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RESEARCH

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Potential biomarker signatures in male infertility: integrative genomic analysis

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Abstract

Background Studies have attributed 50% of infertility cases to male infertility, 15% of which is caused by idiopathic genetic factors. Currently, no specific biomarkers have been revealed for male infertility. Furthermore, research on genetic factors causing male infertility is still limited. As with other multifactorial genetic disorders, numerous risk loci for male infertility have been identified by genome-wide association studies (GWAS), although their clinical significance remains uncertain. Therefore, we utilized an integrative bioinformatics-based approach to identify biomarkers for male infertility. Bioinformatics analysis was performed using Open Targets Platform, DisGeNet, and GWAS Catalog. After that, the STRING database and the Cytoscape program were used to analyze protein–protein interaction. CytoHubba was used to determine the most significant gene candidates. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway analyses were used to assess biological functions that correspond to the male infertility disease pathway.

Results We identified 305 genes associated with male infertility and highlighted 10 biological risk genes as potential biomarkers for male infertility such as *TEX11*, *SPO11*, *SYCP3*, *HORMAD1*, *STAG3*, *MSH4*, *SYCP2*, *SYCE1*, *RAD21L1*, and *AMH*. Of all the genes, we took the top three genes, namely, *TEX11*, *SPO11*, and *SYCP3* as the genes that have the most potential as biomarkers.

Conclusions *TEX11*, *SPO11*, and *SYCP3* are involved in meiosis and spermatogenesis. We propose that further research in regarding these genes in detecting male infertility.

Keywords Bioinformatics, Genes, Male infertility, *SPO11*, *SYCP3*, *TEX11*

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Background

Studies have shown that infertility affects 15% of couples who are unable to conceive after having in regular unprotected intercourse for at least 12 months [1–3]. Approximately half of cases of infertility are caused by male factors, among which 30% and 20% are solely male factors and co-contributing female factors, respectively [4]. Male infertility can cause serious psychological and marital issues [5, 6]. Apart from anatomical conditions, male fertility highly depends on the spermatogenesis, a complex and multifactorial sperm production and functional process involving genetic, hormonal, and environment factors [7, 8].

Genetic factors are involved in approximately 15% of male infertility cases and has been observed in ductal obstruction or dysfunction, hypothalamic-pituitary–gonadal axis dysregulation, and spermatozoa number/quality defects [8, 9]. As sperm count declines, there is a greater chance that genetic factors contributing to male infertility will be present [8]. Genetic factors account for 25% of cases of male infertility linked to azoospermia; in other cases of impaired spermatogenesis, such as those involving variables acting at the pre-testicular, post-testicular and testicular levels, the incidence of genetic factors increase [10].

Unfortunately, 40% of male infertility cases related to impaired spermatogenesis become idiopathic genetic factors that the underlying causes remain unidentified after exhausting all diagnostic options [8, 10]. Thus, genetic testing and procedures have emerged to address this predicament. Genetic studies have generally focused on genes related to spermatogenesis with wide range of factors from hormonal regulation and cell metabolism to meiosis, which involves at least 2000 genes [11, 12]. Over the recent decade, studies have used genome-wide association studies (GWAS) based on various methods, such as single nucleotide polymorphism (SNP) arrays [13, 14], comparative genomic hybridization [15–17], and next-generation sequencing [18–20], to investigate the basic genetic factors involved in male infertility. Although such efforts have contributed little to male infertility diagnostics, some SNP array results related to the hormonal regulation of spermatogenesis have suggested interesting treatment targets [8].

We investigated the consideration of genes that influence male infertility. The result of this study hopefully can contribute further investigation and then can be developed into biomarkers in the future.

