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REVIEW ARTICLE

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Is the primary AZFc duplication a potential risk for male infertility?: A systematic review and meta-analysis

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Abstract

Background: Numerous studies have been performed to investigate the association between the primary AZFc duplication and male infertility risk; however, the sample sizes have been small and the results have been controversial. A meta-analysis was performed to assess these associations.

Methods: A systematic search was conducted to identify all relevant studies from the PubMed, Web of Science, Medline, CNKI, and Wanfang databases up to October 22, 2019. The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of associations. All of the statistical analyses were conducted by using RevMan 5.3.

Results: Eleven studies were identified that involved 3140 infertile men and 2280 fertile men. Overall, there was a statistically significant association between the primary AZFc duplication and male infertility (OR = 1.66, 95% CI = 1.29-2.14, $P < .0001$). In the subgroup analysis by ethnic group, a statistically significant association between the primary AZFc duplication and male infertility was observed in Asian men (OR = 2.26, 95% CI = 1.64-3.12, $P < .00001$), but not in European men (OR = 0.90, 95% CI = 0.59-1.38, $P = .64$). For subtypes of the primary AZFc duplication, a statistically significant association was observed between the gr/gr duplication-only (OR = 2.71, 95% CI = 1.38-5.32, $P = .004$) and infertility in Asian men. Asian men with the primary AZFc duplication resulting in more than four DAZ genes were found to be at an increased risk for infertility (OR = 2.70, 95% CI = 1.49-4.89, $P = .001$).

Conclusion: Our meta-analysis provides an unprecedented illustration of how the association between the primary AZFc duplication and male infertility may be dependent on ethnicity or geographic location. Furthermore, gr/gr duplication or increased DAZ copy number can be detrimental to spermatogenesis in Asian men.

KEYWORDS

copy number variation, male infertility, meta-analysis, primary AZFc duplication

1 | INTRODUCTION

Though the Y chromosome is relatively gene poor, the key roles played by the Y chromosome are in sex determination and spermatogenesis which are associated with the function of SRY on the Yp and AZF on the Yq, respectively. Overall, approximately 2% of otherwise healthy males exhibit idiopathic infertility, and it appears that mutations of genes on the Yq account for a significant proportion of these cases.[1]

The findings suggest that there are three regions on the Yq (AZFa, AZFb, and AZFc) termed azoospermia factors (AZF), which control the different stages of spermatogenesis.[2] The AZF region contains many ampliconic and palindromic sequences making it pre-disposed to non-allelic homologue recombination (NAHR).[3] Subsequently, deletion and duplication rearrangements are very common in this region. The complete deletion of the AZF region causes azoospermia in men, while the phenotype for a partial deletion of AZF regions varies.[4] Deletions of the entire AZFa region invariably result in sertoli cell only syndrome (SCOS) and azoospermia,[5] but spermatid arrest and even crypto/oligozoospermia have been reported in association with complete AZFb or AZFbc (P5/proximal P1, P5/distal P1, P4/distal P1) deletions.[6,7] The AZFc (b2/b4) deletion is the most frequent subtype.[2] The 3.5-Mb-long AZFc region contains 12 genes/transcription units including DAZ, CDY1, BPY2, GOLGA2LY, CSPG4P1Y, and TTY4 gene.[8] AZFc partial deletions can cause a heterogeneous spermatogenic phenotype, ranging from azoospermia to normal sperm count while complete deletion of AZFc by removing b2/b4 results in azoospermia or severe oligozoospermia.[9]

Like AZFc deletion, duplication of AZFc also occurs via NAHR. Nonetheless, there are fewer studies on duplications than there are on deletions, and Lin first reported that the primary AZFc partial duplication (duplications not preceded by any deletion) is a risk factor[10] which is supported by other studies.[11,12] Moreover, a study demonstrated that men with an increased copy number of DAZ genes are at an increased risk for oligozoospermia and azoospermia[13] and another showed that men with primary AZFc duplications resulting in Y chromosomes with eight DAZ genes on their Y chromosomes have a severely diminished TMC (total motile count).[14] However, the conclusion is not supported by other studies.[15,16,17] Given that Kuan and Hsu reported that complete AZFc duplication has no correlation with male infertility,[18,19] whether the primary AZFc duplication is associated with male infertility still remains controversial.

