Original Article

Dysregulated Kinase Expression in Teratozoospermia and Implications for Male Infertility: An Integrated Gene Expression Study

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Abstract

Background: Teratozoospermia, characterized by abnormal sperm morphology, is a major contributor to male infertility. Kinases, enzymes that catalyze the transfer of phosphate groups to proteins, are crucial regulators of cellular signaling pathways and play significant roles in sperm development and maturation. The purpose of the current study was to identify differentially expressed genes (DEGs) between teratozoospermia and normozoospermia samples and to investigate the role of kinases in these expression changes.

Methods: An integrated analysis of transcriptome data was conducted from teratozoospermia and normozoospermia samples using publicly available gene expression omnibus (GEO) datasets. Three gene expression series (GSE) profiles of teratozoospermia from one superseries were selected and combined. Differential expression analysis was performed using the limma package in R, applying linear modeling and empirical Bayes statistics to identify DEGs with a threshold of adjusted $p<0.05$. A comprehensive list of human kinase genes was obtained from the KinHub database, and differentially expressed kinases between the two conditions were identified. Functional enrichment analyses including gene ontology (GO) and kyoto encyclopedia of genes and genomes (KEGG) pathways were conducted. Additionally, receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic potential of identified kinases.

Results: Our analysis identified 1,292 DEGs. Among these, 34 kinases were identified (10 upregulated and 24 downregulated). ROR1 and STK39 showed the most significant changes. ROC analysis demonstrated strong diagnostic values for these kinases.

Conclusion: This study is the first comprehensive analysis integrating transcriptomic data and kinase-focused gene expression profiling specifically in teratozoospermia, suggesting that kinase dysregulation may contribute to teratozoospermia and male infertility.

Keywords: Gene expression, Microarray analysis, Phosphotransferases, Teratozoospermia.

Introduction

Infertility is a significant global health issue, affecting approximately 15% of couples worldwide (1). Clinical infertility is defined as the inability of a couple to conceive after 12 months of unprotected intercourse (2). Male infertility factors account for around half of all infertility cases (1). Teratozoospermia, characterized by abnormal sperm morphology, is a leading cause of male infertility, often involving defects in the sperm head and tail (3). Spermatogenesis is

a complex and dynamic process regulated by intricate mechanisms involving accurate gene expression at different developmental stages (4). Understanding the molecular signaling pathways underlying spermatogenesis is critical for developing interventions to address infertility (5). Protein kinases, which possess a conserved catalytic domain, transfer phosphate groups from ATP to specific amino acids containing a free hydroxyl group, often found on both serine and threonine amino acids (known as serine/threonine kinases). The phosphorylation is vital for proper protein functioning in sperm (6, 7). Understanding the role of kinases is crucial for developing targeted therapeutic strategies to address male infertility. The knowledge of the differential gene expression between normal men and patients with male infertility is essential for understanding the molecular basis of male infertility. Microarray technology is a powerful tool for detecting changes in gene expression between normal and infertile men (8). This study addressed a critical knowledge gap in male infertility research. Although previous studies have examined individual kinases, there remains a lack of comprehensive, integrated transcriptomic analysis specifically focused on kinase gene expression alterations in teratozoospermia. To fill this gap, three publicly available transcriptomic datasets were analyzed comparing teratozoospermia and normozoospermia samples to identify differentially expressed kinase genes. It was hypothesized that dysregulated expression of specific kinases contributes to the abnormal sperm morphology, characteristic of teratozoospermia. Furthermore, the biological pathways involving these kinases were explored and their potential as diagnostic markers associated with male infertility was evaluated.

Methods

Data collection: The gene expression omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo) was searched using the following keywords: "teratozoospermia", "homo sapiens", and "expression profiling by array". Datasets were selected based on the following criteria: (i) inclusion of both teratozoospermia and normozoospermia samples with at least 5 samples per group; (ii) high-quality metadata describing sperm morphology defects; (iii) human-specific expression profiling by microarray; and (iv) availability of raw data for reprocessing. After completing an extensive search, three GSE profiles (GSE6967,

GSE6968, and GSE6872) belonging to GSE6969 superseries were selected. These datasets contained teratozoospermia samples and transcripts expression was profiled using the GPL2507 (Sentrix Human-6 Expression BeadChip), GPL2700 (Sentrix HumanRef-8 Expression BeadChip), and GPL570 ([HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array) platforms. The KinHub database (http://www.kinhub.org/kinases.html) was used to compile a comprehensive list of human kinase genes.