Methods

Dataset selection

A database search was conducted on three platforms accessed on June 23, 2023, namely, Open Targets Platform (https://platform.opentargets.org/), DisGeNet (https://www.disgenet.org/), and GWAS Catalog (https://www.ebi.ac.uk/gwas/), to identify genes related to male infertility. In each database, the keyword "male infertility" was used to identify related genes. For Open Targets and DisGeNet, we limited our search to genes scoring higher than 0.3, whereas for GWAS, we limited our search to genes with a p value of at least 10^{-8} with an odds ratio of ≥ 1. After filtering the data, we deleted data for duplicate genes and finalized our results for male infertility genes. A summary of the research workflow is shown in Fig. 1.

Discovering biomarker genes for male infertility

The STRING database (https://string-db.org/) provided as a source of potential genes and protein for the protein–protein interaction (PPI) investigation. The STRING database provides complete data regarding predicted interactions between proteins, including physical interactions and functional associations. We also used the Cytoscape application version 3.10.0 (Bethesda, MD, USA), accessed on June 24, 2023, to visualize the interaction network between these proteins. Cytoscape allows us to graphically visualize the intricate biological network between proteins. Additionally, we screened and identified significant modules in the PPI network using the cytoscape plugin molecular complex detection (MCODE) with the relevant settings and scores: *k* score = 2, degree cutoff = 2, node score cutoff = 0.2, and maximum depth = 100. The PPI network structure was then generated and examined using Cytoscope's CytoHubba plugin to find hub genes. The CytoHubba software feature eleven topological analysis techniques: Maximal Clique Centrality (MCC), Degree, Edge Percolated Component, Maximum Neighborhood Component, Density of Maximum Neighborhood Component and six centralities based on shortest paths (Bottleneck, Eccentricity, Closeness, Radiality, Betweenness, and Stress). We found that the MCC algorithm predicted important proteins from the yeast PPI network more correctly than the other 10 techniques [21]. The top three high closeness genes from the MCC algorithm were subsequently considered as possible biomarker genes.

Gene Ontology and Kyoto Encyclopedia of Genes and Genomes Pathway enrichment analysis

The web-based Gene Set study toolkit ShinyGO (http://bioinformatics.sdstate.edu/go/), a functional enrichment analysis web tool, was used to collect data for the gene ontology (GO) enrichment study (accesses on July 4, 2023). GO was frequently split into three groups: molecular function (MF), cellular component (CC) and biological process (BP) [21]. Annotations in the GO

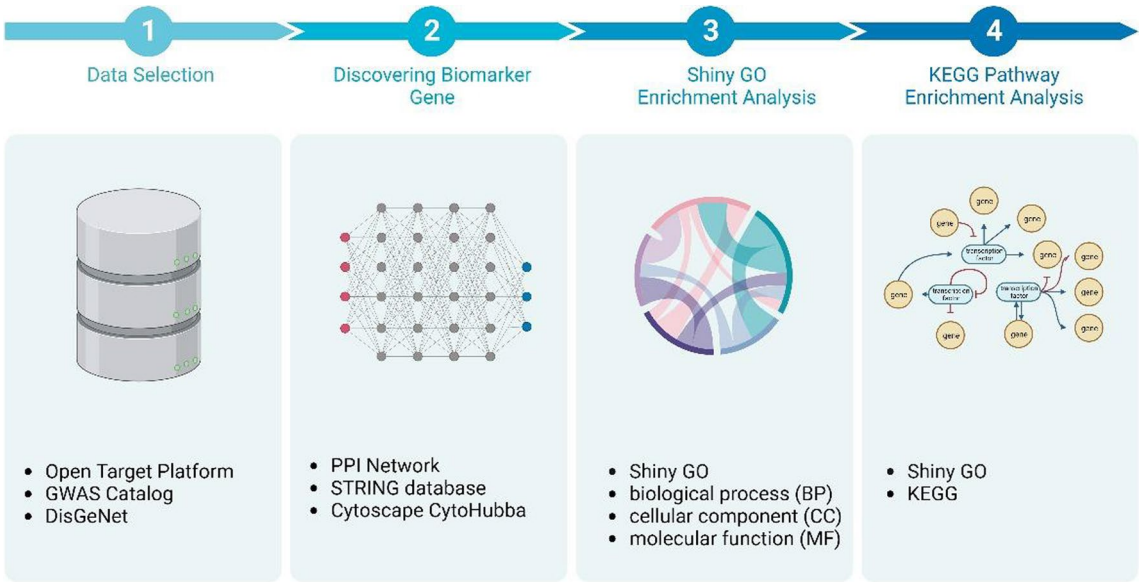

Fig. 1 Flow study chart for genomic analysis to identify biomarkers for male infertility. This figure was created by Biorender.com under license ME25RIS757