Therefore, the aim of our study was to assess the role of the primary AZFc duplication (duplication-only) in male infertility, by reviewing all available English- and Chinese-language literature and performing meta-analysis of the primary AZFc duplication events in infertile and fertile men to determine and demonstrate whether the primary AZFc duplication is a risk factor for male infertility.

2 | METHOD

2.1 | Search strategy

To assess the current evidence of an association between the primary AZFc duplication and male infertility, we performed the present comprehensive meta-analysis of published studies. We searched PubMed, Web of Science, Medline, CNKI, and WanFang for relevant articles published up to October 22, 2019. The following terms were used: (AZFc) AND ([duplication] OR [copy number variants] OR [multi-copies]) AND ([infertility] OR [spermatogenic impairment] OR [impaired spermatogenesis] OR [azoospermia] OR [oligozoospermia]).

2.2 | Inclusion and exclusion criteria

2.2.1 | Inclusion criteria were based on the following features

A Full text of the study is available.
B The genotypes in the cases and controls were clearly described.
C The study was a randomized controlled trial (RCT) or a retrospective comparative study (cohort and case-control studies) that compared the outcomes of spermatogenesis phenotype or fertility status in men with or without the primary AZFc duplication.

2.2.2 | Exclusion criteria were based on the following features

A Repeated or overlapping publications.
B Conference abstracts, letters to the editors, review articles, case reports, and animal research were excluded.
C Studies not concerning the association between the primary AZFc duplication and male infertility risk.

2.3 | Data extraction and quality assessment

Two investigators (Zhang Yangwei and Xie Shengyu) independently extracted the data to ensure homogeneity of the data collection, and any disagreement was resolved through consultation with a third reviewer. The data collected included the study characteristics and various outcomes. The study characteristics included the first authors' name, year of publication, study location, and study methodology. The Newcastle-Ottawa Scale (NOS) was used by 2 authors to assess the quality of included studies by 2 authors,[20] and this assessment involved using a 9-star rating system (where 9 denotes the highest quality) to complete a checklist for each study design, evaluating the risk of bias across three areas: selection (eg, the representativeness of the cohort), comparability (eg, control for potential confounding), and outcomes (eg, use of independent blind assessments) (where 9 denotes the highest quality). Each paper was assessed independently, and the final rating was then discussed and agreed upon by two authors. Studies were then classified as either high quality (score ≥ 7), moderate quality (score 5-6), or low quality (score ≤ 4), with findings were initially reported for all studies initially, then each subgroup was rated.

2.4 | Statistical strategy

All the meta-analyses were carried out by using Review Manager 5.3, and all data retrieved were analyzed by using odds ratios (ORs) with the 95% confidence intervals (CIs). The significance of the pooled ORs was analyzed by the Z test, and $P < .05$ was considered statistically significant. The chi-square-based Q test and I2 statistics were used to calculate heterogeneity among the included studies. The $P > .05$ for Q test

or I2 < 50% indicated a statistically significant degree of heterogeneity among studies. In contrast, a random-effects model was used.

3 | RESULTS

3.1 | Description of included studies

A total of 38 studies were retrieved from online databases. These studies were screened, and 27 studies were excluded based on the inclusion and exclusion criteria. Eventually, 11 studies including 3140 infertile men and 2280 fertile men were included in this meta-analysis. A detailed flow chart of the study selection is shown in Figure 1. The years of publication ranged from 2007 to 2019, and there were 7 studies of individuals of Asian descent and 4 studies of individuals of European descent (Table 1 demonstrates the characteristics of the included studies).

3.2 | Meta-analysis of the association between the primary AZFc duplication and male infertility

3.2.1 | Association between overall types of the primary AZFc duplication and male infertility

There were 11 studies involving a total of 5420 men that evaluated the influence of the primary AZFc duplication on the risk of male infertility (Table 2). Figures 2 and 3 show the meta-analysis results for the overall group (OR = 1.66, 95% CI = 1.29-2.14, $P < .0001$) and European (OR = 0.90, 95% CI = 0.59-1.38, $P = .64$) versus Asian (OR = 2.26, 95% CI = 1.64-3.12, $P < .00001$) group, for which the I^2 value was 41%, 0% and 0%, respectively. Thus, a fixed effect model was used to synthesize the data.

