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Xenobiotic metabolizing gene variants and the risk of male infertility - A systematic review, meta-analysis and *in silico* analysis☆

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ABSTRACT

Many studies have been performed to explore the role of xenobiotic metabolizing gene variants and male infertility risk. However, the results remain inconclusive and contradictory. Therefore, the objective of the present study was to investigate the association among 16 genes and its 24 variants (*CAT* rs1001179, rs7943316, *SOD2* rs4880, *GPX1* rs1050450, *CYP1A1* rs1048943, rs4646903, *GSTP1* rs1695, *MTHFR* rs1801133, rs1801131, rs2274976, rs2066472, *MTHFD1* rs2236225, *MTRR* rs1801394, *CYP2D6* rs3892097, *PON1* rs854560, rs662, *PON2* rs7493, *NAT2* rs1799930, *NRF2* rs6721961, *AHR* rs2066853, rs1476080, rs6960165, null *GSTM1, null GSTT1*) involved in xenobiotic metabolism and their correlation with male infertility. A literature search was done using PubMed, Google Scholar, and Science Direct. Meta-analysis was conducted using Review Manager 5.3 software. Genotype-tissue expression (GTEx) portal and RegulomDB were used to determine genotype and tissue expression. Pathogenicity of significant gene variants was determined using I-Mutant 2.0, PolyPhen 2, SNP & GO, SIFT, and CADD tools. A total of 106 studies were selected for the present study to analyze 16 genes and their variants. *SOD2* rs4880, *CYP1A1* rs4646903, *MTHFR* rs1801133, rs1801131, rs2274976, *PON1* rs854560, *NRF2* rs6721961, and null *GSTM1* gene variants are associated with increased risk of male infertility. *SOD2* rs4880 and *MTHFR* rs1801133, rs1801131, rs2274976 are found to decrease the stability of the protein. However, no significant association was observed between *CAT* rs1001179, rs7943316, *GPX1* rs1050450, *CYP1A1* rs1048943, *GSTP1* rs1695,*MTHFR* rs2066472, *MTHFD1* rs2236225, *MTRR* rs1801394, *CYP2D6* rs3892097, *PON1* rs662, *PON2* rs7493, *NAT2* rs1799930, *AHR* rs2066853, rs1476080, rs6960165, null *GSTT1* gene polymorphisms and the risk of male infertility.

1. Background

Male reproductive health may be altered by various occupational and environmental exposures to certain chemical agents. The majority of these are xenobiotics, which may disrupt the normal endocrine function by binding with other macromolecules such as proteins, and DNA [1]. Xenobiotics are chemical substances that are foreign to the body and it includes pesticides, drugs, metals and non-metal trace elements [2]. Therefore, the body requires elimination of xenobiotics from the body. The xenobiotic metabolism has been divided into three phases: phase I involves bio activation which includes P450 superfamily enzymes (CYPs); phase II involves detoxification, which includes NAT and GST enzymes; phase III involves elimination through transporters [3]. Xenobiotics can directly mediate the generation of reactive oxygen species (such as superoxide, peroxide, and hydroxyl) and cause oxidative stress [4,5]. The xenobiotic-mediated toxic effects on the male

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reproductive function are associated with certain gene variants in the genes involved in detoxification process. Major genes involved in xenobiotic detoxification are *CYP1A1, GSTP1, GSTM1,* and *GSTT1* [6]. The decline in spermatozoa quality, count, and morphology may be the result of exposure to environmental xenobiotics in long-term [7], which leads to infertility in males. The World Health Organization (WHO) defines infertility as the couple's inability to establish a successful clinical pregnancy after one year or more of regular unprotected sexual intercourse [8]. Globally, 10–15 % of couples are affected by infertility, among which male infertility contributes to 50 % of the total cases [3]. Male infertility is a multifactorial and highly complex disease, often its etiology and pathogenesis remain difficult to understand. The influence of genetic variability on the ability to metabolize xenobiotics and their role in male reproductive function has not been studied extensively. Also, phenotypic variation is associated with variability in gene expression; hence variation in gene expression could be an effect of genetic variants leading to differential response to xenobiotics [9]. The largest number of tissue-enriched genes is found in the testis, liver, and brain as identified by RNA sequencing. Almost 50 % of the genes are expressed in all analyzed tissues suggesting that gene products are required to maintain "housekeeping functions" in all cells [10]. Major biological processes such as spermatogenesis, and spermiogenesis occur in germinal cells in the testis [11]. Thus, combined analysis of gene expression and pathway analysis can be helpful in identifying enriched genes that can be associated with disease.

Various studies have been done to explore the association between gene polymorphisms in xenobiotic metabolism and their susceptibility to male infertility [12,13]. However, the results have remained inconsistent, due to the limited sample size and different ethnicities of population under study. Meta-analysis for *NOS3* rs2070744, rs1799983, rs61722009 [14], and *M*TR rs1805087 [15] gene variants has been reported recently, so the *NOS3* and *M*TR gene has been excluded from the analysis in the current meta-analysis. To date, no meta-analysis was reported for specific variants of *CAT*, *SOD2, GPX1, CYP1A1, MTHFR, CYP2D6, PON2*, *NAT2,* and *NRF2* genes with male infertility. Therefore, the present systematic review and meta-analysis have been performed to provide a comprehensive review of published papers that studied polymorphisms in xenobiotic metabolizing genes and male infertility risk. The objective of study was to investigate the association between 16 genes and their 24 genetic variants (*CAT* rs1001179, rs7943316, *SOD2* rs4880*, GPX1* rs1050450*, CYP1A1* rs1048943, rs4646903*, GSTP1* rs1695*, MTHFR* rs1801133, rs1801131, rs2274976, rs2066472, *MTHFD1* rs2236225*, MTRR* rs1801394*, CYP2D6* rs3892097*, PON1* rs854560, rs662*, PON2* rs7493*, NAT2* rs1799930*, NRF2* rs6721961*, AHR* rs2066853, rs1476080, rs6960165*,* null *GSTM1,* null *GSTT1*) involved in metabolism of xenobiotics and infertility in males.

2. Methodology

2.1. Literature search strategy

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as represented in Supplementary Table 1. The protocol of the current meta-analysis is registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42023465815. A literature search was performed using three scientific literature databases; PubMed, Google Scholar, and Science Direct. The last search was updated on 18th March 2024. The following keywords, alone or in combination, were used for literature search: ("xenobiotic metabolizing genes" or "xenobiotic detoxification genes" or "variants" or "SNPs" or "polymorphisms") and ("male infertility" or "semen quality" or "oligospermia" or "azoospermia"). Reference lists of selected articles have been screened to find out any relevant studies, which may have been missed in the initial search.

2.2. Selection criteria

The search strategy to select eligible studies has been represented in Fig. 1. Those studies were selected in the review which fulfilled the following selection criteria: a) observational studies, b) case group defined as infertile male patients with at least one year of infertility and/or being diagnosed with abnormalities in semen parameters, c) control group consists of healthy fertile men (having at least one healthy child), d) research papers that evaluated the association between genetic polymorphisms of predetermined genes and male infertility, are considered for review, e) subjects with no medical history of diseases. Studies were not included, if they were, a) a review, systematic review, or meta-analysis, b) studies on animal models, c) no detailed data regarding allele/genotype frequency, d) studies, in which the case group was not defined. No time limit was applied.

2.3. Assessment of quality

The titles, abstracts, and full texts were examined independently by three authors (MK, SR, and SD) based on the selected inclusion criteria, and relevant studies were identified. Newcastle–Ottawa Scale (NOS) scale was used to evaluate the quality of selected studies and only high-quality studies were included (Supplementary Table 2). NOS comprised a total of 9 stars based on three criteria: sample selection, comparability, and outcome features. Studies with scores of > 7 are considered high-quality studies. Any discrepancies regarding the assessment were resolved by involving the other three authors (RK, LG, and PK).

2.4. Data extraction

The following data was extracted from the selected studies; study design, sample size, country or ethnicity, sample type, genotyping method, gene name, polymorphism, number of cases, and controls, genotypic, and allelic frequencies, risk allele/factor, publication year, and first author.

2.5. Statistical analysis

Meta-analysis was conducted using Review Manager 5.3 software (RevMan software version 5.3) available from the Cochrane Collaboration network. An odds ratio (OR) with 95 % CI was used to evaluate the association between selected gene polymorphisms and the risk of male infertility. The significance of pooled OR was determined by the Z test, which was calculated by RevMan software and a p-value equal to or less than 0.05 was considered significant. The heterogeneity between eligible studies was checked using the chi-square test and I^2 statistics. Single nucleotide polymorphism consists of a major allele (M), and minor allele (m), thus the genotype can be a major allele homozygote (MM), heterozygote (Mm), or a minor allele homozygote (mm) [16]. Therefore, the association was calculated under the four genetic models: dominant model (mm + Mm vs. MM), recessive model (mm vs. Mm + MM), additive model (mm vs. MM), and allele model (m vs. M) using fixed effect or random models as applicable. The type of forest plot model (fixed or random) depends on the results of heterogeneity among the eligible studies. When $I^2 < 50$ % and $p < 0.05$, it indicates no heterogeneity, and a fixed-effect model was applied. If $I^2 > 50$ % and $p < 0.05$, it indicates heterogeneity, and a random-effect model was applied. Subgroup analysis based on ethnicity for comparison of Asian vs. non-Asian was carried out for each gene polymorphism. Publication bias was investigated using funnel plots. Sensitivity analysis was performed by the "leave-one-out" method to examine the impact of individual studies on the overall analysis of results.

2.6. Correlation between genotype and gene expression

Two different databases were used to determine the gene expression

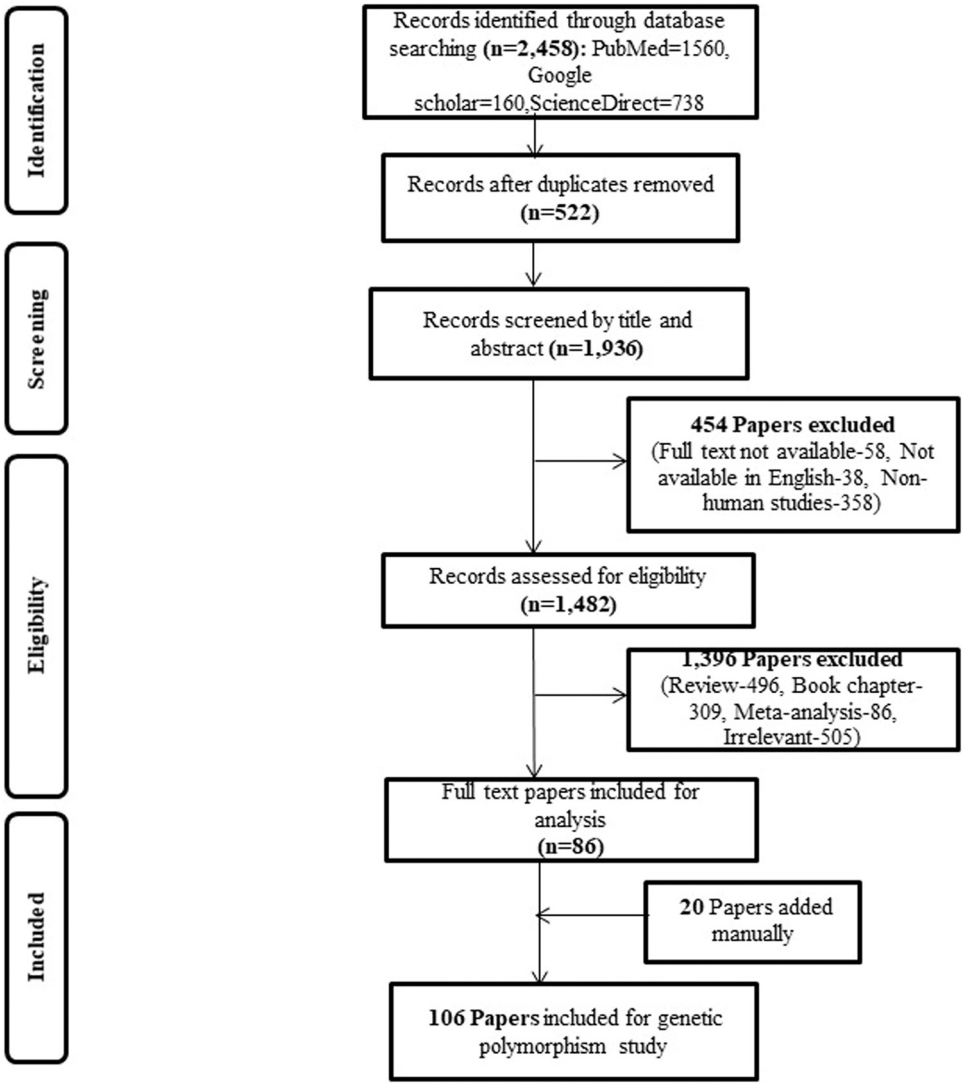

Fig. 1. PRISMA flow diagram for study selection.

according to genotype for significantly associated gene variants. Genotype-Tissue Expression (GTEx) (https://www.gtexportal.org/home/) portal determines the increased or decreased gene expression level in about 54 tissues according to the genotype. RegulomDB (https://regulomedb.org/regulome-search/) was used to determine how the selected variants would affect gene or protein expression.

2.7. Selected gene variant analysis using in silico tools

The pathogenicity of significantly associated gene variants was analyzed by using six different tools based on the type of variant analyzed. PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), SNPs & GO (https://snps-and-go.biocomp.unibo.it/snps-and-go/), SIFT (https://sift.bii.a-star.edu.sg/) tools were used to find out the deleterious SNPs that can alter the structure or function of the protein. Protein structural stability was determined using the I-Mutant tool (https://folding.biofold.org/i-mutant/i-mutant2.0.html). The pathogenicity of intronic variants was determined using the Combined Annotation Dependent Depletion tool (CADD) (https://cadd.gs.washington.edu/) and RegulomDB.

2.8. Gene pathway and PPI network analysis

Pathway enrichment analysis or gene set enrichment analysis identifies the over-represented or underrepresented set of genes. GO integrates information in the context of three aspects: molecular function, cellular function, and biological function. ShinyGO tool (http://bioinformatics.sdstate.edu/go/) was used to perform the gene pathway enrichment analysis of predetermined genes. The protein-protein interaction was performed using STRING database (https://string-db.org/). STRING interaction network or PPI network analysis provides information regarding experimental data, and prediction by computational methods. In a PPI network, nodes represent proteins, edges represent predicted relationship between proteins, and results shown inside the circle represent structure of protein.