database characterizes the traits of genes and gene products from different organisms as well as the proposed activities of enriched genes. BPs are an orderly collection of molecular actions that characterize numerous biological processes. CCs specify the locations, macromolecular complexes and subcellular structures of genes, whereas MF describe how a gene or gene products works [21]. A *q*-value False Discovery Rate (FDR) of 0.05 was used as the significance cutoff by using the filters on the website.

The KEGG database was used to systematically investigate gene function by correlating genomic data and high-level functional data. Significant results with a q(FDR) value of 0.05 were used during KEGG enrichment. The ShinyGO online tools and candidate genes from the KEGG database were used for enrichment analysis to enhance the significantly altered pathways.

Results

Dataset selection

After limiting the gene score to at least 0.3 in Open Targets and DisGeNet, we were able to identify 250 and 50 genes, respectively. Moreover, after limiting the p value to at least 10^{-8} with an odds ratio of ≥ 1 in GWAS, we subsequently identified 86 genes. Interestingly, our data showed overlap between 305 genes associated with male infertility (table S.1.).

Discovering biomarker genes for male infertility

The STRING database was used to create a PPI network of 305 male infertility genes (figure S.1). Furthermore, biomarker genes were extracted from the PPI networks using Cytoscape plugins like MCODE and CytoHubba. MCODE was specifically to find gene clusters within the PPI networks that may be indicative of biomarkers. The MCODE was used to divide the PPI network into 11 subclusters. A complete list of MCODE clusters, with the information of their score, number of nodes, and edges, is provided in table S.2. Top three gene clusters shown in Fig. 2.

Hub genes (i.e., highly connected nodes) for the PPI network were selected using CytoHubba. To rate every node, the MCC method in CytoHubba was applied. We identified 10 genes that could be considered the 10 highest ranked male hub genes visualized in Fig. 3 and table S.3. From these 10 genes, *Human Testis Express 11 (TEX11), Protein initiator of meiotic double-stranded breaks (SPO11),* and *Synaptonemal Complex Protein SYCP3* were identified as the three genes having the most potential to become biomarkers of male infertility.

Gene Ontology and Kyoto Encyclopedia of Genes and Genomes Pathway enrichment analysis

The ShinyGO (http://bioinformatics.sdstate.edu/go/) online resources were used to conduct GO enrichment analysis and examine the biological characteristics of the identified genes and proteins. BPs, CCs, and MF were all included in the GO enrichment study. The degree of relevance was set by using the filters on the website at a p value (FDR) of < 0.05 for each GO enrichment study. Notably, KEGG pathway analysis identified 67 significant