3.2.2 | Association between subtypes of the primary AZFc duplication and infertility in Asian men

The subtypes of the primary AZFc duplication in the included studies are shown in Table 3. Figure 4 shows the meta-analysis results for gr/gr duplication-only (OR = 2.71, 95% CI = 1.38-5.32, $P = .004$), for which the I^2 value was 0%. Therefore, a fixed effect model was used to synthesize the data.

3.2.3 | Association between the primary AZFc duplication with more than four DAZ genes and infertility in Asian men

Data for the Asian men from the included studies with primary AZFc duplication resulting in more than four DAZ genes in the included studies are shown in Table 4. Figure 5 shows the meta-analysis results for the DAZ CNV group (OR = 2.70, 95% CI = 1.49-4.89, $P = .001$), for which the I^2 value was 17%. Therefore, a fixed effect model was used to synthesize the data.

3.3 | Publication bias

A funnel plot was used to assess all 11 studies involved and there was no evidence of obvious asymmetry in the funnel plots (Figure 6), which indicated that no significant publication bias was observed.

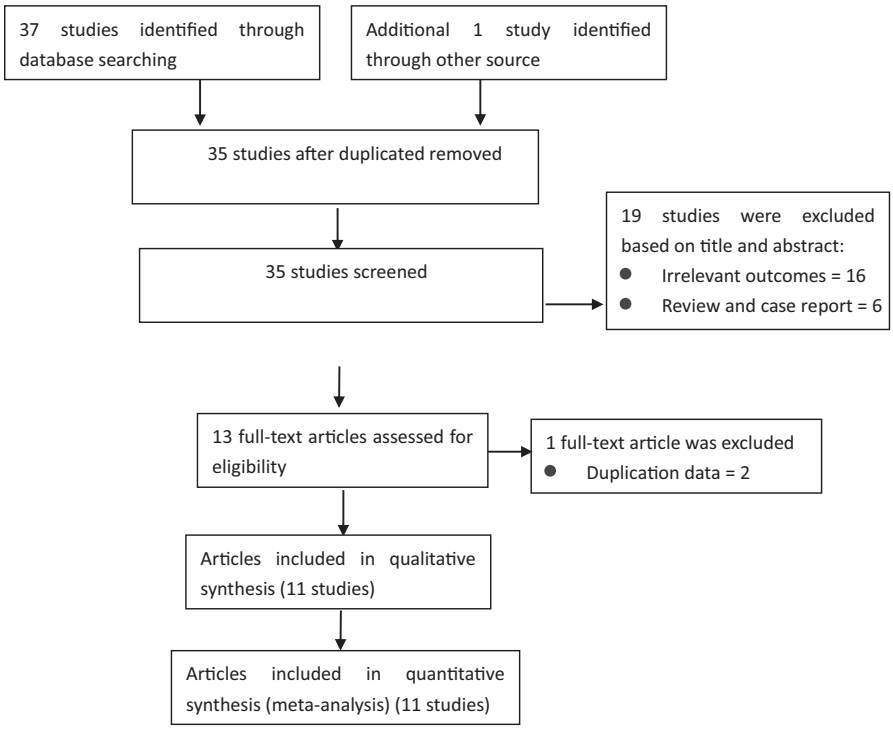

FIGURE 1 Flowchart of the study identification process

TABLE 1 Characteristics of the case-control studies included in the meta-analysis