Microarray data processing: Data processing and integration were performed using the R statistical programming language. After combining three GEO datasets, the ComBat method through SVA package was used to correct for batch effects (9). To address platform heterogeneity beyond batch correction, probe-to-gene mapping was performed using platform-specific annotation files (Bioconductor annotation packages for Affymetrix and Illumina arrays), ensuring consistent gene-level summarization across datasets. Principal component analysis (PCA) and boxplots were utilized to confirm the elimination of batch effects (10). Given the modest sample size (n=22 teratozoospermia *vs.* n=22 normozoospermia), stringent statistical thresholds and integrated multiple datasets were applied to enhance statistical power, although it should be emphasized that larger cohorts would further strengthen the findings. As the final output, a unified expression matrix was generated by combining data from the three datasets.

Identification of differentially expressed genes: Differentially expressed genes (DEGs) were extracted from the unified expression matrix by comparing "teratozoospermia" and "normozoospermia" sample groups using the R package limma (11). A log2 fold change threshold of $\geq|1|$ and an adjusted p-value of <0.01 were applied to determine statistical significance. DEGs belonging to the kinase gene family were prioritized in this study. The Venny 2.0 tool (https://bioinfogp.cnb.csic.es/tools/venny/index2.0.2.html) was used to intersect the kinase gene list from the KinHub database with the set of DEGs.

Validation of DEGs: Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic value of gene expression differences between teratozoospermia and normozoospermia samples (12). To ensure robustness, ROC curves were generated using leave-one-out cross-validation (LOOCV) on the unified dataset, with

the area under the ROC curve (AUC) calculated for each candidate gene to evaluate their diagnostic potential. This statistical analysis was conducted using the Prism software (version 9.1.0; GraphPad, US) (13).

Classification, gene ontology, and pathway enrichment analyses: The list of DEG kinases was comprehensively cross-referenced against the KinBase database (http://kinase.com/web/current/ kinbase/) which is a curated repository of eukaryotic protein kinase sequences and classifications. Pathway and enrichment analyses were conducted to identify biological mechanisms associated with differentially expressed kinase genes. The kyoto encyclopedia of genes and genomes (KEGG) database was used for pathways analysis, while gene ontology (GO) analysis examined enriched biological process (BP), cellular component (CC), and molecular function (MF). The GO terms were visualized using the adjusted p-value, the count of participating genes, and the Enrichr combined score. The Enrichr and SRplot tools were utilized to perform the pathway and enrichment analyses on the DEG kinases (14, 15).

Results

Data collection and expression analysis: The overall analysis pipeline is summarized in figure 1. The details of the three GEO datasets used in this study are provided in table 1. A total of 536 human kinase genes were identified from the KinHub database. The integrated analysis of the three GEO datasets resulted in the identification of 1,292 DEGs between teratozoospermia (n=22) and normozoospermia samples (n=22). By comparing the DEGs with the list of human kinase genes, 34 differentially expressed kinase genes were identified (10 upregulated and 24 downregulated) (Table 2A and 2B). In table 2, "LogFC" refers to the log2 fold change in gene expression, representing the ratio of expression levels between teratozoospermia and normozoospermia samples. A positive LogFC indicates upregulation of the gene in teratozoospermia, while a negative value indicates downregulation compared to normozoospermia. This metric allows for the quantification and comparison of gene expression changes across the studied groups. Among the differentially expressed kinase genes, ROR1 displayed the most significant upregulation (LogFC= 2.89, adjusted p=0.00000000014), whereas STK39 showed the most significant downregulation (LogFC=-2.12, adjusted p=0.000000000018).
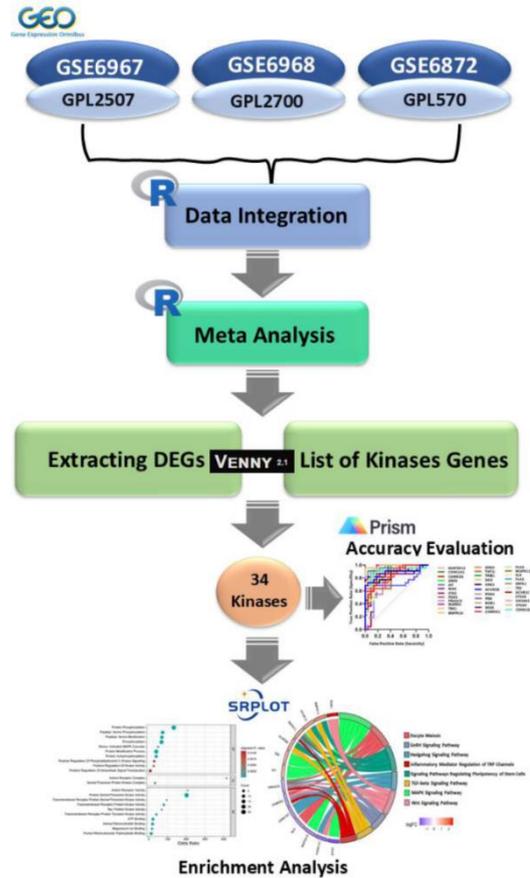