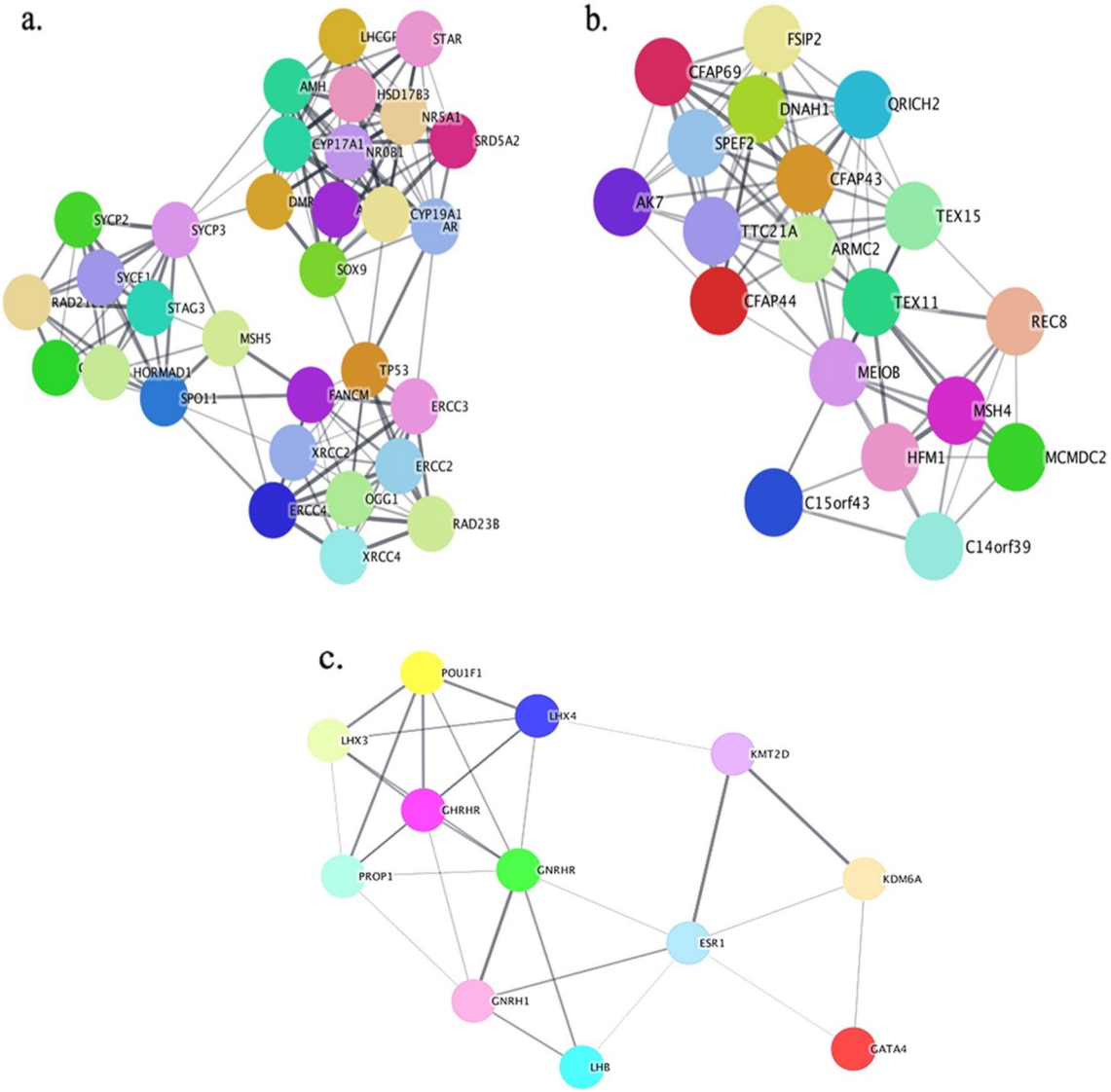

Fig. 2 Visualization of the top three gene clusters using MCODE. **a** Cluster 1, score of 10; **b** Cluster 2, score of 9.556; **c** Cluster 3, score of 5.273

pathways (Table S4), with the 20 most significant pathways being visualized in Fig. 4. BP enrichment analysis showed that 1,000 functions were significantly enriched, such as "male sex differentiation," "sex differentiation," "gonad development," "development of primary sexual characteristic," and "germ cell development." CC enrichment analysis showed that 106 functions were significantly enriched, such as "axonemal dynein complex," "lateral element," "synaptonemal complex," synaptonemal structure," and "condensed nuclear chromosome." MF analysis found that 194 functions were significantly enriched, such as "minus-end-directed microtubule motor activity," "dynein light intermediate chain binding," "dynein intermediate chain binding," "Ribonucleic Acid (RNA) polymerase II general transcription initiation factor binding" and "oxygen binding."