Study	Country	Geographic Region	Ethnicity	Methodology (detecting the AZFc rearrangements)	NOS	Infertile male				Controls	
						AZ (=n)	OZ (=n)	Others (=n)	All cases/ total (%)	Fertile only	NZ
Lin et al (2007)[10]	China	Taiwan	Han Taiwanese	Multiple PCR amplification of STSs	8				10/142	1/107	
Plaseski et al (2008)[21]	Macedonia	Not mentioned	NA	Multiple QF-PCR amplification of STSs and analysis of DAZ and CDY1 SNVs by PCR and restriction enzyme digestion	8	5	8	6	19/205	17/152	
Giachini et al (2008)[15]	Italy	Central Italy	Caucasian	STSs analysis and quantifying the DAZ and CDY1 gene dosage by a standard PCR reaction	8	1	2	3	6/229		10/263
Ye et al (2013)[35]	China	Yunnan province	Yi-population	A standard PCR reaction amplication of STSs; SNV analysis of DAZ and CDY1 genes using a PCR amplification-restriction digestion assay; detecting the DAZ and CDY1 gene copies by qPCR	8	1	8		9/215	1/115	
Lu et al (2011)[11]	China	Nanjing	Han Chinese	Multiple PCR amplication of AZFc-STS and detecting partial duplication types of DAZ gene using restriction fragment length polymorphis	7	20	19	37	76/556	25/330	
Giacco et al (2014)[16]	Spanish	Not mentioned	Caucasian	AZFc-STSs analysis by a standard PCR assay	9				15/305	13/367	
Saito et al (2015)[34]	Japan	Not mentioned	NA	MLPA	9				5/56	1/65	
Yang et al (2015)[27]	China	South-western China	Han Chinese	AZFc-STSs analysis and quantitative analysis of DAZ, BPY2 and CDY1 by PRTs followed by qPCR	8	11	27		38/605		11/308
Zhou et al (2019)[12]	China	Nanjing, Jiangsu province, China	Han Chinese	MLPA, AZFc-STSs analysis and quantitative analysis	9	12	15		27/423	12/402	
Mokánszki et al (2018)[22]	Hungarian	East Hungarian	Caucasian	Quantitative analysis	**7**	3	4		7/347		4/111
Zhao et al (2019)[36]	China	Southern China	Hakka	Multiple PCR	**7**	1	2		3/57	0/60	

Abbreviations: NZ, normozoospermia; AZ, azoospermia; OZ, oligozoospermia.

TABLE 2 The subtypes of the primary AZFc duplication in the studies of Asian men

First author, and year published	Subtypes	Infertile male				Fertile male
		AZ(=n)	OZ(=n)	others(=n)	All cases	All cases
Lin et al (2007)[10]	gr/gr				1/142	0/107
	b2/b3				3/142	0/107
Saito et al (2015)[34]	gr/gr				3/56	0/65
Yang et al (2015)[27]	gr/gr	7/605	17/605		24/605	5/308
	b2/b3	3/605	7/605		10/605	4/308
	b2/b4	1/605	3/605		4/605	2/308
Zhou et al. (2019)[12]	gr/gr	7/423	6/423		13/423	5/402
	b2/b3	3/423	1/423		4/423	1/402
	b2/b4	0/423	3/423		3/423	2/402

Abbreviation: NZ, normozoospermia; AZ, azoospermia; OZ, oligozoospermia.