3. Results

3.1. Characteristics of selected studies

The systematic review and meta-analysis investigated a total of 106 studies examining the role of xenobiotic metabolizing gene variants in causing male infertility. The large numbers of studies were drawn from different regions of Europe and Asia. The characteristics of all selected studies are summarized in Table 1 and genotype information of selected gene variants (only studies for which meta-analysis was possible) is summarized in Table 2. Pooled meta-analysis results under the dominant model, recessive model, additive model, and allele model are

Table 1
Characteristics of studies included in present meta-analysis.

Gene	SNP	Country	Sample type	Cases	Controls	Technique	Risk allele/ Genotype	Inference	Reference
CAT	rs1001179	Iran	Blood	195	190	AS-PCR	T↓	Associated	Sabouhi *et al.*,2015 [17]
		Algeria	Semen	111	104	AS-PCR	NA	No Association	Bousnane *et al.*,2017 [18]
		Spain	Semen	400	80	PCR-RFLP	C↑	Associated	Garcia Rodríguez *et al.*,2018 [19]
		Spain	Semen	313	80	PCR-RFLP	C↑	Associated	Garcia Rodríguez *et al.*,2019 [20]
		Vietnam	Blood	107	85	Sanger sequencing	T↑	Associated	Bach *et al.*,2023 [21]
		Iran	Semen	223	154	PCR-RFLP	NA	No association	Fallah *et al.*,2023 [22]
	rs769214	China	Blood	580	580	Chip-based	NA	No association	Ji *et al.*,2012 [23]
	rs7943316	China	Blood	580	580	Chip-based	NA	No association	Ji *et al.*,2012 [23]
		Pakistan	Blood	55	50	PCR-RFLP	T↑	Associated	Sadia *et al.*,2021 [24]
NOS1	rs2682826	China	Blood	580	580	TaqMan genotyping	NA	No association	Yan *et al.*,2014 [25]
	rs1047735	China	Blood	580	580	TaqMan genotyping	NA	No association	Yan *et al.*,2014 [25]
NOS2	rs2297518	China	Blood	580	580	TaqMan genotyping	NA	No association	Yan *et al.*,2014 [25]
	rs10459953	China	Blood	580	580	TaqMan genotyping	NA	No association	Yan *et al.*,2014 [25]
NOS3	rs1799983	Korea	Semen	371	220	Pyro sequencing	NA	No association	Yun *et al.*,2008 [26]
		Iran	Blood	352	356	PCR-RFLP	T↑	Associated	Safarinejad *et al.*,2010 [27]
		Italy	Blood	70	60	PCR-RFLP	T↑	Associated	Buldreghini *et al.*,2010 [28]
		China	Blood	355	246	PCR-RFLP	NA	No association	Ying *et al.*,2013 [29]
		China	Semen	270	248	iPLEX genotyping assays	NA	No association	Yu *et al.*,2013 [30]
		Brazil	Blood	208	201	q-PCR	NA	No association	Bianco *et al.*,2013 [31]
		China	Blood	580	580	TaqMan genotyping	T↑	Associated	Yan *et al.*,2014 [25]
		China	Blood	340	342	Sequencing	NA	No association	Song *et al.*,2015 [32]
		Egypt	Blood	220	80	PCR-RFLP	T↑	Associated	Mostafa *et al.*,2015 [33]
		Serbia	Buccal swab	131	131	PCR-RFLP	NA	No association	Vučić *et al.*,2017 [34]
	rs2070744	Korea	Semen	371	220	Pyro sequencing	NA	No association	Yun *et al.*,2008 [26]
		Iran	Blood	352	356	PCR-RFLP	C↑	Associated	Safarinejad *et al.*,2010 [27]
		China	Blood	355	246	PCR-RFLP	TC↑	Associated	Ying *et al.*,2013 [29]
		Brazil	Blood	208	201	q-PCR	NA	No association	Bianco *et al.*,2013 [31]
		China	Blood	340	342	Sequencing	NA	No association	Song *et al.*,2015 [32]
		Egypt	Blood	220	80	PCR-RFLP	C↑	Associated	Mostafa *et al.*,2015 [33]
		Serbia	Buccal swab	131	131	PCR-RFLP	NA	No association	Vučić *et al.*,2017 [34]
		Iran	Blood	100	100	PCR-RFLP	NA	No association	Mousavi *et al.*,2020 [35]
		Vietnam	Blood	107	85	Sanger sequencing	C↑	Associated	Bach *et al.*,2023 [21]
	rs61722009	Korea	Semen	371	220	PCR-LP	NA	No association	Yun *et al.*,2008 [26]
		Iran	Blood	352	356	PCR-RFLP	a↑	Associated	Safarinejad *et al.*,2010 [27]
		China	Blood	355	246	PCR-RFLP	ab↑	Associated	Ying *et al.*,2013 [29]
		Brazil	Blood	208	201	PCR	NA	No association	Bianco *et al.*,2013 [31]
		China	Blood	340	342	Sequencing	a↑	Associated	Song *et al.*,2015 [32]
		Serbia	Buccal swab	131	131	PCR	NA	No association	Vučić *et al.*,2017 [34]
SOD1	rs4998557	Vietnam	Blood	107	85	Sanger sequencing	G↑	Associated	Bach *et al.*,2023 [21]
SOD2	rs4880	China	Blood	580	580	Chip based	G↑	Associated	Ji *et al.*, 2012 [23]
		Spain	Semen	313	80	PCR-RFLP	NA	No Association	Garcia Rodríguez et al.,2019 [20]
		Iran	Semen	223	154	PCR-RFLP	C↑	Associated	Fallah *et al.*,2023 [22]
		Vietnam	Blood	107	85	Sanger sequencing	C↑	Associated	Bach *et al.*,2023 [21]
	rs5746136	China	Blood	580	580	Chip based	NA	No association	Ji *et al.*,2012 [23]
	rs1141718	Spain	Semen	313	80	PCR-RFLP	NA	No association	Garcia Rodríguez *et al.*,2019 [20]
SOD3	rs2536512	China	Blood	580	580	Chip based	NA	No association	Ji *et al.*,2012 [23]
	rs2695232	China	Blood	580	580	Chip based	NA	No association	Ji *et al.*,2012 [23]
CYP1A1	rs4646903	China	Blood	192	226	PCR-RFLP	NA	No association	Lu *et al.*,2008 [36]
		India	Blood	206	230	PCR-RFLP	C↑	Associated	Vani *et al.*,2009 [37]
		Iran	Blood	150	200	PCR-RFLP	NA	No association	Salehi *et al.*,2012 [38]
		Russia	Blood	203	227	PCR-RFLP	NA	No association	Yarosh *et al.*,2013 [39]
		Iran	Blood	100	100	PCR-RFLP	C↑	Associated	Nejati *et al.*,2016 [40]
		India	Blood	120	80	PCR-RFLP	CT↑	Associated	Ramgir *et al.*,2017 [41]
		China	Blood	1759	1826	PCR-RFLP	C↑	Associated	Wang *et al.*,2017 [42]
		China	Blood	105	104	PCR-RFLP	C↑	Associated	Javidan *et al.*,2018 [43]
		Uzbekistan	Blood	140	155	AS-PCR	C↓	Associated	Saatovich *et al.*,2023 [44]
	rs1048943	China	Blood	192	226	PCR-RFLP	C↑	Associated	Lu *et al.*,2008 [36]
		Turkey	Blood	110	105	PCR-RFLP	G↑	Associated	Aydos *et al.*,2009 [45]
		Russia	Blood	203	227	PCR-RFLP	AG↑	Associated	Yarosh *et al.*,2013 [39]
		China	Blood	105	104	PCR-RFLP	NA	No association	Javidan *et al.*,2018 [43]
		Uzbekistan	Blood	140	155	AS-PCR	A↓	Associated	Saatovich *et al.*,2023 [44]
	rs41279188	China	Blood	310	170	PCR-RFLP	NA	No association	Zhang *et al.*,2022 [46]
CYP1A2	rs762551	Turkey	Blood	306	129	PCR-RFLP	AA↑	Associated	Hekim *et al.*,2019 [47]
CYP1B1	rs10916	China	Blood	591	419	TaqMan assay	G↓	Associated	Hu *et al.*,2011 [48]
	rs162562	China	Blood	591	419	TaqMan assay	NA	No association	Hu *et al.*,2011 [48]
	rs9341266	China	Blood	591	419	Sequencing	NA	No association	Hu *et al.*,2011 [48]
	rs2855658	China	Blood	591	419	Sequencing	NA	No association	Hu *et al.*,2011 [48]

(*continued on next page*)

Table 1 (*continued*)

Gene	SNP	Country	Sample type	Cases	Controls	Technique	Risk allele/ Genotype	Inference	Reference
	rs1056836	China	Blood	591	419	TaqMan assay	NA	No association	Hu *et al.*,2011 [48]
CYP2D6	rs3892097	Egypt	Blood	231	77	PCR-RFLP	G↓	Associated	Zalata *et al.*,2014 [49]
		Turkey	Blood	306	129	PCR-RFLP	GG↑	Associated	Hekim *et al.*,2019 [47]
	rs16947	China	Blood	310	170	PCR-RFLP	NA	No Association	Zhang *et al.*,2022 [46]
GPX1	rs1050450	Iran	Blood	100	150	PCR-RFLP	NA	No association	Mazjin *et al.*,2016 [50]
		Spain	Semen	313	80	PCR-RFLP	NA	No association	Rodríguez *et al.*,2019 [20]
		Iran	Semen	223	154	PCR-RFLP	T↓	Associated	Fallah *et al.*,2023 [22]
	rs1800668	China	Blood	580	580	Chip based	NA	No association	Ji *et al.*,2012 [23]
GPX3	rs8177404	Iran	Semen	100	100	ARMS-PCR	C↑	Associated	Pournasir *et al.*,2021 [51]
	rs3828599	Iran	Semen	100	100	ARMS-PCR	G↓	Associated	Pournasir *et al.*,2021 [51]
GSTM1	null	India	Semen	179	200	RT-PCR	NA	No association	Dhillon *et al.*,2007 [52]
		Turkey	Blood	52	60	PCR based	null ↑	Associated	Aydemir *et al.*,2007 [53]
		Turkey	Blood	110	105	Multiplex PCR	null ↑	Associated	Aydos *et al.*,2009 [45]
		Iran	Blood	166	166	PCR-RFLP	null ↑	Associated	Safarinejad *et al.*,2010 [27]
		Russia	Blood	203	227	Multiplex PCR	NA	No association	Polonikov *et al.*,2010 [54]
		Slovenia	Blood	187	194	PCR-RFLP	NA	No association	Volk *et al.*,2011 [55]
		India	Blood	113	91	PCR based	null↓	Associated	Jaiswal *et al.*,2012 [56]
		Iran	Blood	150	200	Multiplex PCR	null ↑	Associated	Salehi *et al.*,2012 [38]
		Iran	Blood	95	26	PCR-RFLP	NA	No association	Lakpour *et al.*,2013 [57]
		China	Blood	353	201	Multiplex PCR	null ↑	Associated	Xu *et al.*,2013 [58]
		China	Blood	1476	895	PCR based	NA	No Association	Wu *et al.*,2013 [59]
		Egypt	Blood	60	60	PCR-RFLP	NA	No association	Roshdy *et al.*,2014 [60]
		China	Blood	479	234	Multiplex PCR	NA	No association	Xiong *et al.*,2015 [61]
		Iran	Blood	51	52	Multiplex PCR	null↑	Associated	Fatahi *et al.*,2016 [62]
		Spain	Semen	313	80	Multiplex PCR	NA	No association	Rodríguez *et al.*,2019 [20]
		Turkey	Blood	306	129	Multiplex PCR	NA	No association	Hekim *et al.*,2019 [47]
		Iran	Semen	193	157	Multiplex PCR	null↑	Associated	Barati *et al.*,2020 [63]
		China	Blood	246	117	PCR-RFLP	null ↑	Associated	Zhang *et al.*,2021 [64]
		China	Blood	310	170	PCR-RFLP	null ↑	Associated	Zhang *et al.*,2022 [46]
		China	Blood	215	345	Multiplex PCR	null↓	Associated	He *et al.*,2023 [65]
		Greece	Semen	51	39	PCR based	null↑	Associated	Potiris *et al.*,2023 [66]
	rs1192077068	Iran	Blood	120	120	ARMS-PCR	NA	No association	Ghadirkhomi *et al.*,2021 [67]
GSTT1	null	China	Blood	181	156	Multiplex PCR	null↑	Associated	Wu *et al.*,2008 [68]
		Turkey	Blood	110	105	Multiplex PCR	NA	Associated	Aydos *et al.*,2009 [45]
		Iran	Blood	166	166	PCR-RFLP	null ↑	Associated	Safarinejad *et al.*,2010 [27]
		Russia	Blood	203	227	Multiplex PCR	NA	No Association	Polonikov *et al.*,2010 [54]
		Slovenia	Blood	187	194	PCR-RFLP	NA	No association	Volk *et al.*,2011 [55]
		India	Blood	113	91	PCR based	null↓	Associated	Jaiswal *et al.*,2012 [56]
		Iran	Blood	150	200	Multiplex PCR	null ↑	Associated	Salehi *et al.*,2012 [38]
		China	Blood	353	201	Multiplex PCR	null ↑	Associated	Xu *et al.*,2013 [58]
		China	Blood	1476	895	PCR based	NA	No Association	Wu *et al.*,2013 [59]
		China	Blood	479	234	Multiplex PCR	NA	No association	Xiong *et al.*,2015 [61]
		Iran	Blood	51	52	Multiplex PCR	null↑	Associated	Fatahi *et al.*,2016 [62]
		Turkey	Blood	306	129	Multiplex PCR	NA	No association	Hekim *et al.*,2019 [47]
		Spain	Semen	313	80	Multiplex PCR	NA	No association	Rodríguez *et al.*,2019 [20]
		Iran	Semen	193	157	Multiplex PCR	null↑	Associated	Barati *et al.*,2020 [63]
		China	Blood	246	117	PCR-RFLP	null ↑	Associated	Zhang *et al.*,2021 [64]
		China	Blood	310	170	PCR-RFLP	null ↑	Associated	Zhang *et al.*,2022 [46]
		China	Blood	215	345	Multiplex PCR	null↓	Associated	He *et al.*,2023 [65]
GSTP1	rs1695	Iran	Blood	166	166	PCR-RFLP	A↓	Associated	Safarinejad *et al.*,2010 [27]
		Iran	Blood	95	26	PCR-RFLP	NA	No association	Lakpour *et al.*,2013 [57]
		China	Blood	479	234	PCR-RFLP	NA	No Association	Xiong *et al.*,2015 [61]
		Vietnam	Blood	150	150	ARMS-PCR	A↑	Associated	Trang *et al.,2018* [69]
		Turkey	Blood	306	129	PCR-RFLP	NA	No association	Hekim *et al.*,2019 [47]
		China	Blood	246	117	PCR-RFLP	A/G+G/G↑	Associated	Zhang *et al.*,2021 [64]
		China	Blood	310	170	PCR-RFLP	NA	No Association	Zhang *et al.*,2022 [46]
		China	Blood	215	345	PCR-RFLP	A↑	Associated	He *et al.*,2023 [65]
	rs1138272	Iran	Blood	95	26	PCR-RFLP	NA	No association	Lakpour *et al.*,2013 [57]
		Vietnam	Blood	150	150	ARMS-PCR	T↑	Associated	Trang *et al.*,2018 [69]
MTHFR	rs1801131	Korea	Blood	373	396	PCR-RFLP	T↑	Associated	Park *et al.*,2005 [70]
		Korea	Blood	360	325	PCR-RFLP	NA	No association	Lee *et al.*,2006 [71]
		India	Semen	179	200	PCR-RFLP	NA	No association	Dhillon *et al.*,2007 [52]
		France	Semen	252	114	PCR-RFLP	NA	No association	Ravel *et al.*,2009 [72]
		India	Blood	151	140	PCR-RFLP	C↑	Associated	Singh *et al.*,2010 [73]
		Iran	Blood	164	328	PCR-RFLP	NA	No association	Safarinejad *et al.*,2011 [74]
		Brazil	Blood	156	233	q-PCR	C↑	Associated	Gava *et al.*,2011 [75]
		Brazil	Blood	133	173	q-PCR	NA	No association	Gava *et al.*,2011 [76]
		Morocco	Blood	344	690	PCR-RFLP	C↑	Associated	Eloualid *et al.*,2012 [77]