Discussion

Male infertility affects at least 180 million people worldwide [2]. Given the substantial number of genes involved in spermatogenesis, idiopathic infertility accounts for about 50% of cases in males. As such, the current study was conducted to identify the most significant genes affecting male infertility to establish biomarkers for this condition. We initially searched the STRING database for PPIs in male infertility. Thereafter, we searched Cytoscape using MCODE and CytoHubba applications, through which we identified the three most significant

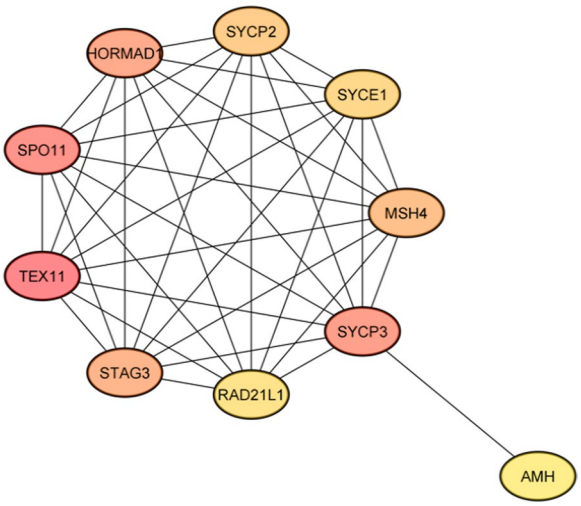

Fig. 3 Visualization of the top 10 genes associated with male infertility using MCC. A darker color indicates greater potential for the gene to be considered a biomarker

genes that could potentially as indicators of male infertility biomarkers, namely, *TEX11*, *SPO11*, and *SYCP3*.

TEX11 (Human testis express) is a meiosis-specific X-linked gene that plays a role in the spermatogenesis process. According to research by Bellil H, et al. [22] *TEX11* (at Xq13.1), is the gene most commonly linked to azoospermia. The cytoplasm and nucleus of type B spermatogonia in mice contain the *TEX11* protein, which most abundant in zygotene spermatocytes and at least abundant late pachytene spermatocytes, thus indicating an important role for *TEX11* in the initial phases of the formation of germ cell.

Based on research by Yang, et al. [23, 24] loss of the *TEX11* gene will cause meiosis failure in men, thus explaining the role of the encoded protein in spermatogenesis. Human infertility results from spermatocytes undergoing apoptosis at the pachytene stage and surviving cells displaying chromosome nondisjunction during the first miotic division. He also discovered that altering this allele genetically can be a tactic to ascertain the in vivo effect of human *TEX11* mutations. Yu et al. [25] claims that *TEX11* prevents ERβ from binding to a protein that interacts with the transcription factor associated with hematopoietic pre-B cell leukemia, hence suppressing the phosphorylation of the AKT and ERK signaling pathways.

In two brothers who had azoospermia, Sha [26] found a novel mutation in exon 29 *TEX11* (2653G–T; GenBank accession number, NM_031276). First, whole-exome sequencing (WES) was used to confirm this mutation. Then, specific exon 29 was amplified and sequenced. The same missense exonic mutation (W856C) was present in the two brothers but not in their mother, carried. According to the testicular biopsy's histological study, meiosis had stopped, and the seminiferous tubules had neither mature spermatozoa nor post-meiotic spherical spermatids. Sertoli cells and interstitial cells did not express *TEX11;* spermatogonia expressed it strongly, whereas spermatocyte expressed it weakly.