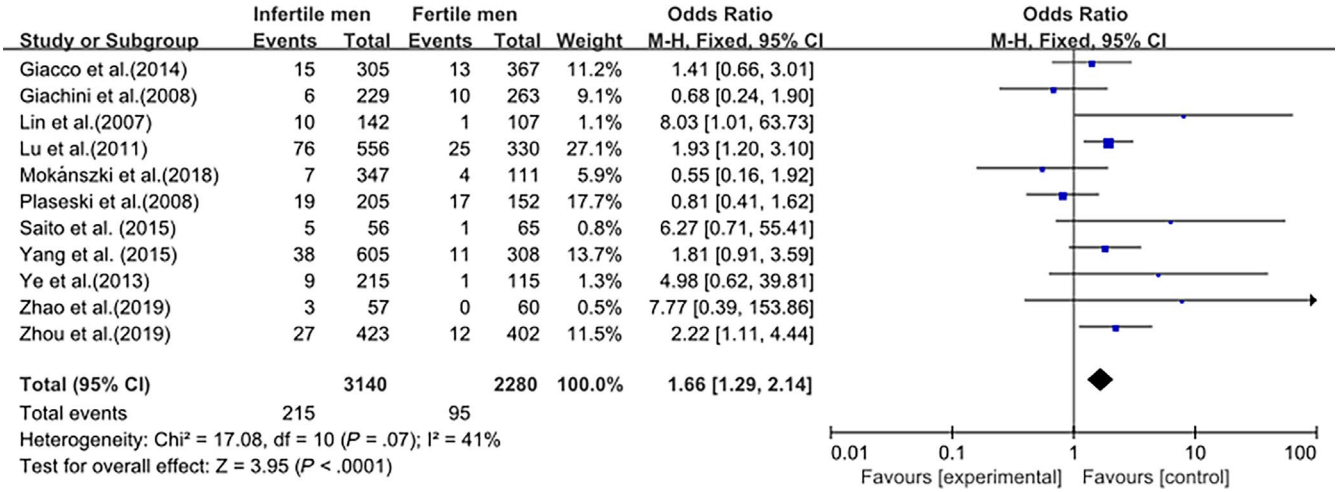

FIGURE 2 Forest plot of the studies assessing the association between the primary AZFc duplication and male infertility. (overall assess)

4 | DISCUSSION

In this study, we performed a meta-analysis to evaluate the association between primary AZFc duplication and male infertility. Our study suggests that primary AZFc duplication might be associated with male infertility (OR = 1.66, 95% CI = =1.29-2.14, $P < .0001$). However, this kind of effect seems to not be general; rather, according to Figure 2, the effect is population-specific (ORs of studies conducted in Europe are relatively smaller and most of them are less than 1 Plaseski et al,[21] Giachini et al,[15] and Mokánszki et al.[22] Hence, population-specific analyses were conducted. Figure 3 shows that the duplications play vital roles in Asian men (OR = 2.26, 95% CI = 1.64-3.12, $P < .00001$), but for European men the evidence is not statistically significant enough to support the conclusion that the primary AZFc duplication contributes to male infertility (OR = 0.90, 95% CI = 0.59-1.38, $P = .64$). Moreover, among the several subtypes of the primary AZFc duplication, gr/gr duplication (OR = 2.71, 95% CI = 1.38-5.32, $P = .004$) shows a significant link with male infertility. Asian men with the primary AZFc duplication resulting in more than four DAZ genes are at increased risk for male infertility (OR = 2.70, 95% CI = 1.49-4.89, $P = .001$).

The characteristic of AZFc makes the eight gene families that are harbored within it prone to deletion, duplication, and copy number variation.[3] To this point, among the genetic variations of AZFc, a wealth of information regarding AZFc partial deletions has accumulated in the past 15 years and it is clear that the association of partial AZFc deletions and male infertility is significant.[23-26] Some studies carried out in non-Asian regions suggest that there was no significant difference between individuals with and without primary AZFc duplication, neither among males with decreased sperm count nor among controls.[15,16] However, our study suggests that the primary AZFc duplication is more likely to contribute to individual susceptibility to male infertility in Asian men than in European men,therefore, duplication of the AZFc locus has been associated with infertility, but the effect seems to be ethnicity dependent. This conclusion can be supported by some studies,[25,27,28] because their studies confirmed that the primary duplication in the AZFc subregion may disrupt the spermatogenesis process,further, the studies associated with duplication analyses showed variation in outcome, which may be due to the difference in geographical and ethnic populations, aligning with our meta-analysis. Increased dosages of several segments in the