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Table 1 (*continued*)

Gene	SNP	Country	Sample type	Cases	Controls	Technique	Risk allele/ Genotype	Inference	Reference
		Russia	Blood	275	349	q-PCR	NA	No Association	Weiner *et al.*,2013 [78]
		India	Blood	630	250	PCR-RFLP	NA	No association	Gupta *et al.*,2013 [79]
		Turkey	Blood	108	125	q-PCR	NA	No association	Balkan *et al.*,2013 [80]
		Jordan	Blood	150	150	PCR-RFLP	NA	No association	Mfady *et al.*,2014 [81]
		Turkey	Blood	137	134	Multiplex PCR	NA	No association	Gürkan *et al.*,2014 [82]
		Korea	Blood	85	246	PCR-RFLP	C↑	Associated	Kim *et al.*,2015 [83]
		China	Blood	296	204	SNaPshot Multiplex	NA	No association	Ni *et al.*,2015 [84]
		Poland	Blood	284	352	q-PCR	NA	No association	Kurzawski *et al.*,2015 [85]
		China	Blood	162	120	PCR based	NA	No association	Li *et al.*,2015 [86]
		Iran	Blood	118	132	PCR-RFLP	NA	No association	Karimian *et al.*,2016 [87]
		Algeria	Blood	89	84	PCR-RFLP	NA	No association	Rezgoune *et al.*,2016 [88]
		China	Blood	1759	1826	PCR-RFLP	C↑	Associated	Wang *et al.*,2017 [42]
		Pakistan	Blood	232	114	PCR-RFLP	C↑	Associated	Ullah *et al.*,2019 [89]
		India	Blood	50	50	Sequencing	C↑	Associated	Balunathan *et al.*,2021 [90]
		Iran	Blood	120	120	ARMS-PCR	NA	No association	Ghadirkhomi *et al.*,2021 [67]
		Egypt	Blood	100	100	ARMS-PCR	C↑	Associated	Barakat *et al.*,2024 [91]
	rs1801133	Italy	Blood	93	105	PCR-RFLP	NA	No association	Stuppia *et al.*,2003 [92]
		India	Blood	151	200	PCR-RFLP	T↑	Associated	Singh *et al.*,2005 [93]
		Korea	Blood	373	396	PCR-RFLP	T↑	Associated	Park *et al.*,2005 [70]
		Korea	Blood	360	325	PCR-RFLP	T↑	Associated	Lee *et al.*,2006 [71]
		India	Semen	179	200	PCR-RFLP	NA	No association	Dhillon *et al.*,2007 [52]
		China	Blood	355	252	PCR-RFLP	T↑	Associated	Yang *et al.*,2007 [94]
		France	Semen	252	114	PCR-RFLP	NA	No association	Ravel *et al.*,2009 [72]
		India	Semen	100	100	PCR-RFLP	NA	No association	Kumar *et al.*,2011 [95]
		India	Blood	206	230	PCR-RFLP	NA	No association	Vani *et al.*,2011 [96]
		Iran	Blood	164	328	PCR-RFLP	T↑	Associated	Safarinejad *et al.*,2011 [74]
		India	Blood	522	315	Sequencing	T↑	Associated	Gupta *et al.*,2011 [97]
		Brazil	Blood	156	233	q-PCR	T↑	Associated	Gava *et al.*,2011 [75]
		Brazil	Blood	133	173	q-PCR	T↑	Associated	Gava *et al.*,2011 [76]
		Algeria	Blood	74	84	PCR-RFLP	NA	No association	Chellat *et al.*,2012 [98]
		Morocco	Blood	344	690	PCR-RFLP	NA	No association	Eloualid *et al.*,2012 [77]
		Russia	Blood	275	349	q-PCR	NA	No association	Weiner *et al.*,2013 [78]
		Turkey	Blood	108	125	q-PCR	NA	No association	Balkan *et al.*,2013 [80]
		India	Blood	637	364	PCR-RFLP	T↑	Associated	Naqvi *et al.*,2014 [99]
		Jordan	Blood	150	150	PCR-RFLP	T↑	Associated	Mfady *et al.*,2014 [81]
		Turkey	Blood	137	134	Multiplex PCR	T↑	Associated	Gürkan *et al.*,2014 [82]
		Korea	Blood	85	246	PCR-RFLP	NA	No association	Kim *et al.*,2015 [83]
		China	Blood	296	204	SNaPshot Multiplex	NA	No association	Ni *et al.*,2015 [84]
		Poland	Blood	284	352	q-PCR	NA	No association	Kurzawski *et al.*,2015 [85]
		Iran	Blood	242	255	PCR-RFLP	T↑	Associated	Nikzad *et al.*,2015 [100]
		China	Blood	162	120	PCR based	NA	No association	Li *et al.*,2015 [86]
		Iran	Blood	118	132	PCR-RFLP	T↑	Associated	Karimian *et al.*,2016 [87]
		Pakistan	Blood	437	218	PCR-RFLP	T↑	Associated	Irfan *et al.*,2016 [101]
		China	Blood	1759	1826	PCR-RFLP	T↑	Associated	Wang *et al.*,2017 [42]
		India	Blood	58	55	PCR-RFLP	C↑	Associated	Anand *et al.*,2017 [102]
		Pakistan	Blood	232	114	PCR-RFLP	T↑	Associated	Ullah *et al.*,2019 [89]
		India	Blood	50	50	Sequencing	NA	No association	Balunathan *et al.*,2021 [90]
		Iran	Blood	254	77	PCR-RFLP	NA	No association	Raigani *et al.*,2021 [103]
		Iraq	Blood	353	100	PCR-RFLP	T↑	Associated	Al Janabi *et al.*,2022 [104]
		Egypt	Blood	100	100	ARMS-PCR	T↑	Associated	Barakat *et al.*,2024 [91]
	rs2066472	France	Semen	252	114	PCR-RFLP	NA	No association	Ravel *et al.*,2009 [72]
		India	Blood	630	250	PCR-RFLP	NA	No association	Gupta *et al.*,2013 [79]
	rs2274976	Iran	Blood	164	328	PCR-RFLP	NA	No association	Safarinejad *et al.*,2011 [74]
		Brazil	Blood	133	173	q-PCR	NA	No association	Gava *et al.*,2011 [76]
		Iran	Blood	120	120	ARMS-PCR	A↑	Associated	Ghadirkhomi *et al.*,2021 [67]
	rs3818762	India	Blood	630	250	Sequencing	NA	No association	Gupta *et al.*,2013 [79]
MTHFD1	rs2236225	Turkey	Blood	108	125	q-PCR	NA	No association	Balkan *et al.*,2013 [80]
		Russia	Blood	275	349	Multiplex PCR	A↑	Associated	Weiner *et al.*,2013 [78]
		Iran	Blood	100	100	PCR-RFLP	A↑	Associated	Khaki *et al.*,2019 [105]
MTRR	rs1801394	Korea	Blood	360	325	PCR-RFLP	G↑	Associated	Lee *et al.*,2006 [71]
		France	Semen	252	114	PCR-RFLP	NA	No association	Ravel *et al.*,2009 [72]
		Brazil	Blood	133	173	q-PCR	G↑	No association	Gava *et al.*,2011 [76]
		Russia	Blood	275	349	q-PCR	NA	No Association	Weiner *et al.*,2013 [78]
		Turkey	Blood	108	125	q-PCR	NA	No association	Balkan *et al.*,2013 [80]
		Jordan	Blood	150	150	PCR-RFLP	NA	No association	Mfady *et al.*,2014 [81]
		Korea	Blood	85	246	PCR-RFLP	NA	No association	Kim *et al.*,2015 [83]
		China	Blood	296	204	SNaPshot Multiplex	NA	No association	Ni *et al.*,2015 [84]
		Poland	Blood	284	352	q-PCR	NA	No association	Kurzawski *et al.*,2015 [85]
		China	Blood	162	120	PCR based	AG↑	Associated	Li *et al.*,2015 [86]
		Iran	Blood	254	77	PCR-RFLP	NA	No association	Raigani *et al.*,2021 [103]
	rs1532268	France	Semen	252	114	PCR-RFLP	NA	No association	Ravel *et al.*,2009 [72]
MTR	rs1805087	Korea	Blood	360	325	PCR-RFLP	G↑	Associated	Lee *et al.*,2006 [71]
		Brazil	Blood	133	173	q-PCR	G↑	Associated	Gava *et al.*,2011 [76]

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Table 1 (*continued*)

Gene	SNP	Country	Sample type	Cases	Controls	Technique	Risk allele/ Genotype	Inference	Reference
		Russia	Blood	275	349	q-PCR	G↑	Associated	Weiner *et al.*,2013 [78]
		Korea	Blood	85	246	PCR-RFLP	NA	No association	Kim *et al.*,2015 [83]
		China	Blood	296	204	SNaPshot Multiplex	NA	No association	Ni *et al.*,2015 [84]
		Poland	Blood	284	352	q-PCR	NA	No association	Kurzawski *et al.*,2015 [85]
		China	Blood	162	120	PCR based	NA	No association	Li *et al.*,2015 [86]
		Iran	Blood	217	223	PCR-RFLP	G↑	Associated	Karimian *et al.*,2016 [106]
		Iran	Blood	100	100	PCR-RFLP	NA	No association	Tanoomand *et al.*,2019 [107]
PON1	rs662	Slovenia	Blood	187	194	PCR-RFLP	NA	No association	Volk *et al.*,2011 [55]
		Greece	Semen	120	170	PCR-RFLP	C↑	Associated	Lazaros *et al.*,2011 [108]
		China	Blood	580	580	Chip based	C↑	Associated	Ji *et al.*,2012 [23]
		Iran	Blood	150	150	PCR-RFLP	NA	No association	Tavilani *et al.*,2014 [109]
		Iran	Blood	100	100	PCR-RFLP	T↑	Associated	Rastegar *et al.*,2019 [110]
	rs854560	Slovenia	Blood	187	194	PCR-RFLP	T↑	Associated	Volk *et al.*,2011 [55]
		Greece	Semen	120	170	PCR-RFLP	A↑	Associated	Lazaros *et al.*,2011 [108]
		Iran	Blood	128	77	PCR-RFLP	T↑	Associated	Mortezapour *et al.*,2023 [109]
	rs854552	China	Blood	580	580	Chip based	NA	No association	Ji *et al.*,2012 [23]
PON2	rs7493	Greece	Semen	120	170	PCR-RFLP	C↑	Associated	Lazaros *et al.*,2011 [108]
		Slovenia	Blood	187	194	PCR-RFLP	NA	No association	Volk *et al.*,2011 [55]
		Vietnam	Blood	175	201	PCR-RFLP	NA	No association	Dinh *et al.*,2021 [111]
NAT2	rs1799929	Russia	Blood	203	227	PCR-RFLP	NA	No association	Yarosh *et al.*,2014 [112]
		Vietnam	Blood	150	150	ARMS PCR	T↑	Associated	Trang *et al.*,2018 [69]
	rs1799930	Russia	Blood	203	227	PCR-RFLP	NA	No association	Yarosh *et al.*,2014 [112]
		Vietnam	Blood	150	150	ARMS PCR	A↑	Associated	Trang *et al.*,2018 [69]
Nrf2	rs6721961	Turkey	Blood	100	100	PCR-RFLP	A↑	Associated	Aydos *et al.*,2021 [113]
		Pakistan	Blood	144	144	Multiplex PCR	NA	Associated	Rehman *et al.*,2022 [114]
AHR	rs2066853	Japan	Blood	123	112	PCR based	NA	No association	Watanabe *et al.*,2004 [115]
		Estonia	Blood	112	212	AS-PCR	NA	No association	Merisalu *et al.*,2007 [116]
		China	Semen	580	580	Chip based	NA	No association	Gu *et al.*,2011 [117]
		Iran	Blood	176	352	PCR-RFLP	A↑	Associated	Safarinejad *et al.*,2013 [118]
		Egypt	Blood	120	50	PCR-RFLP	A↑	Associated	Mostafa *et al.*,2017 [119]
		Iran	Blood	135	130	PCR-RFLP	NA	No Association	Aftabi *et al.*,2017 [120]
	rs2158041	China	Semen	580	580	Chip based	G↑	Associated	Gu *et al.*,2011 [117]
	rs1476080	China	Semen	580	580	Chip based	NA	No association	Gu *et al.*,2011[117]
		Iran	Blood	176	352	PCR-RFLP	NA	No association	Safarinejad *et al.*,2013 [118]
	rs2106728	China	Semen	580	580	Chip based	NA	No association	Gu *et al.*,2011 [117]
	rs713150	China	Semen	580	580	Chip based	NA	No association	Gu *et al.*,2011 [117]
	rs6960165	China	Semen	580	580	Chip based	NA	No association	Gu *et al.*,2011 [117]
		Iran	Blood	176	352	PCR-RFLP	NA	No association	Safarinejad *et al.*,2013 [118]
	rs2282885	Iran	Blood	176	352	PCR-RFLP	C↑	Associated	Safarinejad *et al.*,2013 [118]
	rs10250822	Iran	Blood	176	352	PCR-RFLP	NA	No association	Safarinejad *et al.*,2013 [118]
	rs10247158	Iran	Blood	176	352	PCR-RFLP	NA	No association	Safarinejad *et al.*,2013 [118]
	rs7811989	Iran	Blood	176	352	PCR-RFLP	NA	No association	Safarinejad *et al.*,2013 [118]
	rs10249788	Iran	Blood	135	130	PCR-RFLP	NA	No association	Aftabi *et al.*,2017 [120]

summarized in Table 3 and pooled forest plots for analysis are represented in Supplementary Figure 1.