SPO11 is a 13 exons gene that is found on chromosome 20 (20q13 0.2–13.3) in human and is involved in the processes of meiosis and spermatogenesis, where in humans this gene is located with. Research regarding Spo11 with male infertility is still limited. A case–control of SNP (rs28368082) in exon 7 of the *SPO11* gene and its potential correlation with male infertility was carried out in three Iranian provinces by Galkhani et al. in 2014. This study showed that polymorphisms in the *SPO11* gene may be linked to azoospermia and oligospermia susceptibility in three Iranian provinces [27]. This contrasts with research conducted by Karimian [28], on 200 samples with 100 healthy men and 100 infertile men, the findings demonstrated that while Spo11-C631T can damage mRNA and protein, it does not raised the risk of male infertility. According to a meta-analysis study by Ren SZ, et al., 2017, the *SPO11* C631T gene polymorphism may be a hereditary factor that can lead to male infertility [29].

SYCP3 (synaptonemal complex protein 3) is a synapse-associated DNA-binding protein involved in germ cell meiosis, located on chromosome 12 (12q23), that is a testicular specificity to the expression. *SYCP3* contains two coil-over domains and encodes 236 amino acids. A mutation analysis was performed on all coding regions and adjacent introns in 19 patients with azoospermia, which had been histologically shown to be caused by anomalies in meiosis. The azoospermia gene, *SYCP3*, was discovered by Miyamoto on the human chromosome, outside the AZF region of the Y chromosome. *SYCP3* mutation cause azoospermia in males by arresting meiosis [30]. On the other hand, research on Caucasian-Spanish or Maghribians individuals without Y chromosomal loss revealed no abnormalities in the *SYCP3* gene's coding region in samples of azoospermia or severe oligozoospermia infertile male patients [31].

The aforementioned research suggests that the *TEX11*, *SPO11* and *SYCP3* genes play a role in meiosis and spermatogenesis. This is consistent with the results of our analysis, which found that these three genes play a role in male infertility. Therefore, we suppose that such genes can become biomarkers for patients with male infertility.