Figure 1. Schematic flowchart of the study

Table 1. Three GEO datasets used in this study

GEO profile	Platform	Samples	
		Teratozoospermia	Normozoospermia
GSE6967	GPL2507	8	5
GSE6968	GPL2700	6	4
GSE6872	GPL570	8	13
Total		22	22

Both kinases also demonstrated strong diagnostic value, with AUC values of 0.96 and 0.98 for ROR1 and STK39, respectively. These high LogFC values and low p-values highlight ROR1 and STK39 as potential key drivers of kinase-mediated defects in sperm morphology, consistent with prior reports of their roles in cellular signaling pathways relevant to spermatogenesis.

ROC analysis: ROC analysis evaluated the accuracy of the selected DEG kinases in predicting diagnostic status. The expression levels of the 34 differentially expressed kinase genes showed significant diagnostic value, as indicated by their

Table 2A. List of upregulated DEG kinases and AUC scores of ROC plots

Symbol	Official full name	Expression condition	LogFC	Adj. p-value	ROC AUC
BMPR1A	Bone morphogenetic protein receptor type-1A	Up	1.631108906	0.000000147	0.93
GRK5	G protein-coupled receptor kinase 5	Up	1.735332	0.000000182	0.93
KIT	Mast/stem cell growth factor receptor kit	Up	1.001294	0.000049	0.84
ROR1	Tyrosine-protein kinase transmembrane receptor ROR1	Up	2.889551	0.00000000014	0.96
MAPK11	Mitogen-activated protein kinase 11	Up	1.255455	0.000799	0.82
TEK	Angiopoietin-1 receptor	Up	1.072098603	0.0000105	0.88
ACVR1C	Activin receptor type-1C	Up	1.310127	0.00000726	0.88
CAMKK1	Calcium/calmodulin-dependent protein kinase kinase 1	Up	1.111033287	0.0000307	0.86
TAF1L	Transcription initiation factor TFIID subunit 1-like	Up	1.173132	0.0000988	0.84
ACVR2B	Activin receptor type-2B	Up	1.191191	0.0000171	0.88

Table 2B. List of downregulated DEG kinases and AUC scores of ROC plots

Symbol	Official full name	Expression condition	LogFC	Adj. p-value	ROC AUC
TRIB1	Tribbles pseudokinase 1	Down	-1.78082	0.00000563	0.89
CAMK2G	Calcium/calmodulin-dependent protein kinase II gamma	Down	-1.12417	0.000204	0.81
CSNK1A1	Casein kinase I isoform alpha	Down	-1.68187	0.00000000203	0.95
MARK3	MAP/microtubule affinity-regulating kinase 3	Down	-1.46852	0.0000000375	0.95
MAP3K12	Mitogen-activated protein kinase kinase kinase 12	Down	-1.36294	0.0000000213	0.95
GRK4	G protein-coupled receptor kinase 4	Down	-1.17869	0.0000122	0.88
MAK	Serine/threonine-protein kinase MAK	Down	-1.07864	0.000651	0.81
STK3	Serine/threonine-protein kinase 3	Down	-1.09188	0.000137	0.80
PDK3	Pyruvate dehydrogenase kinase isozyme 3	Down	-1.37341	1.36E-07	0.92
PDK4	Pyruvate dehydrogenase lipoamide kinase isozyme 4	Down	-1.0508	0.000388	0.81
PRKACG	cAMP-dependent protein kinase catalytic subunit gamma	Down	-1.02202	0.001211	0.79
PLK4	Serine/threonine-protein kinase PLK4	Down	-1.4574	0.00000165	0.89
SLK	STE20-like serine/threonine-protein kinase	Down	-1.26533	0.000781	0.80
PLK2	Serine/threonine-protein kinase PLK2	Down	-1.62855	0.00000000542	0.95
SRPK1	SRSF protein kinase 1	Down	-1.15565	0.00000867	0.88
STK26	Serine/threonine-protein kinase MST4	Down	-1.05917	0.000273739	0.82
STK39	STE20/SPS1-related proline-alanine-rich protein kinase	Down	-2.12129	0.000000000018	0.98
EIF2AK1	Eukaryotic translation initiation factor 2-alpha kinase 1	Down	-1.26015	0.00000015	0.90
SIK3	Serine/threonine-protein kinase SIK3	Down	-1.03895	0.000023	0.85
MOK	MAPK/MAK/MRK overlapping kinase	Down	-1.44084	0.00000341	0.89
PBK	Lymphokine-activated killer T-cell-originated protein kinase	Down	-1.12039	0.002721558	0.73
TBK1	Serine/threonine-protein kinase TBK1	Down	-1.56174	0.000000131	0.92
VRK3	Inactive serine/threonine-protein kinase VRK3	Down	-1.31768	0.000122	0.83
CSNK1G1	Casein kinase I isoform gamma-1	Down	-1.15939	0.00000541	0.87