3.2. Quantitative synthesis

3.2.1. CAT rs1001179, rs7943316 gene variants and male infertility risk

A total eight studies investigated the association between the *CAT* gene variant and male infertility risk. Meta-analysis was conducted with 6 studies for rs1001179 with 1342 cases and 700 controls [21,22,17,18–20] (Supplementary Figure 1.1) and with 2 studies for rs7943316 with 632 cases and 623 controls [23,24] (Supplementary Figure 1.2). Results showed that both polymorphisms were not significantly associated with male infertility risk under all genetic models.

3.2.2. SOD2 rs4880 gene variant and male infertility risk

A total of 4 studies were found that examined the role of *SOD2* gene variants and the male infertility risk. Out of them, 4 case-control studies with 1216 cases and 893 controls describe the frequency distribution for the rs4880 variant [21,22,19,23]. Pooled analysis showed a significant association between the rs4880 variant and the male infertility risk under the dominant model (OR = 1.52, 95 % CI = 1.24, 1.84, p = 0.00001), recessive model (OR = 2.12, 95 % CI = 1.35, 3.34, p = 0.001), additive model (OR = 2.80, 95 % CI = 1.73, 4.55, p = 0.0001), and allele model (OR = 1.49, 955 CI = 1.26, 1.75, p = 0.00001) (Supplementary Figure 1.3).

3.2.3. GPX1 rs1050450 gene variant and male infertility risk

A total of 4 studies investigated the association between *GPX1* gene variants and male infertility risk. For the rs1050450 gene variant, we obtained allele frequency distribution from 3 eligible studies with 616 cases and 384 controls [22,20,50]. Meta-analysis results found that this variant is not statistically significant with the risk of male infertility under all four genetic models namely; the dominant model, recessive model additive model, and allele model (Supplementary Figure 1.4).

3.2.4. CYP1A1 rs1048943, rs4646903 gene variants and male infertility risk

We found a total of 11 studies that investigated the *CYP1A1* gene polymorphisms and male infertility risk. Meta-analysis for rs1048943 variant was performed based on 5 eligible studies with 750 cases and 817 controls [45,44,36,39,43]. Insignificant association was found between selected gene polymorphism and male infertility risk under all studied genetic models (Supplementary Figure 1.5). For another variant rs4646903, we obtained 9 studies with 2975 cases and 3148 controls [44,36,39,43,40,41,37,38,42]. A significant association was found between the rs4646903 variant and increased male infertility risk under the dominant model (OR = 1.38, 95 % CI = 1.08, 1.76 p = 0.009), recessive model (OR = 1.47, 95 % CI = 1.02, 2.13, p = 0.04), and

Table 2
Genotype distribution of studies included in present meta-analysis.

Author	Sample size		Genotype distribution									
	Cases	Controls	Cases					Controls				
***CAT* (rs1001179)**			**CC**	**CT**	**TT**	**C**	**T**	**CC**	**CT**	**TT**	**C**	**T**
Bach *et al.*,2023 [21]	107	85	88	18	1	194	20	75	10	0	160	10
Fallah *et al.*,2023 [22]	223	154	159	56	8	374	72	114	34	6	262	46
Sabouhi *et al.*,2014 [17]	195	190	62	127	6	251	139	47	105	38	199	181
Bousnane *et al.*,2017 [18]	104	111	77	24	3	178	30	82	25	4	189	33
Rodríguez *et al.*,2019 [20]	313	80	215	82	16	512	114	40	37	3	117	43
Rodríguez *et al.*,2018 [19]	400	80	263	119	18	645	155	40	37	3	117	43
***CAT* (rs7943316)**			**AA**	**AT**	**TT**	**A**	**T**	**AA**	**AT**	**TT**	**A**	**T**
Sadia *et al.*,2021 [24]	55	50	13	3	39	29	81	31	12	7	74	26
Ji *et al.*,2012 [23]	577	573	285	235	57	805	349	294	231	48	819	327
***SOD2* (rs4880)**			**TT**	**TC**	**CC**	**T**	**C**	**TT**	**TC**	**CC**	**T**	**C**
Bach *et al.*,2023 [21]	107	85	51	48	8	150	64	56	27	2	139	31
Fallah *et al.*,2023 [22]	223	154	151	62	10	364	82	118	33	3	269	39
Ji *et al.*,2012 [23]	573	574	390	160	23	940	206	442	123	9	1007	141
Rodríguez *et al.*,2019 [20]	313	80	94	150	69	338	288	23	45	12	91	69
***GPX1* (rs1050450)**			**CC**	**CT**	**TT**	**C**	**T**	**CC**	**CT**	**TT**	**C**	**T**
Fallah *et al.*,2023 [22]	223	154	101	96	26	298	148	43	95	16	181	127
Rodríguez *et al.*,2019 [20]	293	80	139	138	16	416	170	31	38	11	100	60
Mazjin *et al.*,2016 [50]	100	100	13	76	11	102	98	36	101	13	173	127
***CYP1A1* (rs1048943)**			**AA**	**AG**	**GG**	**A**	**G**	**AA**	**AG**	**GG**	**A**	**G**
Aydos *et al.*,2009 [45]	110	105	78	30	2	186	34	95	10	0	200	10
Saatovich *et al.*,2023 [44]	140	155	84	50	6	218	62	116	37	2	269	41
Lu *et al.*,2008 [36]	192	226	114	61	17	289	95	106	102	18	314	138
Javidan *et al.*,2018 [43]	105	104	10	89	6	109	101	5	98	1	108	100
Yarosh *et al.*,2013 [39]	203	227	153	49	1	355	51	193	33	1	419	35
***CYP1A1* (rs4646903)**			**TT**	**TC**	**CC**	**T**	**C**	**TT**	**TC**	**CC**	**T**	**C**
Nejati *et al.*,2016 [40]	100	100	48	34	18	130	70	64	28	8	156	44
Ramgir *et al.*,2017 [41]	120	80	40	70	10	150	90	52	27	1	131	29
Javidan *et al.*,2018 [43]	105	104	55	41	9	151	59	66	36	2	168	40
Yarosh *et al.*,2013 [39]	203	227	165	35	3	365	41	176	48	3	400	54
Lu *et al.*,2008 [36]	192	226	69	96	27	234	150	95	104	27	294	1588
Wang *et al.*,2017 [42]	1759	1826	625	860	274	2110	1408	723	849	254	2295	1357
Salehi *et al.*,2012 [38]	150	200	58	72	20	188	112	85	91	24	261	139
Vani *et al.*,2009 [37]	206	230	108	80	18	296	116	146	80	4	372	88
Saatovich *et al.*,2023 [44]	140	155	7	48	85	62	218	4	47	104	55	255
***GSTP1* (rs1695)**			**AA**	**AG**	**GG**	**A**	**G**	**AA**	**AG**	**GG**	**A**	**G**
Hekim *et al.*,2019 [47]	306	129	146	138	22	430	182	65	49	15	179	79
Xiong *et al.*,2015 [61]	479	234	249	221	9	718	239	146	83	5	375	93
Safarinejad *et al.*,2010 [27]	166	166	102	59	5	263	69	86	76	4	248	84
Zhang *et al.*,2021 [64]	246	117	167	79	0	413	79	85	32	0	202	32
He *et al.*,2023 [65]	215	345	135	80	0	350	80	224	121	0	569	121
Zhang *et al.*,2022 [46]	310	170	210	69	31	489	131	114	40	16	268	72
Trang *et al.*,2018 [69]	150	150	76	55	19	207	93	126	24	0	276	24
***MTHFR* (rs1801133)**			**CC**	**CT**	**TT**	**C**	**T**	**CC**	**CT**	**TT**	**C**	**T**
Barakat *et al.*,2024 [91]	100	100	1	56	43	58	142	60	40	0	160	40
Dhillon *et al.*,2007 [52]	179	200	81	77	21	239	119	70	100	30	240	160
Wang *et al.*,2017 [42]	1759	1826	513	907	339	1933	1585	638	887	301	2163	1489
Balkan *et al.*,2013 [80]	108	125	57	40	11	154	62	78	36	11	192	58
Weiner *et al.*,2013 [78]	271	301	129	116	26	374	168	153	115	33	421	181
Stuppia *et al.*,2003 [92]	93	105	37	37	19	111	75	33	43	29	210	109
Mfady *et al.*,2014 [81]	150	150	67	63	20	197	103	74	67	9	215	85
Park *et al.*,2005 [70]	373	396	105	205	63	415	331	145	200	51	490	302
Karimian *et al.*,2016 [87]	118	132	51	59	8	161	75	77	52	3	206	58
Gupta *et al.*,2011 [97]	522	315	378	116	28	872	172	251	58	6	560	70
Ravel *et al.*,2009 [72]	250	114	118	101	31	337	163	49	52	13	150	78
Kumar *et al.*,2011 [95]	100	100	86	14	0	186	14	81	19	0	181	19
Naqvi *et al.*,2014 [99]	637	364	447	154	36	1048	226	275	79	10	629	99
Kim *et al.*,2015 [83]	85	246	30	44	11	104	66	87	106	53	280	212
Ni *et al.*,2015 [84]	296	204	117	135	44	369	223	84	94	26	260	144
Singh *et al.*,2005 [93]	151	200	105	40	6	250	52	163	37	0	363	37
Vani *et al.*,2011 [96]	206	230	158	42	6	179	27	188	42	0	209	21
Safarinejad *et al.*,2011 [74]	164	328	58	80	26	196	132	144	148	36	436	220
Lee *et al.*,2006 [71]	360	325	115	181	64	411	309	118	166	41	402	248
Balunathan *et al.*,2021 [90]	50	50	33	15	2	81	19	42	6	2	90	10

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Table 2 (*continued*)

Author	Sample size		Genotype distribution									
	Cases	Controls	Cases					Controls				
***CAT* (rs1001179)**			**CC**	**CT**	**TT**	**C**	**T**	**CC**	**CT**	**TT**	**C**	**T**
Yang *et al.*,2007 [94]	355	252	130	160	65	420	290	128	95	29	351	153
Chellat *et al.*,2012 [98]	74	84	31	33	10	95	53	36	38	10	110	58
Eloualid *et al.*,2012 [77]	344	450	199	125	20	523	165	351	286	53	988	392
Gava *et al.*,2011 [75]	156	233	81	60	15	222	90	167	53	13	387	79
Raigani *et al.*,2021 [103]	254	77	152	87	15	152	102	33	36	8	33	44
Kurzawski *et al.*,2015 [85]	284	352	143	113	28	399	169	166	150	36	482	222
Gava *et al.*,2011 [76]	133	173	66	51	16	183	83	136	27	10	299	47
Li *et al.*,2015 [86]	162	120	61	77	24	199	125	48	54	18	150	90
Ullah *et al.*,2019 [89]	232	114	169	53	10	391	73	99	12	3	210	18
Irfan *et al.*,2016 [101]	437	218	285	136	16	706	168	187	30	1	404	32
Al Janabi *et al.*,2022 [104]	353	100	167	116	70	450	256	70	25	5	165	35
Nikzad *et al.*,2015 [100]	242	255	109	109	24	327	157	144	98	13	386	124
Gürkan *et al.*,2014 [82]	137	134	70	49	18	189	85	71	55	8	197	71
Anand *et al.*,2017 [102]	58	55	23	28	7	74	42	38	17	0	93	17
***MTHFR* (rs1801131)**			**AA**	**AC**	**CC**	**A**	**C**	**AA**	**AC**	**CC**	**A**	**C**
Barakat *et al.*,2024 [91]	100	100	3	29	68	35	165	22	39	39	83	117
Dhillon *et al.*,2007 [52]	179	200	90	80	9	260	98	103	84	13	290	110
Wang *et al.*,2017 [42]	1759	1826	957	670	132	2584	934	1097	632	97	2826	826
Balkan *et al.*,2013 [80]	108	125	47	42	19	136	80	45	56	24	146	104
Weiner *et al.*,2013 [78]	274	314	126	125	23	377	171	142	142	30	426	202
Mfady *et al.*,2014 [81]	150	150	71	61	18	203	97	59	75	16	193	107
Park *et al.*,2005 [70]	373	396	237	118	18	592	154	269	111	16	649	143
Karimian *et al.*,2016 [87]	118	132	59	44	15	162	74	70	48	14	188	76
Gupta *et al.*,2013 [79]	611	136	165	320	126	650	572	27	74	35	128	144
Ravel *et al.*,2009 [72]	250	113	131	94	25	356	144	54	46	13	154	72
Kim *et al.*,2015 [83]	85	246	52	28	5	132	38	184	56	6	424	68
Ni *et al.*,2015 [84]	296	204	181	106	9	468	124	137	62	5	336	72
Safarinejad *et al.*,2011 [74]	164	328	75	70	19	220	108	149	141	38	439	217
Lee *et al.*,2006 [71]	360	325	222	120	18	564	156	213	98	14	524	126
Balunathan *et al.*,2021 [90]	40	46	12	24	4	48	32	8	24	14	40	52
Eloualid *et al.*,2012 [77]	344	450	205	122	17	532	156	370	303	17	1043	337
Gava *et al.*,2011 [75]	156	233	71	62	23	204	108	130	89	14	349	117
Kurzawski *et al.*,2015 [85]	284	352	128	130	26	386	182	156	156	40	468	236
Gava *et al.*,2011 [76]	133	173	30	67	36	127	139	18	121	34	157	189
Li *et al.*,2015 [86]	162	120	101	54	7	256	68	80	38	2	198	42
Ullah *et al.*,2019 [89]	237	109	59	133	45	251	223	47	59	3	153	65
Rezgoune *et al.*,2016 [88]	89	84	53	34	2	140	38	43	40	1	126	42
Gürkan *et al.*,2014 [82]	137	134	63	59	15	185	89	49	66	19	164	104
Singh *et al.*,2010 [73]	151	140	66	76	9	208	94	64	74	2	202	78
***MTHFR* (rs2274976)**			**GG**	**GA**	**AA**	**G**	**A**	**GG**	**GA**	**AA**	**G**	**A**
Ghadirkhomi *et al.*,2021 [67]	120	120	32	56	32	120	120	40	76	4	156	84
Safarinejad *et al.*,2011 [74]	164	328	151	13	0	315	13	304	24	0	632	24
Gava *et al.*,2011 [76]	133	173	126	6	1	258	8	161	12	0	334	12
***MTHFR* (rs2066472)**			**GG**	**GA**	**AA**	**G**	**A**	**GG**	**GA**	**AA**	**G**	**A**
Gupta *et al.*,2013 [79]	623	201	618	3	2	1239	7	201	0	0	402	0
Ravel *et al.*,2009 [72]	252	114	244	6	2	494	10	113	1	0	227	1
***MTHFD1* (rs2236225)**			**GG**	**GA**	**AA**	**G**	**A**	**GG**	**GA**	**AA**	**G**	**A**
Balkan *et al.*,2013 [80]	108	125	35	57	16	127	89	44	61	20	149	101
Khaki *et al.*,2019 [105]	100	100	25	45	30	95	105	37	42	21	116	84
Weiner *et al.*,2013 [78]	270	344	90	124	56	304	236	87	174	83	348	340
***MTRR* (rs1801394)**			**AA**	**AG**	**GG**	**A**	**G**	**AA**	**AG**	**GG**	**A**	**G**
Balkan *et al.*,2013 [80]	108	125	36	52	20	124	92	35	61	29	131	119
Weiner *et al.*,2013 [78]	272	324	54	136	82	244	300	57	170	97	284	364
Mfady *et al.*,2014 [81]	150	150	48	78	24	174	126	61	67	22	189	111
Ravel *et al.*,2009 [72]	239	111	27	132	80	186	292	12	57	42	81	141
Kim *et al.*,2015 [83]	85	246	52	29	4	133	37	125	107	14	357	135
Ni *et al.*,2015 [84]	296	204	158	119	19	435	157	99	91	14	289	119
Lee *et al.*,2006 [71]	360	325	64	250	46	378	342	72	224	29	368	282
Raigani *et al.*,2021 [103]	254	77	56	154	44	266	242	20	47	10	87	67
Kurzawski *et al.*,2015 [85]	284	352	51	139	94	241	327	70	171	111	311	393
Gava *et al.*,2011 [76]	133	173	37	62	34	136	130	59	84	30	202	144
Li *et al.*,2015 [86]	162	120	83	65	14	231	93	70	44	6	184	56
***CYP2D6* (rs3892097)**			**GG**	**AG**	**AA**	**G**	**A**	**GG**	**AG**	**AA**	**G**	**A**
Hekim *et al.*,2019 [47]	306	129	232	67	7	531	81	76	43	10	195	63
Zalata *et al.*,2014 [49]	231	77	150	27	54	327	135	60	11	6	131	23

