAP44 and CFAP43 cause Multiple Morphological Abnormalities of the Sperm Flagella (MMAF). Reprod Sci. 2019;26:26–34.
[18] Wu H, Li W, He X, et al. NovelCFAP43 andCFAP44 mutations cause male infertility with multiple morphological abnormalities of the sperm flagella (MMAF). Reprod Biomed Online. 2019;38:769–78.
[19] Ferreux L, Bourdon M, Chargui A, et al. Genetic diagnosis, sperm phenotype and ICSI outcome in case of severe asthenozoospermia with multiple morphological abnormalities of the flagellum. Hum Reprod. 2021;36:2848–60.
[20] Oud MS, Houston BJ, Volozonoka L, et al. Exome sequencing reveals variants in known and novel candidate genes for severe sperm motility disorders. Hum Reprod. 2021;36:2597–611.
[21] Cannarella R, Condorelli RA, Duca Y, La Vignera S, Calogero AE. New insights into the genetics of spermatogenic failure: a review of the literature. Hum Genet. 2019;138:125–40.
[22] Greenbaum MP, Yan W, Wu MH, et al. TEX14 is essential for intercellular bridges and fertility in male mice. Proc Natl Acad Sci U S A. 2006;103:4982–7.
[23] Kim HJ, Yoon J, Matsuura A, et al. Structural and biochemical insights into the role of testis-expressed gene 14 (TEX14) in forming the stable intercellular bridges of germ cells. Proc Natl Acad Sci U S A. 2015;112:12372–7.
[24] Rezende-Melo CA, Caldeira-Brant AL, Drumond-Bock AL, et al. Spermatogonial asynchrony in Tex14 mutant mice lacking intercellular bridges. Reproduction. 2020;160:205–15.
[25] Araujo TF, Friedrich C, Grangeiro CHP, et al. Sequence analysis of 37 candidate genes for male infertility: challenges in variant assessment and validating genes. Andrology. 2020;8:434–41.
[26] Fakhro KA, Elbardisi H, Arafa M, et al. Point-of-care whole-exome sequencing of idiopathic male infertility. Genet Med. 2018;20:1365–73.
[27] Gershoni M, Hauser R, Yogev L, et al. A familial study of azoospermic men identifies three novel causative mutations in three new human azoospermia genes. Genet Med. 2017;19:998–1006.
[28] Krausz C, Riera-Escamilla A, Moreno-Mendoza D, et al. Genetic dissection of spermatogenic arrest through exome analysis: clinical implications for the management of azoospermic men. Genet Med. 2020;22:1956–66.
[29] Chung CC, Kanetsky PA, Wang Z, et al. Meta-analysis identifies four new loci associated with testicular germ cell tumor. Nat Genet. 2013;45:680–5.
[30] Kelemen LE, Wang X, Fredericksen ZS, et al. Genetic variation in the chromosome 17q23 amplicon and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2009;18:1864–8.

[31] Houston BJ, Riera-Escamilla A, Wyrwoll MJ, et al. A systematic review of the validated monogenic causes of human male infertility: 2020 update and a discussion of emerging gene-disease relationships. Hum Reprod Update. 2021;28:15–29.
[32] Mahyari E, Guo J, Lima AC, et al. Comparative single-cell analysis of biopsies clarifies pathogenic mechanisms in Klinefelter syndrome. Am J Hum Genet. 2021;108:1924–45.
[33] Hammal F, de Langen P, Bergon A, Lopez F, Ballester B. ReMap 2022: a database of Human, Mouse, Drosophila and Arabidopsis regulatory regions from an integrative analysis of DNA-binding sequencing experiments. Nucleic Acids Res. 2022;50:D316–25.
[34] R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing. Available at: https://www.R-project.org/. Accessed June 2022.
[35] Graffelman J. Exploring diallelic genetic markers: the HardyWeinberg package. J Stat Softw. 2015;64:1–23.
[36] Graffelman J, Camarena JM. Graphical tests for Hardy-Weinberg equilibrium based on the ternary plot. Hum Hered. 2008;65:77–84.
[37] Graffelman J, Weir BS. Testing for Hardy-Weinberg equilibrium at biallelic genetic markers on the X chromosome. Heredity (Edinb). 2016;116:558–68.
[38] Aragon T. epitools: Epidemiology Tools. Available at: https://CRAN.R-project.org/package=epitools. Accessed June 2022.
[39] Wang WL, Tu CF, Tan YQ. Insight on multiple morphological abnormalities of sperm flagella in male infertility: what is new? Asian J Androl. 2020;22:236–45.
[40] An M, Liu Y, Zhang M, et al. Targeted next-generation sequencing panel screening of 668 Chinese patients with non-obstructive azoospermia. J Assist Reprod Genet. 2021;38:1997–2005.
[41] Aston KI, Krausz C, Laface I, Ruiz-Castane E, Carrell DT. Evaluation of 172 candidate polymorphisms for association with oligozoospermia or azoospermia in a large cohort of men of European descent. Hum Reprod. 2010;25:1383–97.
[42] Grupe A, Li Y, Rowland C, et al. A scan of chromosome 10 identifies a novel locus showing strong association with late-onset Alzheimer disease. Am J Hum Genet. 2006;78:78–88.