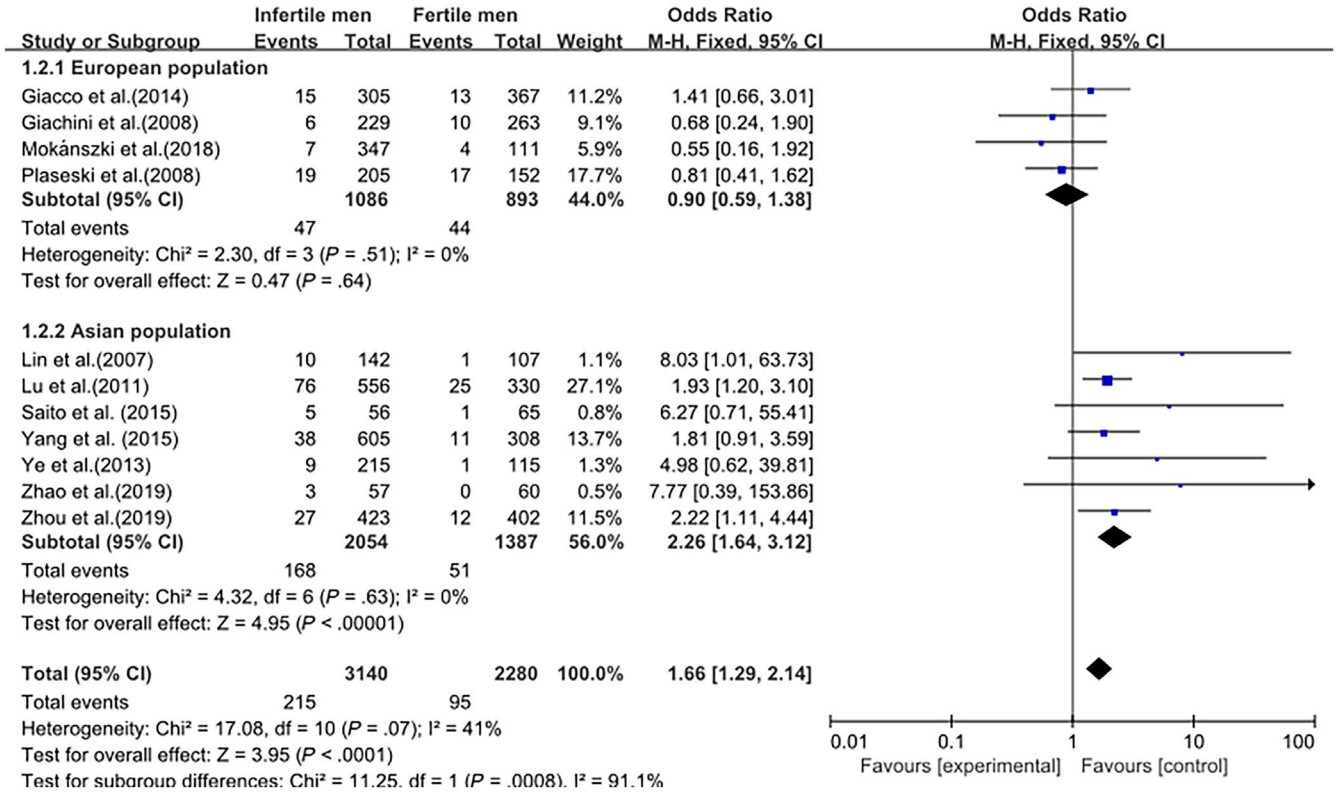

FIGURE 3 Forest plot of the studies assessing the association between the primary AZFc duplication and male infertility in different populations

TABLE 3 Asian men with the primary AZFc duplication resulting in more than four DAZ genes in the case-control studies

Study		DAZ dosage	Infertile male	Fertile male
Lin et al (2007)[10]		6	10/142	1/107
Ye et al (2013)[35]		6	9/215	1/115
Yang et al (2015)[27]	Total	6	34/605	9/308
		8	4/605	2/308
			38/605	11/308
Saito et al (2015)[34]	Total	6	3/56	0/65
		8	1/56	0/65
			4/56	0/65

human genome have been found to interrupt normal development. In this study, genes in the duplicated regions included DAZ, CDY1, and BPY2, all of which are involved in spermatogenesis and/or male infertility.[29,30] Some of these genes are likely to be dosage sensitive, and their increased expression may interfere with normal spermatogenesis. We speculated that higher protein eating habits and androgen levels of European men may be a compensatory mechanism that rescues the deleterious effect of the primary AZFc duplication,this may contribute to the population-specific difference.

gr/gr partial duplication in the AZFc subregion is one of the most common subtypes of AZFc partial duplication. In our second subgroup meta-analysis, though the available datasets are relatively small, our results show that Asian men with gr/gr duplication-only are at increased risk for infertility. gr/gr deletion may cause men with less sperm concentration, total sperm count, and total motility of spermatozoa when compared with males with no gr/gr deletion.[3,31,32] These findings, coupled with the results of our study, could be a strong evidence that genes in this region are vital to spermatogenesis and their variants are prone to cause infertility in Asian men, hence, we should pay more attention to this region when we screening the Y chromosome. However, because of the lack of data, the effect of the b2/b3 or b2/b4 duplication-only cannot be excluded until further investigation is performed with larger samples.