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Table 2 (*continued*)

Author	Sample size		Genotype distribution									
	Cases	Controls	Cases					Controls				
***CAT* (rs1001179)**			**CC**	**CT**	**TT**	**C**	**T**	**CC**	**CT**	**TT**	**C**	**T**
***PON1* [rs854560]**			**TT**	**TA**	**AA**	**T**	**A**	**TT**	**TA**	**AA**	**T**	**A**
Volk *et al.*,2011 [55]	187	194	73	93	21	239	135	97	87	10	281	107
Lazaros *et al.*,2011 [108]	120	170	40	64	16	144	96	86	70	14	242	98
Mortezapour *et al.*,2023 [109]	128	78	28	84	16	140	116	38	39	1	115	41
***PON1* (rs662)**			**AA**	**AG**	**GG**	**A**	**G**	**AA**	**AG**	**GG**	**A**	**G**
Volk *et al.*,2011 [55]	187	194	98	74	15	270	104	91	90	13	272	116
Lazaros *et al.*,2011 [108]	120	170	44	64	12	152	88	88	74	8	250	90
Tavilani *et al.*,2014 [121]	150	150	94	48	8	236	64	86	59	5	231	69
Ji *et al.*,2012 [23]	574	571	97	272	205	466	682	79	252	240	410	732
Rastegar *et al.*,2019 [110]	100	100	67	27	6	161	39	46	39	15	131	69
***PON2* (rs7493)**			**GG**	**GC**	**CC**	**G**	**C**	**GG**	**GC**	**CC**	**G**	**C**
Volk *et al.*,2011 [55]	187	194	106	72	9	284	90	92	85	17	269	119
Lazaros *et al.*,2011 [108]	120	170	66	37	17	169	71	107	60	3	274	66
Dinh *et al.*,2021 [111]	80	98	54	24	2	132	28	68	29	1	165	31
***NAT2* (rs1799930)**			**GG**	**GA**	**AA**	**G**	**A**	**GG**	**GA**	**AA**	**G**	**A**
Trang *et al.*,2018 [69]	150	150	61	82	7	204	96	108	42	0	258	42
Yarosh *et al.*,2014 [112]	203	227	103	88	12	294	112	128	82	17	338	116
***NRF2* (rs6721961)**			**CC**	**CA**	**AA**	**C**	**A**	**CC**	**CA**	**AA**	**C**	**A**
Aydos *et al.*,2021 [113]	100	100	38	48	14	124	76	59	38	3	156	44
Rehman *et al.*,2022 [114]	33	111	14	10	9	38	28	86	22	3	194	28
***AHR* (rs2066853)**			**GG**	**GA**	**AA**	**G**	**A**	**GG**	**GA**	**AA**	**G**	**A**
Gu *et al.*,2011 [117]	567	573	255	231	81	741	393	249	244	80	742	404
Safarinejad *et al.*,2013 [118]	176	352	73	89	14	235	117	131	152	69	414	290
Mostafa *et al.*,2017 [119]	120	50	43	21	56	107	133	28	15	7	71	29
Aftabi *et al.*,2017 [120]	135	130	68	62	5	198	72	73	53	4	199	61
Watanabe *et al.*,2004 [115]	123	112	36	64	23	136	110	32	58	22	122	102
Merisalu *et al.*,2007 [116]	110	211	96	14	0	206	14	175	36	0	386	36
***AHR* (rs1476080)**			**AA**	**AC**	**CC**	**A**	**C**	**AA**	**AC**	**CC**	**A**	**C**
Gu *et al.*,2011 [117]	572	568	178	260	134	616	528	188	269	111	645	491
Safarinejad *et al.*,2013 [118]	176	352	128	41	7	297	55	274	66	12	614	90
***AHR* (rs6960165)**			**AA**	**AG**	**GG**	**A**	**G**	**AA**	**AG**	**GG**	**A**	**G**
Gu *et al.*,2011 [117]	566	568	295	229	42	819	313	308	212	48	828	308
Safarinejad *et al.*,2013 [118]	176	352	104	54	18	262	90	221	105	26	547	157
***GSTM1* (null)**			**Cases**					**Controls**				
			Present		**Null**			**Present**		**Null**		
Aydos *et al.*,2009 [45]	110	105	51		59			63		42		
Salehi *et al.*,2012 [38]	150	200	58		92			134		66		
Zhang *et al.*,2021 [64]	246	117	97		149			68		49		
Xiong *et al.*,2015 [61]	479	234	232		247			115		119		
Wu *et al.*,2013 [59]	1476	895	893		583			569		326		
Polonikov *et al.*,2010 [54]	203	227	89		114			107		120		
Zhang *et al.*,2022 [46]	310	170	126		184			109		61		
Aydemir *et al.*,2007 [53]	52	60	25		27			32		28		
He *et al.*,2023 [65]	215	345	131		84			141		204		
Barati *et al.*,2020 [63]	193	157	184		9			157		0		
Safarinejad *et al.*,2010 [27]	166	166	93		73			120		46		
Jaiswal *et al.*,2012 [56]	113	91	84		29			60		31		
Dhillon *et al.*,2007 [52]	179	200	120		59			124		76		
Potiris *et al.*,2023 [66]	51	39	31		20			16		23		
Roshdy *et al.*,2014 [60]	60	60	36		24			40		20		
Lakpour *et al.*,2013 [57]	94	26	45		49			12		14		
Volk *et al.*,2011 [55]	187	194	90		97			102		92		
Xu *et al.*,2013 [58]	353	201	115		238			85		116		
Rodríguez *et al.*,2019 [20]	313	80	151		162			43		37		
Fatahi *et al.*,2016 [62]	51	52	37		14			47		5		
***GSTT1* (null)**												
Aydos *et al.*,2009 [45]	110	105	90		20			85		20		
Salehi *et al.*,2012 [38]	150	200	99		51			166		34		
Zhang *et al.*,2021 [64]	246	117	92		154			61		56		
Xiong *et al.*,2015 [61]	479	234	230		249			124		110		
Wu *et al.*,2013 [59]	1476	895	805		671			536		359		

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Table 2 (*continued*)

Author	Sample size		Genotype distribution									
	Cases	Controls	Cases					Controls				
***CAT* (rs1001179)**			**CC**	**CT**	**TT**	**C**	**T**	**CC**	**CT**	**TT**	**C**	**T**
Polonikov *et al.*,2010 [54]	203	227	202		1			198		29		
Zhang *et al.*,2022 [46]	310	170	118		192			92		78		
He *et al.*,2023 [65]	215	345	113		102			142		203		
Barati *et al.*,2020 [63]	193	157	109		84			142		15		
Safarinejad *et al.*,2010 [27]	166	166	119		47			134		32		
Jaiswal *et al.*,2012 [56]	113	91	107		6			79		12		
Wu *et al.*,2008 [68]	181	156	121		60			76		80		
Volk *et al.*,2011 [55]	187	194	152		35			148		46		
Xu *et al.*,2013 [58]	353	201	135		218			107		94		
Rodríguez *et al.*,2019 [20]	313	80	246		67			63		17		
Fatahi *et al.*,2016 [62]	51	52	30		21			45		7		

additive model (OR = 1.80, 95 % CI = 1.14, 2.84, p = 0.01). No association was found under the allele model (OR = 1.02, 95 % CI = 0.55, 1.92, p = 0.94) (Supplementary Figure 1.6).

3.2.5. *GSTP1 rs1695 gene variant and male infertility risk*

A total of 9 studies investigated the role of *GSTP1* gene polymorphisms and their correlation with infertility in males. The association of rs1695 variant with male infertility was evaluated in total 7 studies with 1872 cases and 1311 controls [47,61,27,64,65,46,69]. No significant association was found between rs1695 variant and the risk of male infertility under any of the genetic models namely, the dominant model (OR =1.32, 95 % CI = 0.89, 1.94, p = 0.16), except for the recessive model (OR =1.14, 95 % CI = 0.52, 2.49, p = 0.75), additive model (OR =1.30, 95 % CI = 0.56, 3.00, p = 0.54), and allele model (OR = 1.28, 95 % CI = 0.90, 1.83, p = 0.18) (Supplementary Figure 1.7).

3.2.6. *MTHFR rs1801133, rs1801131, rs2274976, rs2066472 gene variants and male infertility risk*

The association of *MTHFR* gene with male infertility risk was evaluated by total 40 studies. Meta-analysis was conducted with 34 eligible studies for rs1801133 variant involving 9193 cases and 8860 controls [42,91,52,80,78,92,81,70,87,95,99,83,84,93,96,74,71,90,94,98,77,75,103,85,76,86,89,101,104,100,82,102,88,79,72]. The results suggested that rs1801133 variant is significantly related with increased risk of male infertility under the dominant model (OR = 1.41, 95 % CI = 1.14, 1.74, p = 0.001), additive model (OR = 1.59, 95 % CI = 1.26, 2.01, p = 0.0001), and allele model (OR = 1.41, 95 % CI = 1.23, 1.61, p = 0.00001), except for recessive model (OR = 1.24, 95 % CI = 0.92, 1.67, p = 0.15) (Supplementary Figure 1.8). Allele frequency data distribution for the rs1801131 variant was compiled from a total of 24 studies with 6544 cases and 6676 controls [42,91,52,80,78,81,70,87,83,84,74,71,90,77,75,85,76,86,89,82,88,79,72,73]. There was significant association between studied gene variant and male infertility under the recessive model (OR = 1.30, 95 % CI = 1.03, 1.64, p = 0.03), and insignificant association under the dominant model (OR = 0.94, 95 % CI = 0.67, 1.32, p = 0.72), additive model (OR = 1.25, 95 % CI = 0.94, 1.64, p = 0.12) and allele model (OR = 1.07, 95 % CI = 0.95, 1.21, p = 0.26) (Supplementary Figure 1.9). Meta-analysis for another variant rs2274976 was performed based on frequency data obtained from 3 studies with 417 cases and 621 controls [74,76,67]. Significant association was found between rs2274976 variant and increased risk of male infertility under recessive model (OR = 9.70, 95 % CI = 3.52, 26.76, p = 0.0001), additive model (OR = 9.04, 95 % CI = 3.10, 26.33), p = 0.0001), and allele model (OR = 1.53, 95 % CI = 1.13, 2.07, p = 0.005) except for dominant model (OR = 1.15, 95 % CI = 0.77, 1.70, p = 0.49) (Supplementary Figure 1.10). The association of another variant rs2066472 was investigated by 2 studies with 875 cases and 315 controls [72,79]. There is insignificant association between studied variant and the risk of male infertility under all genetic models (Supplementary Figure 1.11).

3.2.7. *MTHFD1 rs2236225 gene variant and male infertility risk*

A total of 3 studies investigated the correlation between rs2236225 gene variant and the risk of male infertility with 478 cases and 569 controls [80,78,105]. Meta-analysis results suggested no significant association between studied variant and male infertility risk under dominant model (OR = 1.06, 95 % CI = 0.60, 1.87, p = 0.84), recessive model (OR = 0.97, 95 % CI = 0.72, 1.31, p = 0.84), additive model (OR = 1.06, 95 % CI = 0.52, 2.16, p = 0.86), and allele model (OR = 1.05, 95 % CI = 0.72, 1.54, p = 0.80) (Supplementary Figure 1.12).

3.2.8. *MTRR rs1801394 gene variant and male infertility risk*

The meta-analysis for rs1801394 gene variant was performed based on the data extracted from total 11 studies with 2343 cases and 2207 controls [80,78,81,83,84,71,103,85,76,86,72]. The results suggested no significant association between studied gene variant and the risk of male infertility under any of the genetic models namely the dominant model (OR = 1.05, 95 % CI = 0.91, 1.20, p = 0.49), recessive model (OR = 1.10, 95 % CI = 0.94, 1.29, p = 0.25), additive model (OR = 1.16, 95 % CI = 0.96, 1.42, p = 0.13), and allele model (OR = 1.05, 95 % CI = 0.96, 1.15, p = 0.28) (Supplementary Figure 1.13).