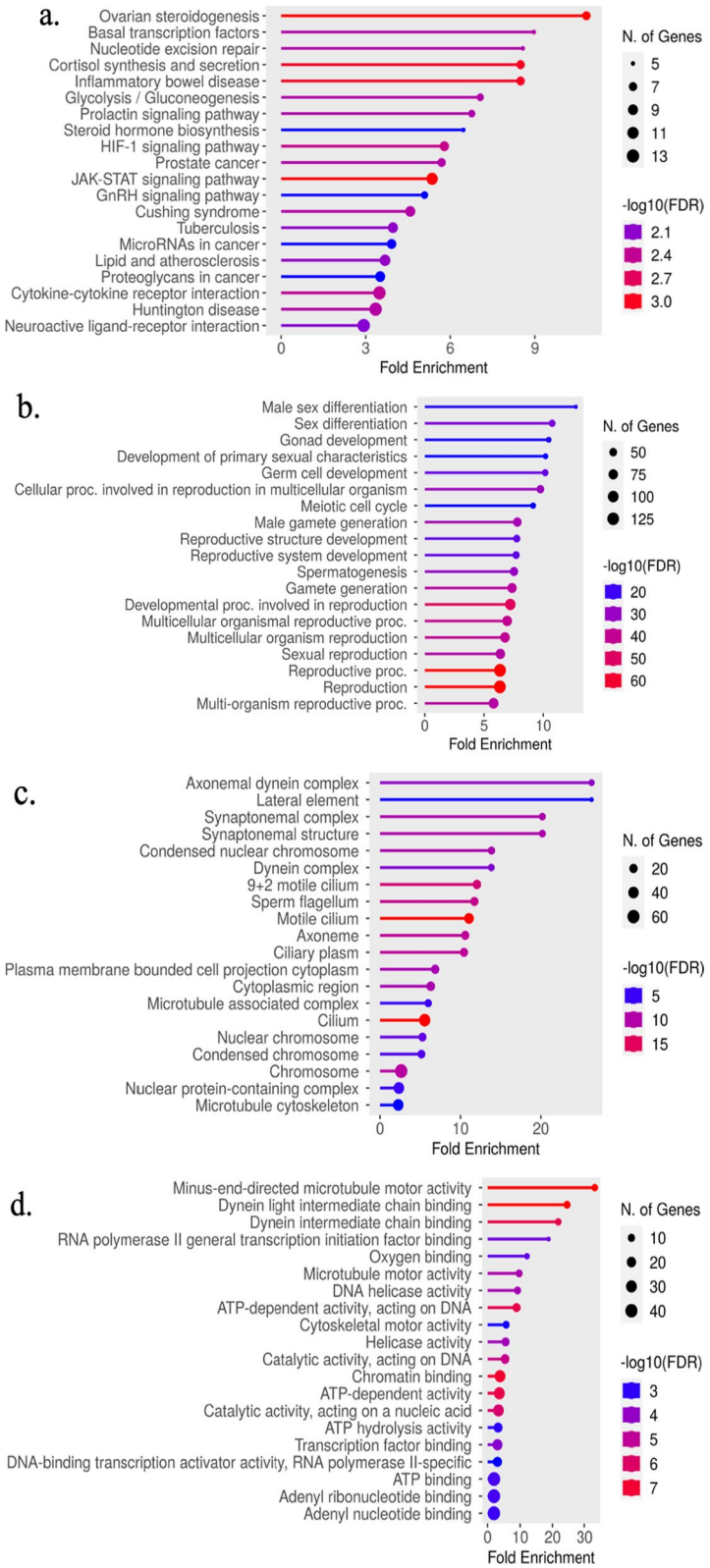

Fig. 4 The 20 most significant pathways identified following functional enrichment analysis using Gene Ontology (GO). **a** Kyoto Encyclopedia of Gene and Genome (KEGG); **b** Biological Process (BP); **c** Cellular Component (CC); **d** Molecular Function (MF). A pathway on the GO analysis is shown by each circle in the diagram. The pathways that were indicated in blue had a less significant FDR than the pathways that were highlighted in red. The number of pathways is represented by the size of the circle; bigger circle denote more pathway enrichment

Conclusions

The current study identified potential biomarkers for male infertility. Accordingly, our bioinformatics analysis found that significant hub genes, such as *TEX11*, *SPO11*, *SYCP3*, *HORMAD1*, *STAG3*, *MSH4*, *SYCP2*, *SYCE1*, *RAD21L1*, and *AMH* might induce male infertility. Our findings suggest that *TEX11*, *SPO11*, and *SYCP3*, which play a significant role in meiosis and spermatogenesis and were the three most significant genes based on the MCC algorithm in CytoHubba, could be potential biomarkers for male infertility. More research is required to better understand their regulatory actions and confirm the utility of these genes as clinical indicators and therapeutic targets.

Abbreviations

AMH	Anti-Mullerian hormone
BP	Biological process
CC	Cellular component
FDR	False discovery rate
GO	Gene ontology
GWAS	Genome-wide association studies
HORMAD1	HORMA domain-containing protein 1
KEEG	Kyoto Encyclopedia of Gene and Genome
MCC	Maximal clique centrality
MCODE	Molecular complex detection
MF	Molecular function
MSH4	MutS homolog 4
PPI	Protein–protein interaction
RAD21L1	RAD21 cohesin complex component like 1
RNA	Ribonucleic acid
SNP	Single nucleotide polymorphism
SPO11	Protein initiator of meiotic double-stranded breaks
STAG3	Mutations in the stromal antigen 3
STRING	Protein–protein interaction networks functional enrichment analysis
SYCE1	Synaptonemal complex central element protein 1
SYCP2	Synaptonemal complex protein 2
SYCP3	Synaptonemal complex protein 3
TEX11	Human testis express 11
WES	Whole-exome sequencing

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Author contributions

DJ and RD helped in data collection, analysis, writing-original draft preparation. WA designing the research and methodology, writing (review and editing). DD designing the research and methodology, visualization, writing (review and editing). AA done data curation, visualization, writing (review and editing). LMI helped in data analysis, designing the research and methodology, writing (review and editing). SS organizing the research, funding acquisition, writing (review and editing).

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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