DAZ genes, which encode testis-specific RNA-binding proteins, are known to be expressed exclusively in the human male germ line and are candidate genes for the expression of the azoospermia factor AZFc.[33] Men with more than four DAZ genes in the AZFc region are considered as abnormal, and Lu suggested that the DAZ1/2 cluster was the main duplicated copy in the

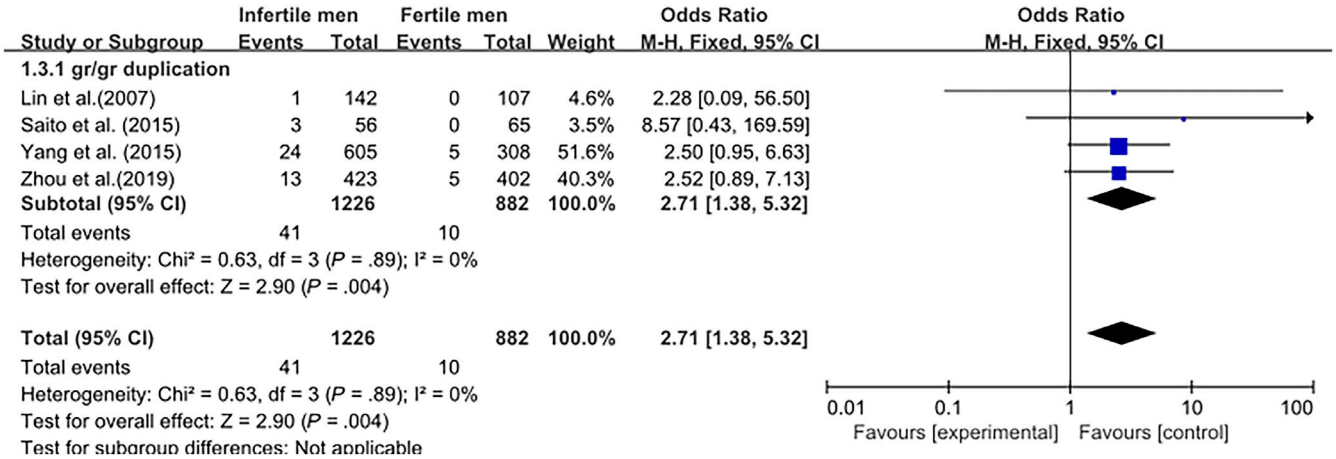

FIGURE 4 Forest plot of the studies assessing the association between the primary AZFc duplication and infertility in Asian men. (gr/gr group)

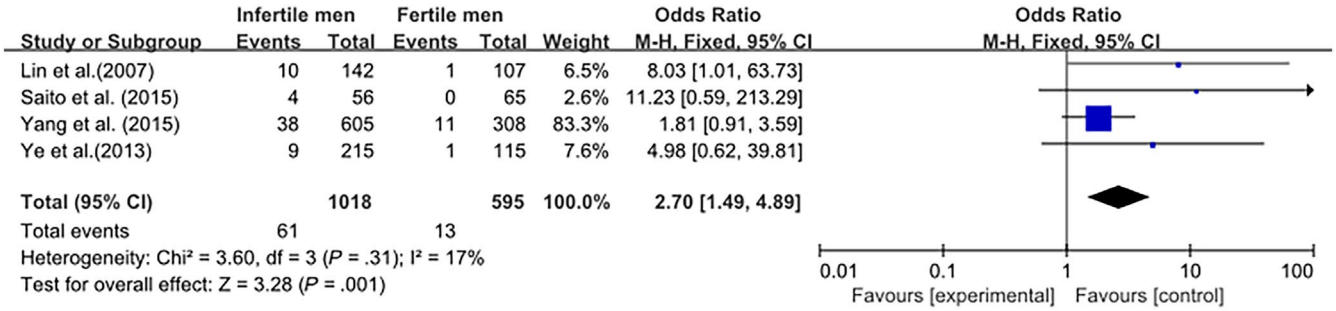

FIGURE 5 Forest plot of the studies assessing the association between AZFc duplication and infertility in Asian men. (DAZ CNV group)