3.2.9. *CYP2D6 rs3892097 gene variant and male infertility risk*

A total of 3 studies examined the association between the *CYP2D6* gene variant and male infertility. The association of rs3892097 polymorphism was described by 2 studies with 537 cases and 206 controls [47,49]. There was no significant association of studied variant with male infertility risk in any of the genetic models namely, the dominant model (OR = 0.92, 95 % CI = 0.23, 3.73, p = 0.91), recessive model (OR = 1.01, 95 % CI = 0.08, 12.81, p = 0.99), additive model (OR = 0.92, 95 % CI = 0.06, 14.05, p = 0.95), and allele model (OR = 1.05, 95 % CI = 0.21, 5.09, p = 0.96) (Supplementary Figure 1.14).

3.2.10. *PON1 rs854560, rs662 gene variant and male infertility risk*

The association of *PON1* gene variants with the risk of male infertility was evaluated by a total of 7 studies. The meta-analysis of the rs854560 variant was conducted on 3 studies with 435 cases and 442 controls [55,108,109]. The results found a significant association between the studied variant and increased risk of male infertility under the recessive model (OR = 2.49, 95 % CI = 1.50, 4.15, p = 0.0004), additive model (OR = 3.48, 95 % CI = 2.04, 5.91, p = 0.00001), and allele model (OR = 1.70, 95 % CI = 1.39, 2.08, p = 0.00001), and decreased risk under the dominant model (OR = 0.17, 95 % CI = 0.10, 0.23, p = 0.00001) (Supplementary Figure 1.15). The meta-analysis of another variant rs662 was conducted based on data extracted from 5 studies with 1131 cases and 1185 controls [23,55,108,121,110]. There was an insignificant association between the studied variant and male infertility risk under any of the genetic models namely, the dominant

Table 3
Pooled meta-analysis results under four genetic models.

Gene	SNP	No. of studies	Dominant model			Recessive model			Additive model			Allelic model		
			OR (95 % CI)	p value	I^2 (%)	OR (95 % CI)	p value	I^2 (%)	OR (95 % CI)	p value	I^2 (%)	OR (95 % CI)	p value	I^2 (%)
CAT	rs1001179	6	0.78 (0.55,1.12)	0.18	63 %	0.71 (0.27,1.89)	0.49	69 %	0.42 (0.16,1.13)	0.08	71 %	0.77 (0.56,1.04)	0.09	67 %
	rs7943316	2	2.26 (0.48,10.66)	0.30	92 %	4.06 (0.34,48.57)	0.27	95 %	3.84 (0.37,39.86)	0.26	94 %	2.87 (0.41,20.22)	0.29	97 %
SOD2	rs4880	4	1.52 (1.24,1.84)	0.00001 *	31 %	2.12 (1.35,3.34)	0.001 *	0 %	2.80 (1.73,4.55)	0.0001 *	0 %	1.49 (1.26,1.75)	0.00001 *	19 %
GPX1	rs1050450	3	0.85 (0.39,1.87)	0.69	85 %	0.82 (0.38,1.77)	0.62	67 %	0.78 (0.28,2.16)	0.63	76 %	0.85 (0.57,1.28)	0.44	76 %
CYP1A1	rs1048943	5	1.37 (0.67,2.78)	0.39	87 %	1.69 (0.97,2.95)	0.07	1 %	1.37 (0.77,2.44)	0.28	13 %	1.46 (0.90,2.37)	0.13	84 %
	rs4646903	9	1.38 (1.08,1.76)	0.009 *	66 %	1.47 (1.02,2.13)	0.04 *	60 %	1.80 (1.14,2.84)	0.01 *	62 %	1.02 (0.55,1.92)	0.94	98 %
GSTP1	rs1695	7	1.32 (0.89,1.94)	0.16	79 %	1.14 (0.52,2.49)	0.75	65 %	1.30 (0.56,3.00)	0.54	68 %	1.28 (0.90,1.83)	0.18	87 %
MTHFR	rs1801133	34	1.41 (1.14,1.74)	0.001 *	89 %	1.24 (0.92,1.67)	0.15	84 %	1.59 (1.26,2.01)	0.0001 *	70 %	1.41 (1.23,1.61)	0.00001 *	85 %
	rs1801131	24	0.94 (0.67,1.32)	0.72	94 %	1.30 (1.03,1.64)	0.03 *	61 %	1.25 (0.94,1.64)	0.12	67 %	1.07 (0.95,1.21)	0.26	75 %
	rs2274976	3	1.15 (0.77,1.70)	0.49	0 %	9.70 (3.52,26.76)	0.0001 *	0 %	9.04 (3.10,26.33)	0.0001 *	0 %	1.53 (1.13,2.07)	0.005 *	44 %
	rs2066472	2	3.66 (0.67,19.98)	0.13	0 %	1.94 (0.23,16.64)	0.55	0 %	1.96 (0.23,16.81)	0.54	0 %	4.69 (0.88,25.05)	0.07	0 %
MTHFD1	rs2236225	3	1.06 (0.60,1.87)	0.84	75 %	0.97 (0.72,1.31)	0.84	36 %	1.06 (0.52,2.16)	0.86	71 %	1.05 (0.72,1.54)	0.80	75 %
MTRR	rs1801394	11	1.05 (0.91,1.20)	0.49	22 %	1.10 (0.94,1.29)	0.25	0 %	1.16 (0.96,1.42)	0.13	11 %	1.05 (0.96,1.15)	0.28	27 %
CYP2D6	rs3892097	2	0.92 (0.23,3.73)	0.91	93 %	1.01 (0.08,12.81)	0.99	93 %	0.92 (0.06,14.05)	0.95	94 %	1.05 (0.21,5.09)	0.96	96 %
PON1	rs854560	3	0.17 (0.10,0.23)	0.00001 *	44 %	2.49 (1.50,4.15)	0.0004 *	33 %	3.48 (2.04,5.91)	0.00001 *	50 %	1.70 (1.39,2.08)	0.00001 *	28 %
	rs662	5	0.84 (0.57,1.25)	0.39	76 %	0.99 (0.59,1.66)	0.97	59 %	0.95 (0.49,1.83)	0.88	71 %	0.88 (0.65,1.20)	0.43	80 %
PON2	rs7493	3	0.99 (0.63,1.57)	0.98	61 %	2.19 (0.27,18.02)	0.47	86 %	2.09 (0.23,18.98)	0.51	87 %	1.11 (0.62,2.00)	0.72	84 %
NAT2	rs1799930	2	2.15 (0.73,6.28)	0.16	92 %	2.60 (0.12,55.79)	0.54	77 %	3.72 (0.11,124.40)	0.46	82 %	1.77 (0.69,4.53)	0.23	93 %
NRF2	rs6721961	2	2.90 (1.82,4.62)	0.00001 *	45 %	7.56 (2.89,19.80)	0.0001 *	0 %	10.30 (3.83,27.69)	0.00001 *	0 %	3.23 (1.40,7.46)	0.006 *	79 %
AHR	rs2066853	6	0.99 (0.84,1.16)	0.87	43 %	1.12 (0.53,2.35)	0.77	84 %	1.12 (0.53,2.35)	0.77	82 %	1.08 (0.78,1.49)	0.65	81 %
	rs1476080	2	1.15 (0.93,1.42)	0.20	0 %	1.25 (0.95,1.64)	0.10	0 %	1.27 (0.94,1.73)	0.12	0 %	1.15 (0.99,1.33)	0.07	0 %
	rs6960165	2	1.11 (0.91,1.35)	0.30	0 %	1.01 (0.71,1.45)	0.94	39 %	1.06 (0.74,1.53)	0.75	30 %	1.07 (0.92,1.25)	0.39	0 %

Null genotype

	SNP	No. of studies	OR (95 %CI)	p value	I^2 (%)
GSTM1	rs1183423000	20	1.30 (1.02,1.64)	0.03 *	81 %
GSTT1	rs1601993659	16	1.27 (0.93,1.73)	0.14	87 %

Abbreviations used: OR=odds ratio, 95 % CI=confidence interval, *p value < 0.05

model (OR = 0.84, 95 % CI = 0.57, 1.25, p = 0.39), recessive model (OR = 0.99, 95 % CI = 0.59, 1.66, p = 0.97), additive model (OR = 0.95, 95 % CI = 0.49, 1.83, p = 0.88) and allele model (OR = 0.88, 95 % CI = 0.65, 1.20, p = 0.43) (Supplementary Figure 1.16).

3.2.11. *PON2 rs7493 gene variant and male infertility risk*

A total of 3 studies evaluated the correlation between the rs7493 gene variant and the risk of male infertility with 387 cases and 462 controls [55,108,111]. Meta-analysis results found no significant association between the studied variant and the risk of male infertility under any of the studied genetic models (Supplementary Figure 1.17).

3.2.12. *NAT2 rs1799930 gene variant and male infertility risk*

The rs1799930 gene polymorphism was investigated in 2 studies with 353 cases and 377 controls [69,112]. No significant association was observed between the studied variant and male infertility risk under any of the studied genetic models (Supplementary Figure 1.18).

3.2.13. *NRF2 rs6721961 gene variant and male infertility risk*

The association of rs6721961 gene polymorphism was compiled from 2 studies with 133 cases and 211 controls [113,114]. There was significant association between the studied variant and increased male infertility risk under the dominant model (OR = 2.90, 95 % CI = 1.82, 4.62, p = 0.00001), recessive model (OR = 7.56, 95 % CI = 2.89, 19.80, p = 0.0001), additive model (OR = 10.30, 95 % CI = 3.83, 27.69, p = 0.00001), and allele model (OR = 3.23, 95 % CI = 1.40, 7.46, p = 0.006) (Supplementary Figure 1.19).

3.2.14. *AHR rs2066853, rs1476080, rs6960165 gene variant and male infertility risk*

A total of 7 studies investigated the association between *AHR* gene variants and the risk of male infertility. Meta-analysis of 6 studies with 1231 cases and 1428 controls for *r*s2066853 variant [117–120,115,116] suggested insignificant association between studied variant and male infertility risk under the dominant model (OR = 0.99, 95 % CI = 0.84, 1.16, p = 0.87), recessive model (OR = 1.12, 95 % CI = 0.53, 2.35, p = 0.77), additive model (OR = 1.12, 95 % CI = 0.53, 2.35, p = 0.77), and allele model (OR = 1.08, 95 % CI = 0.78, 1.49, p = 0.65) (Supplementary Figure 1.20). For another variant rs1476080, data was extracted from 2 studies with 748 cases and 920 controls [117,118]. No significant association was observed between studied variant and the risk of male infertility under the dominant model (OR = 1.15, 95 % CI = 0.93, 1.42, p = 0.20), recessive model (OR = 1.25, 95 % CI = 0.95, 1.64, p = 0.10), additive model (OR = 1.27, 95 % CI = 0.94, 1.73, p = 0.12), and allele model (OR = 1.15, 95 % CI = 0.99, 1.33, p = 0.07) (Supplementary Figure 1.21). The association of rs6960165 gene variant was compiled from 2 studies with 742 cases and 920 controls [117,118]. The meta-analysis results found insignificant association between studied variant and the risk of male infertility under the dominant model (OR = 1.11, 95 % CI = 0.91, 1.35, p = 0.30), recessive model (OR = 1.01, 95 % CI = 0.71, 1.45, p = 0.94), additive model (OR = 1.06, 95 % CI = 0.74, 1.53, p = 0.75), and allele model (OR = 1.07, 95 % CI = 0.92, 1.25, p = 0.39) (Supplementary Figure 1.22).

3.2.15. *GSTM1 null genotype and male infertility risk*

A total of 22 studies have examined the association between the *GSTM1* gene and male infertility risk. For *GSTM1* null genotype, meta-analysis was conducted based on the data obtained from a total of 20 studies with 5001 cases and 3619 controls [20,45,38,61,27,64,65,46,52,55,60,58,56,57,63,53,54,66,62,59]. Results found a significant association between the *GSTM1* null genotype and the risk of male infertility (OR = 1.30, 95 % CI = 1.02, 1.64, p = 0.03) (Supplementary Figure 1.23).

3.2.16. *GSTT1 null genotype and male infertility risk*

The association of the *GSTT1* gene variant and male infertility was observed in 17 studies. For *GSTT1* null genotype, meta-analysis was performed based on 16 studies with 4746 cases and 3390 controls [20,45,38,61,27,64,65,46,55,58,56,63,54,62,59,68]. The results indicate no significant association between the studied variant and the risk of male infertility (OR = 1.27, 95 % CI = 0.93, 1.73, p = 0.14) (Supplementary Figure 1.24).

3.3. *Subgroup analysis*

The association between studied gene polymorphisms and male infertility risk was further categorized based on ethnicity for comparison of the Asian vs. non-Asian population (Table 4). Subgroup analysis was conducted only for *CAT* rs1001179, *MTHFR* rs1801133, rs1801131, *MTRR* rs1801394, *PON1* rs662, *AHR* rs2066853, null *GSTM1*, and null *GSTT1*, based upon the availability of sufficient number of studies to perform the analysis. Forest plots for pooled analysis are represented in Supplementary Figure 3. Significant association was observed for *CAT* rs1001179 gene variant which was significantly associated with decreased male infertility risk among non-Asian population under the dominant model (OR = 0.60, 95 % CI = 0.39, 0.92, p = 0.02), and Asian population under the additive model (OR = 0.14, 95 % CI= 0.08, 0.26, p = 0.00001). No significant association was observed in overall analysis of population (Supplementary Figure 3.1). Another polymorphism *MTHFR* rs1801133 was significantly associated with increased risk of male infertility among Asian population and overall population analysis under the dominant model (OR = 1.43, 95 % CI = 1.15, 1.79, p = 0.002; OR = 1.41, 95 % CI = 1.14, 1.74, p = 0.001), additive model (OR = 1.57, 95 % CI = 1.25, 1.97, p = 0.0001; OR = 1.59, 95 % CI = 1.26, 2.01, p = 0.0001), and allele model (OR = 1.32, 95 % CI = 1.17, 1.49, p = 0.00001; OR = 1.41, 95 % CI = 1.23, 1.61, p = 0.00001) respectively (Supplementary Figure 3.2). For another gene variant rs1801131 of *MTHFR,* significant increased risk of male infertility was observed among non-Asian and overall population under the recessive model (OR = 1.74, 95 % CI = 1.07, 2.84, p = 0.03; OR = 1.30, 95 % CI = 1.03, 1.64, p = 0.03). However, no association was found among the Asian population under all four models (Supplementary Figure 3.3). Meta-analysis for *PON1* rs662 gene polymorphism suggested a significantly decreased risk of male infertility among the Asian population under the dominant model (OR = 0.71, 95 % CI = 0.56, 0.90, p = 0.005), and recessive model (OR = 0.76, 95 % CI = 0.60, 0.95, p = 0.02). No such association was found among non-Asian and overall population analysis in any of the four studied genetic models (Supplementary Figure 3.5). In the case of null *GSTM1*, a significant association between the studied gene variant and increased risk of male infertility was found among Asians (OR = 1.37, 95 % CI = 1.04, 1.81, p = 0.03) and overall population analysis (OR = 1.30, 95 % CI = 1.02, 1.64, p = 0.03) (Supplementary Figure 3.7). The association was absent for *MTRR* rs1801394, *AHR* rs2066853, and null *GSTT1*.