AUC values (Table 2). High AUC scores (>0.9) across most genes indicate robust discriminatory power, suggesting these kinases could serve as reliable transcriptomic markers for early teratozoospermia detection in clinical semen analysis (Figure 2).

Classification and validation of DEG kinases: Table 3 provides a detailed breakdown of the various groups and families represented within the set of identified DEG kinases according to the KinBase database. Specifically, the DEG kinases were found to span multiple major kinase groups, including the MAP kinase cascades, calcium/ calmodulin dependent protein kinases, casein kinase 1, tyrosine kinase, and tyrosine kinase-like groups. Within these broader groups, the kinases were further classified into families. This broad representation underscores the involvement of
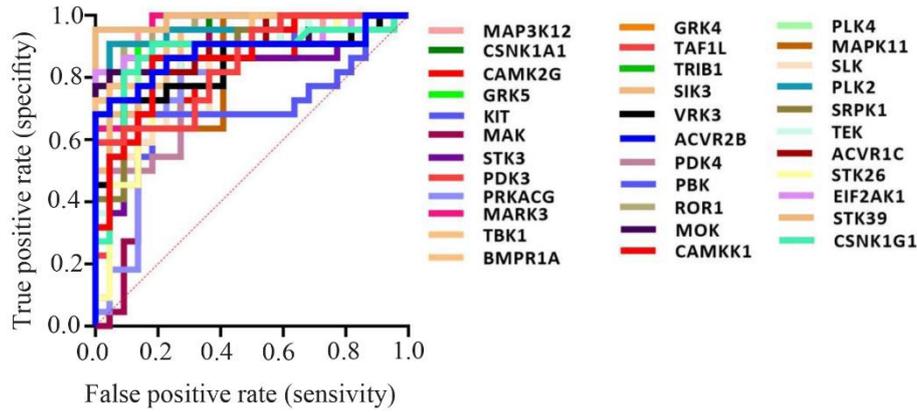
Figure 2. ROC curves for 34 DEG kinases (all AUC >0.7)

Table 3. Classification of DEG kinases by KinBase database in terms of group, family, and subfamily