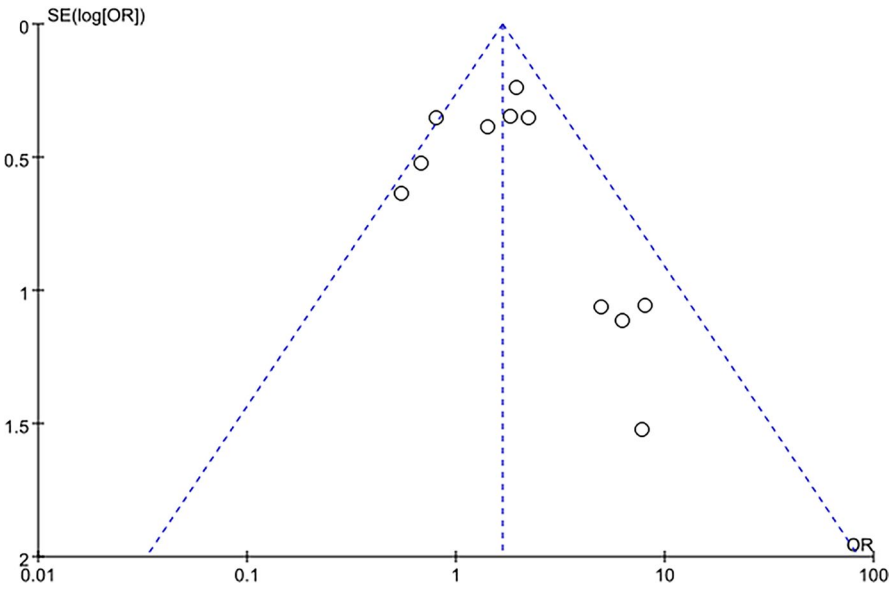

FIGURE 6 Funnel plot for the AZFc partial duplication and the risk of male infertility. (overall assess)

partial AZFc duplications associated with spermatogenic impairment,[11] thus, DAZ duplication might contribute to infertility in Asian men. Although the available datasets are relatively small, our meta-analysis of the third subgroup suggests that Asian men with the primary AZFc duplication resulting in more than four DAZ genes are at increased risk for infertility.

Our review has limitations. First, the included studies are relatively scant and more than half (7/11) are Asian populations, which limits the generalizability of our meta-analysis. Another limitation is that some included studies identified the primary AZFc duplication based on the mechanism of NAHR, for example, gr/gr duplication and b2/b3 duplication; others identified the primary AZFc

duplication based on the gene copy number variants. Hence, these differences limited ability to analyze the effects of increased gene copy numbers or duplicated segments of AZFc for male infertility. Last, Kazuki et al compared MLPA to the STS-marker assay for detecting AZFc duplication and found that the MLPA assay was superior to the traditional assay.[34] Given that the included studies detected the AZFc duplication by using different methods, false positive and false negative are inevitable. Therefore, the included studies could contain some undetectable AZFc duplication cases. Moreover, two types of controls (testified fertile males and normozoospermia males) in the included studies may contribute to smaller ORs, because men with normozoospermia men might be infertile.

5 | CONCLUSION

This review and meta-analysis provide an unprecedented illustration that association between primary AZFc duplication and male infertility may be dependent on ethnicity or geographic location. Furthermore, gr/gr duplication or increased DAZ copy number can be detrimental to spermatogenesis in Asian men. Though the effect of primary duplication of the eight gene families of AZFc on male infertility is rarely reported, our study shows the importance of detecting the AZFc duplication especially in gr/gr duplication and DAZ dosage through genetic screening and counseling those infertile men with the primary AZFc duplication who planned to use assisted reproduction techniques such as undergoing intracytoplasmic sperm injection or in vitro fertilization.

AUTHORS CONTRIBUTIONS

Shengyu Xie and Yangwei Zhang and Yuan Yang contributed to conceptualization. Shengyu Xie contributed to data curation. Shengyu Xie contributed to formal analysis. Shengyu Xie and Yangwei Zhang contributed to methodology. Shengyu Xie contributed to software. Shengyu Xie and Yangwei Zhang contributed to writing—original draft. Shengyu Xie and Yuan Yang contributed to writing—review and editing.

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