3.4. *Sensitivity analysis and publication bias*

Sensitivity analysis was performed to examine the impact of individual studies on overall meta-analysis results by the "leave-one-out" method to assess the consistency of results obtained. The findings suggested that the significance of pooled ORs for the *CAT, SOD2* rs4880, *CYP1A1* rs4646903, *GSTP1* rs1695, *MTHFD1* rs2236225, *MTRR* rs1801394, *PON1* rs854560, *AHR* rs2066853 gene variants were not affected after removing individual studies one by one. In the case of *GPX1* after removing one study [50] from the analysis, the rs1050450 gene variant becomes statistically significant under the dominant model (OR = 0.56, 95 % CI = 0.38, 0.83, p = 0.004) and allele model (OR = 0.70, 95 % CI = 0.55, 0.88, p = 0.002). Similarly, after removing Lu *et al.*, 2008 [36], the results become significant for *CYP1A1* rs1048943 gene variant under the dominant model (OR = 1.81, 95 % CI = 1.01, 3.23, p = 0.04), recessive model (OR = 3.72, 95 % CI = 1.29, 10.73, p = 0.02), additive model (OR = 3.44, 95 % CI = 1.15, 10.32, p = 0.03),

Table 4
Subgroup analysis results based on ethnicity (Asian vs. Non-Asian).

	No. of studies	Dominant model			Recessive model			Additive model			Allelic model		
		OR (95 % CI)	p value	I^2 (%)	OR (95 % CI)	p value	I^2 (%)	OR (95 % CI)	p value	I^2 (%)	OR (95 % CI)	p value	I^2 (%)
***CAT* (rs1001179)**													
Asian	3	0.97 (0.72,1.30)	0.82	49 %	0.48 (0.08,2.70)	0.40	79 %	0.14 (0.08,0.26)	0.00001 *	40 %	0.95 (0.55,1.65)	0.86	78 %
Non-Asian	3	0.60 (0.39,0.92)	0.02 *	51 %	1.15 (0.54,2.44)	0.72	0 %	0.91 (0.42,1.96)	0.81	10 %	0.74 (0.48,1.15)	0.18	65 %
Overall	6	0.78 (0.55,1.12)	0.18	63 %	0.71 (0.27,1.89)	0.49	69 %	0.42 (0.16,1.13)	0.08	71 %	0.77 (0.56,1.04)	0.09	67 %
***MTHFR* (rs1801133)**													
Asian	26	1.43 (1.15,1.79)	0.002 *	88 %	1.28 (0.91,1.80)	0.16	85 %	1.57 (1.25,1.97)	0.0001 *	59 %	1.32 (1.17,1.49)	0.00001 *	75 %
Non-Asian	8	1.43 (0.82,2.50)	0.21	92 %	1.47 (0.84,2.57)	0.18	76 %	1.89 (0.88,4.08)	0.10	86 %	1.73 (1.07,2.79)	0.03	94 %
Overall	34	1.41 (1.14,1.74)	0.001 *	89 %	1.24 (0.92,1.67)	0.15	84 %	1.59 (1.26, 2.01)	0.0001 *	70 %	1.41 (1.23,1.61)	0.00001 *	85 %
***MTHFR* (rs1801131)**													
Asian	17	0.90 (0.57,1.42)	0.66	95 %	1.13 (0.88,1.46)	0.33	51 %	1.15 (0.85,1.56)	0.37	63 %	1.05 (0.92,1.21)	0.45	72 %
Non-Asian	7	0.96 (0.67,1.40)	0.85	79 %	1.74 (1.07,2.84)	0.03 *	72 %	1.57 (0.80,3.06)	0.19	78 %	1.14 (0.85,1.53)	0.38	84 %
Overall	24	0.94 (0.67,1.32)	0.72	94 %	1.30 (1.03,1.64)	0.03 *	61 %	1.25 (0.94,1.64)	0.12	67 %	1.07 (0.95,1.21)	0.26	75 %
***MTRR* (rs1801394)**													
Asian	8	1.02 (0.87,1.19)	0.85	39 %	1.11 (0.90,1.36)	0.34	0 %	1.13 (0.88,1.44)	0.34	19 %	1.03 (0.93,1.15)	0.54	34 %
Non-Asian	3	1.17 (0.88,1.55)	0.28	0 %	1.09 (0.85,1.39)	0.51	41 %	1.23 (0.89,1.72)	0.21	14 %	1.09 (0.93,1.28)	0.30	31 %
Overall	11	1.05 (0.91,1.20)	0.49	22 %	1.10 (0.94,1.29)	0.25	0 %	1.16 (0.96,1.42)	0.13	11 %	1.05 (0.96,1.15)	0.28	27 %
***PON1* (rs662)**													
Asian	3	0.71 (0.56,0.90)	0.005 *	49 %	0.76 (0.60,0.95)	0.02 *	49 %	0.64 (0.31,1.33)	0.23	58 %	0.73 (0.52,1.01)	0.06	67 %
Non-Asian	2	1.21 (0.53,2.74)	0.65	86 %	1.56 (0.87,2.82)	0.14	0 %	1.73 (0.63,4.72)	0.29	62 %	1.20 (0.68,2.11)	0.53	82 %
Overall	5	0.84 (0.57,1.25)	0.39	76 %	0.99 (0.59,1.66)	0.97	59 %	0.95 (0.49,1.83)	0.88	71 %	0.88 (0.65,1.20)	0.43	80 %
***AHR* (rs2066853)**													
Asian	4	0.95 (0.80,1.14)	0.60	0 %	0.77 (0.44,1.35)	0.36	69 %	0.77 (0.44,1.33)	0.35	62 %	0.92 (0.81,1.05)	0.22	47 %
Non-Asian	2	1.27 (0.40,3.99)	0.68	83 %	-	-	-	-	-	-	1.51 (0.37,6.13)	0.56	92 %
Overall	6	0.99 (0.84,1.16)	0.87	43 %	1.12 (0.53,2.35)	0.77	84 %	1.12 (0.53,2.35)	0.77	82 %	1.08 (0.78,1.49)	0.65	81 %

Null genotype	**No. of studies**	**OR (95 %CI)**	**p value**	**I^2 (%)**	**Model used**
GSTM1					
Asian	16	1.37 (1.04,1.81)	0.03 *	84 %	REM
Non-Asian	4	1.11 (0.85,1.45)	0.46	39 %	FEM
Overall	20	1.30 (1.02,1.64)	0.03 *	81 %	REM
GSTT1					
Asian	14	1.34 (0.95,1.89)	0.10	88 %	REM
Non-Asian	2	0.84 (0.57,1.23)	0.36	0 %	FEM
Overall	16	1.27 (0.93,1.73)	0.14	87 %	REM

Abbreviations used: OR=odds ratio, 95 % CI=confidence interval, *p value < 0.05

and allele model (OR = 1.74, 95 % CI = 1.09, 2.76, p = 0.02). For *MTHFR* rs2274976, after removing Ghadirkhomi *et al.*, 2021 [67] and Safarinejad *et al.*, 2011 [74] results become insignificant under allele model (OR = 1.00, 95 % CI = 0.58, 1.73, p = 0.99; OR = 1.00, 95 % CI = 0.58, 1.73, p = 0.99 respectively). After removing Fatahi *et al.*, 2016 [62], OR = 1.26, 95 % CI = 0.99, 1.60, p = 0.06), Safarinezad *et al.*, 2010 [27] (OR = 1.26, 95 % CI = 0.99, 1.61, p = 0.06), Salehi *et al.*, 2012 [38] (OR = 1.22, 95 % CI = 0.98, 1.54, p = 0.08), Zhang *et al.*, 2021 [64] (OR = 1.26, 95 % CI = 0.99, 1.60, p = 0.06), Zhang *et al.*, 2022 [46] (OR = 1.24, 95 % CI = 0.98, 1.56 p = 0.07) for *GSTM1* null genotype gene polymorphism results become insignificant. In the case of the *GSTT* null genotype, after removing Wu *et al.*, 2008 [68] (OR = 1.37, 95 % CI = 1.01, 1.86, p = 0.04), and Polonikov *et al.*, 2010 [54] (OR = 1.36, 95 % CI = 1.00, 1.83, p = 0.05), the results become significant. To assess the publication bias among the selected studies, funnel plots were used. The shape of funnel plots did not reveal any evidence of asymmetry and is represented in Supplementary Figure 2 (Supplementary Figure 2.1 - 2.24).

3.5. Correlation between genotype and gene expression

Significant gene variants (*SOD2* rs4880, *CYP1A1* rs4646903, *MTHFR* rs1801133, rs1801131, rs2274976, *PON1* rs854560, *NRF2* rs6721961, null *GSTM1*) were investigated for genotype tissue expression by using GTEx portal. Fig. 2 summarizes the correlation of gene expression according to the genotype of the variant. Testis tissue was used to correlate the gene expression with the genotype of the selected variant. Significant association of *MTHFR* rs1801133, 1801131, and *PON1* rs854560 gene expression levels in the testis was observed with the linear regression model using the GTEx portal (Supplementary file 1). The white line in the box plots shows the median value of gene expression at each genotype. So far, *GSTM1* rs1183423000 gene polymorphism has not been introduced in the GTEx portal and no results were obtained for the rs4880 gene variant. Another tool used for gene expression was RegulomeDB. Variants showing the strongest evidence of being regulatory are scored as 1 and variants with the least evidence of being regulatory are scored as 6 in the RegulomeDB tool [49]. *SOD2* rs4880, *PON1* rs854560, *MTHFR* rs1801131, rs2274976, *CYP1A1* rs4646903, and *NRF2* rs6721961 are found to be ranked with 1 f, which shows that they are likely to influence the binding and linked to expression of a gene target. *MTHFR* rs1801133 was ranked with 1c, which appears to affect the binding and linked to the expression of a gene target. Null *GSTM1* had a score of 6, which suggests minimal binding evidence of the studied gene variant.

3.6. In silico analysis predicting deleterious effects of selected gene variants

Significant variants (*SOD2* rs4880, *CYP1A1* rs4646903, *MTHFR* rs1801133, rs1801131, rs2274976, *PON1* rs854560, *NRF2* rs6721961, null *GSTM1*) are further analyzed using different *in silico* tools for prediction of their pathogenicity (Table 5). The pathogenicity of intronic variants was determined using RegulomeDB and CADD tools. *SOD2* rs4880 and *MTHFR* rs1801133, rs1801131, rs2274976 are found to decrease the stability of protein. *MTHFR* rs1801133 gene variant was found to be deleterious in all studied *in silico* tools namely, I-Mutant 2.0, PolyPhen 2, SNP & GO, SIFT, and CADD.

3.7. Pathway enrichment and PPI network analysis

Gene ontology analysis of three aspects for the top 20 pathways is represented in Fig. 3. In terms of biological processes, the most significantly enriched GO terms are hydrogen peroxide biosynthetic process, response to hyperoxia, response to immobilization stress, and xenobiotic catabolic processes (Fig. 3a). Most overexpressed terms of the GO cellular process include spherical high-density lipoprotein particles, and plasma lipoprotein particles (Fig. 3b). In the case of molecular function, the most expressed GO terms are oxygen binding, modified amino acid binding, and superoxide dismutase activity (Fig. 3c). In the case of KEGG pathway enrichment analysis, the most over-expressed pathways are chemical carcinogenesis-reactive oxygen species, metabolism of xenobiotics by cytochrome P450, and chemical carcinogenesis- DNA adducts (Fig. 3d). In PPI network analysis, we obtained 16 nodes, 72 edges, 0.818 clustering coefficient, and PPI enrichment p-value: $< 1.0e\text{-}16$. Line thickness shows the strength of PPI (Fig. 3e).

4. Discussion

The present systematic review and meta-analysis investigate the association of gene variants in xenobiotic metabolizing genes with the risk of male infertility. A total of 25 genes are compiled in the present study, from which meta-analysis was conducted for 16 genes and their 24 variants (only for which meta-analysis was possible). The findings of this

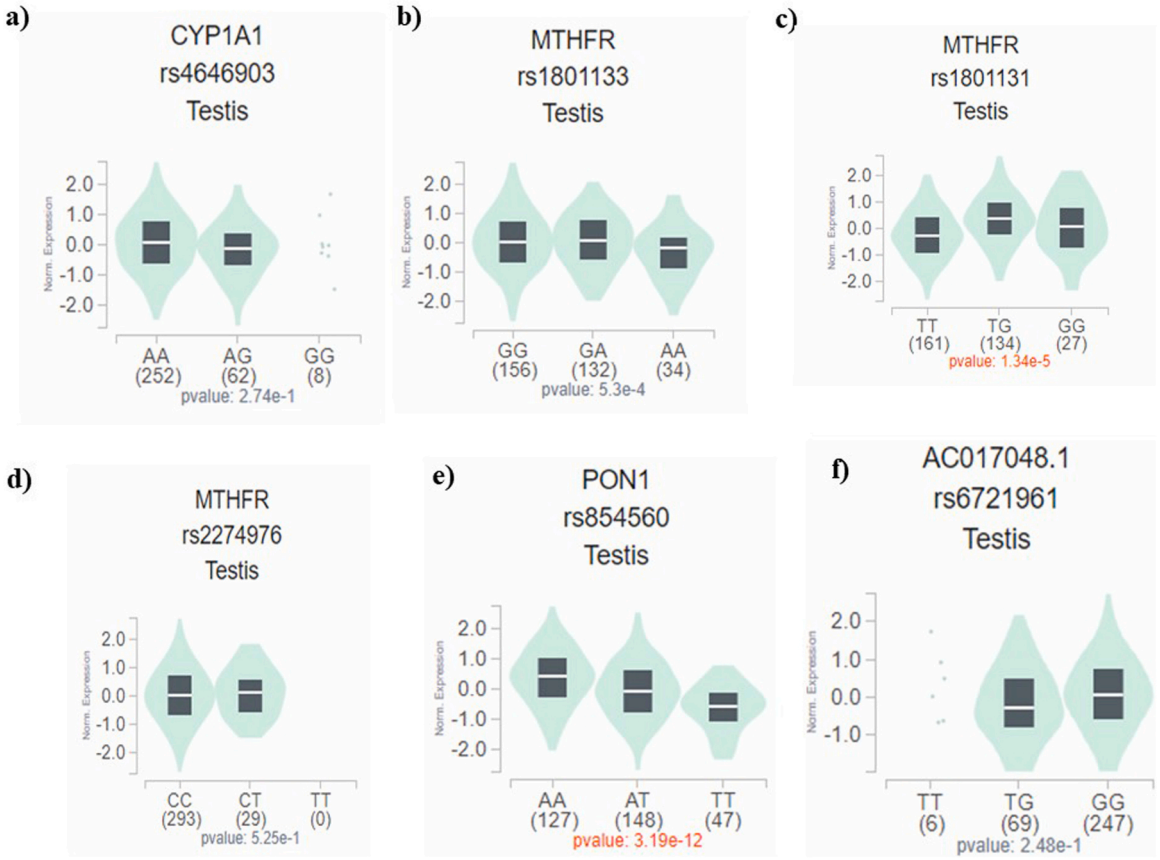

Fig. 2. Violin plots of significant gene variants for gene expression in Testis.

Table 5
In silico analysis of significant gene variants.

Gene	Gene variant	Cytogenetic location	Variant Class	I-Mutant 2.0		PolyPhen-2		SNPs & GO		SIFT		RegulomeDB		CADD
				Stability	RI	Score	Effect	Effect	RI	Score	Prediction	Rank	Score	PHRED score
SOD2	rs4880	chr6:159692840	Missense	**Decrease**	7	0	Benign	Neutral	8	0.295	Tolerated	1 f	0.55	15.73
MTHFR	rs1801133	chr1:11796321	Missense	**Decrease**	2	0.996	**Probably Damaging**	**Disease**	6	0.048	**Deleterious**	1c	0.58	**29.4**
MTHFR	rs1801131	chr1:11794419	Missense	**Decrease**	4	0.021	Benign	Neutral	2	0.201	Tolerated	1 f	0.55	**32**
PON1	rs854560	chr7:95316772	Missense	Increase	4	0.111	Benign	Neutral	9	0.057	Tolerated	1 f	0.55	18.11
MTHFR	rs2274976	chr1:11802878	Missense	**Decrease**	6	0.000	Benign	Neutral	3	1.0	Tolerated	1 f	0.554	18.51
CYP1A1	rs4646903	chr15:74719300	Downstream	NA	NA	NA	NA	NA	NA	NA	NA	1 f	0.05	3.40
NRF2	rs6721961	chr2:177265309	Upstream	NA	NA	NA	NA	NA	NA	NA	NA	1 f	0.55436	9.63
GSTM1	rs1183423000	chr1:109689287–109689288	Frame shift	NA	NA	NA	NA	NA	NA	NA	NA	6	0.18	16.01

study based upon 106 studies found that SOD2 rs4880, *CYP1A1* rs4646903, *MTHFR* rs1801133, rs1801131, rs2274976, *PON1* rs854560, *NRF2* rs6721961, and null *GSTM1* gene polymorphisms are significantly associated with male infertility risk. However, no association was found for *CAT* rs1001179, rs7943316, *GPX1* rs1050450, *CYP1A1* rs1048943, *GSTP1* rs1695, *MTHFR* rs2066472, *MTHFD1* rs2236225, *MTRR* rs1801394, *CYP2D6* rs3892097, *PON1* rs662, *PON2* rs7493, *NAT2* rs1799930, *AHR* rs2066853, rs1476080, rs6960165, null *GSTT1* gene polymorphisms.

Environmental factors and genetic susceptibility, both are important factors in determining the etiology of infertility in males. Certain polymorphisms in xenobiotic metabolizing genes have also been implicated in adversely affecting the reproductive health of males. Meta-analysis is conducted for the first time for *CAT* rs7943316, *SOD2, GPX1, CYP1A1* rs1048943*, MTHFR* rs2066472*, CYP2D6, PON2*, *NAT2,* and *NRF2.* With the inclusion of new studies, an updated meta-analysis was performed for *CAT* rs1001179, *MTHFR* rs1801133, rs1801131, rs2274976, *MTRR, GSTM1, GSTT1, CYP1A1* rs4646903 gene polymorphisms. *GSTM1* null genotype leads to the production of a defective protein with no enzymatic activity [55]. Earlier meta-analysis on *GSTM1/T1* involving 3302 cases and 1959 controls among 10 studies for *GSTM1* and 3048 cases and 1861 controls among 10 studies reported that the null genotype of *GSTM1/T1* was significantly associated with increased male infertility risk in Chinese population [122]. However, the present study with 20 studies for the *GSTM1* null genotype and 16 studies for the *GSTT1* null genotype showed the association of the *GSTM1* null genotype with male infertility risk. Three main enzymes involved in folate metabolism (which plays vital role during spermatogenesis) include Methylene tetrahydro folate reductase (*MTHFR*), 5-methyltetrahydrofolate-homocysteine methyl transferase reductase (*MTRR*), 5-methyl tetra hydrofolate homocysteine methyl transferase (*M*TR), and 5, 10-methylene tetra hydro folate dehydrogenase (*MTHFD*) [78]. Previously conducted a meta-analysis based on 13 studies for *M*TR and 15 studies for *MTRR* involving 3621 cases and 3327 controls reported the significant association between *M*TR rs1805087 polymorphism with male infertility and no association for *MTRR* rs1801394 [15]. Similar results are found for *MTRR* rs1801394 gene polymorphism in the present meta-analysis, whereas, the *M*TR gene was excluded from analysis as results for polymorphisms in this gene were reported recently by Tariq and colleagues [15]. One recently conducted meta-analysis of the *eNOS* gene by Teng and colleagues (2023) reported the significant association of rs2070744 and rs1799983 gene polymorphisms with increased male infertility risk [14]. So, the *eNOS* gene was also removed from the analysis as no new studies were found to conduct the meta-analysis. CYP (Polymorphic Cytochrome P450 Enzymes) superfamily enzymes are another major enzyme involved in phase 1 detoxification of xenobiotics. A study reported that polymorphisms in *CYP2D6* and *CYP1A2* genes may play an important role in idiopathic male infertility [47]. A meta-analysis conducted for *CYP1A1* rs4646903 gene polymorphism based on 10 studies with 3028 cases and 3258 controls found a significant association between the studied variant and increased risk of male infertility [123], which is consistent with the results obtained from present meta-analysis. A case-control study reported that gene variants in *PON* and *GST* genes (*PON1*–55/192, *PON2*–311, and *GSTM1/T1*) are not significantly associated with male infertility, however, *PON1*–55 M allele may represent a possible risk factor for male infertility [55]. The frequency of allele distribution varies in different subpopulations. Each subpopulation is further exposed to different environmental exposures. Since each subpopulation has its unique lifestyle and dietary habits, the differential role of the involved genetic variants to these modifiable factors cannot be ruled out and may further be investigated. The understanding of the role of metabolizing gene variants also have the clinical applications in personalized therapeutics in future.

Combined meta-analysis and *in silico* analysis can provide a better understanding of how genetic variants can interact with metabolic pathways and lead to the pathogenesis of disease. Gene-set enrichment

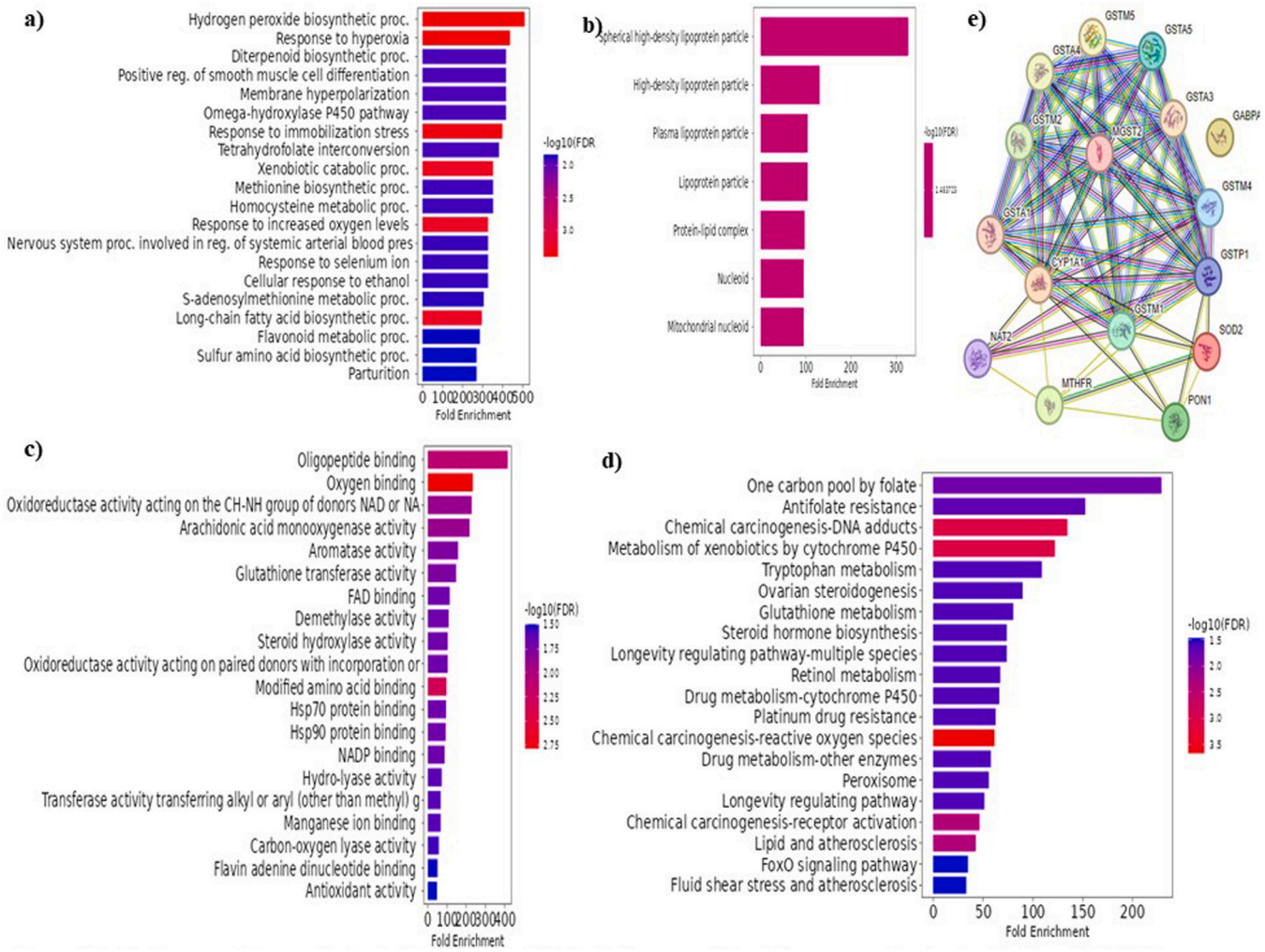

Fig. 3. Enriched gene ontology analysis of obtained genes: (a) biological process; (b) cellular process; c) molecular function; (d) KEGG pathway; e) STRING protein-protein analysis.

analysis was summarized in Supplementary File 1. A GO biological overexpressed process includes a hydrogen peroxide biosynthetic process involving *SOD2*, *CYP1A1,* and a response to hypoxia involving *SOD2, CYP1A1, and MTHFR* genes. In the case of GO cellular function categories most over-expressed terms are spherical high-density lipoprotein particles involving the *PON1* gene. Two genes are involved in oxygen binding in the GO molecular function category (*SOD2* and *CYP1A1*); modified amino acid binding involving three genes (*GSTM1* and *MTHFR*) and *SOD2* is involved in superoxide dismutase activity. Pathway enrichment data shows the highly enriched pathways are related to chemical carcinogenesis-reactive oxygen species, which include 3 genes (*CYP1A1, GSTM1,* and *SOD2*) and metabolism of xenobiotics by cytochrome P450 involving *CYP1A1, GSTM1* genes.

We have tried to understand the impacts of polymorphisms in xenobiotic metabolizing gene variants on the adverse reproductive health of males through systematic review, meta-analysis, and *in silico* analysis. Out of 16 studied genes and its 24 variants, 6 genes and 8 variants are found to be significant. *MTHFR* rs1801133 gene variant was found to be damaging in all studied *in silico* tools namely, I-Mutant 2.0, PolyPhen 2, SNP & GO, SIFT, CADD, RegulomDB. A few limitations may be pointed out in the current meta-analysis, firstly, confounding variables such as age, body mass index, lifestyle, and environmental factors may have caused discrepancies in analysis and it could not be analyzed in the present meta-analysis due to the absence of sufficient data. Secondly, subgroup analysis (Asian vs. non-Asian) was not performed for certain gene variants due to a lack of sufficient studies. Third, the *in silico* tools rely on predictive algorithms and their results are often not experimentally validated. However, the present study provides strong statistical evidence that certain variants in some of the genes involved in xenobiotic metabolism are associated with the decline of male fertility. Furthermore, extensive sample size studies from different ethnicities are needed to evaluate the gene variants in xenobiotic metabolizing genes and their correlation with male infertility.

5. Conclusion

SOD2 rs4880, *CYP1A1* rs4646903, *MTHFR* rs1801133, rs1801131, rs2274976, *PON1* rs854560, *NRF2* rs6721961, and null *GSTM1* gene variants are associated with increased male infertility risk. However, no significant association was observed between *CAT* rs1001179, rs7943316, *GPX1* rs1050450, *CYP1A1* rs1048943, *GSTP1* rs1695, *MTHFR* rs2066472, *MTHFD1* rs2236225, *MTRR* rs1801394, *CYP2D6* rs3892097, *PON1* rs662, *PON2* rs7493, *NAT2* rs1799930, *AHR* rs2066853, rs1476080, rs6960165, null *GSTT1* gene polymorphisms. Certain gene variants in the xenobiotic metabolizing gene variants are possible risk factors for male infertility risk. Due to the small effect of many variants, there is a possibility of genetic predisposition to infertility among males which may be investigated further in large cohorts. Identification of potential genetic risk factors associated with male infertility can lead to improved diagnosis, treatment strategies and

enabling more effective approaches to manage the disease.

CRediT authorship contribution statement

Khetarpal Preeti: Writing – review & editing, Supervision, Project administration, Investigation, Conceptualization. **Devi Goyal Lajya:** Visualization, Supervision. **Singh Kapoor Harmanpreet:** Writing – review & editing, Supervision, Methodology, Investigation. **Kaur Rajinder:** Visualization, Supervision, Project administration, Investigation. **Dolma Sangay:** Methodology, Formal analysis, Data curation. **Rahman T K Shahil:** Methodology, Formal analysis, Data curation. **Kaur Mandeep:** Writing – original draft, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Consent to participate

Not applicable

Consent to publish

Not applicable

Ethical Approval

Not applicable

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Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.toxrep.2025.102019.

Data availability

Data will be made available on request.

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