| Symbol	Group	Family
STK3	MAPK cascade kinases	MAP4K (MAP kinase kinase kinase kinase)
SLK	MAP cascade kinases	MAP4K (MAP kinase kinase kinase kinase)
STK26	MAP cascade kinases	MAP4K (MAP kinase kinase kinase kinase)
STK39	MAP cascade kinases	MAP4K (MAP kinase kinase kinase kinase)
CAMK2G	Calcium/calmodulin-dependent kinases	Calcium/calmodulin-dependent protein kinase family II
MARK3	Calcium/calmodulin-dependent kinases	CAMK (calcium/calmodulin regulated kinase) -like
SIK3	Calcium/calmodulin-dependent kinases	CAMK (calcium/calmodulin regulated kinase) -like
CSNK1A1	Casein kinase 1	Casein kinase 1 alpha (CK1α)
VRK3	Casein kinase 1	Vaccinia-related kinase
CSNK1G1	Casein kinase 1	Casein kinase 1
TEK	Tyrosine kinase	Receptor tyrosine kinase
KIT	Tyrosine kinase	Platelet-derived growth factor receptor
ROR1	Tyrosine kinase	Ror
BMPR1A	Tyrosine kinase-like	Serine/threonine kinase receptors
ACVR1C	Tyrosine kinase-like	Serine/threonine kinase receptors
TRIB1	Tyrosine kinase-like	Serine/threonine kinase receptors
ACVR2B	Tyrosine kinase-like	Serine/threonine kinase receptors
MAP3K12	Tyrosine kinase-like	Mixed lineage kinases
CAMKK1	Other*	Calcium/calmodulin-dependent protein kinase
PLK4	Other	Polo like kinases
PLK2	Other	Polo like kinases
PBK	Other	Poorly named as T-cell originated kinase
TBK1	Other	IκB kinase
EIF2AK1	Other	PEK
PDK3	Atypical*	Pyruvate dehydrogenase kinase
PDK4	Atypical	Pyruvate dehydrogenase kinase
TAF1L	Atypical	TATA-box binding protein associated factor 1
GRK5	Group named after member families PKA, PKG, and PKC	G-protein coupled receptor kinase
GRK4	Group named after member families PKA, PKG, and PKC	G-protein coupled receptor kinase
MOK	Group named after member families CDK, MAPK, GSK3, and CLK	RCK
SRPK1	Group named after member families CDK, MAPK, GSK3, and CLK	SR protein kinase
MAPK11	Group named after member families CDK, MAPK, GSK3, and CLK	Mitogen activated protein kinase
MAK	Group named after member families CDK, MAPK, GSK3, and CLK	MAP kinase kinase kinase kinase
PRKACG	Group named after member families PKA, PKG, and PKC	Protein kinase A

* Other: The Other group contains several kinase families that do not fit within any of the other main kinase groups
* Atypical: Atypical kinases whose kinase domains do not have significant sequence similarity to eukaryotic protein kinases
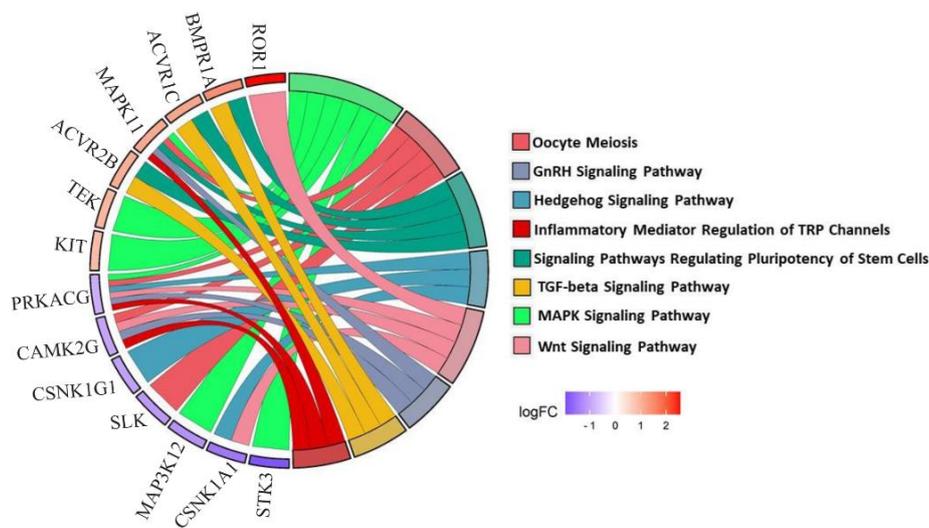
diverse signaling cascades in teratozoospermia, where disruptions in MAP kinase or tyrosine kinase families may impair sperm motility and acrosome reaction, as evidenced in related infertility studies.

Gene ontology and KEGG pathway enrichment analysis: The Enrichr database identified enriched KEGG pathways and gene ontology terms associated with the differentially expressed kinase genes, using a p-adjusted value threshold of <0.01. The results of the most significant and predominant top 10 GO terms and enrichment pathways, based on the number of genes involved in, are presented using bubble plots for the enriched

GO terms and chord plots for the KEGG pathways, including BP, CC, and MF as shown in figures 3 and 4, respectively. The significant enrichment of specific KEGG path-ways and GO terms suggests that altered kinase activity may directly contribute to the intracellular signaling disruptions seen in teratozoospermia. Notably, enrichments in pathways like MAPK signaling and GO terms related to cytoskeletal organization provide mechanistic insights into how kinase dysregulation could lead to abnormal sperm head/tail structures, linking transcriptomic changes to phenotypic outcomes.
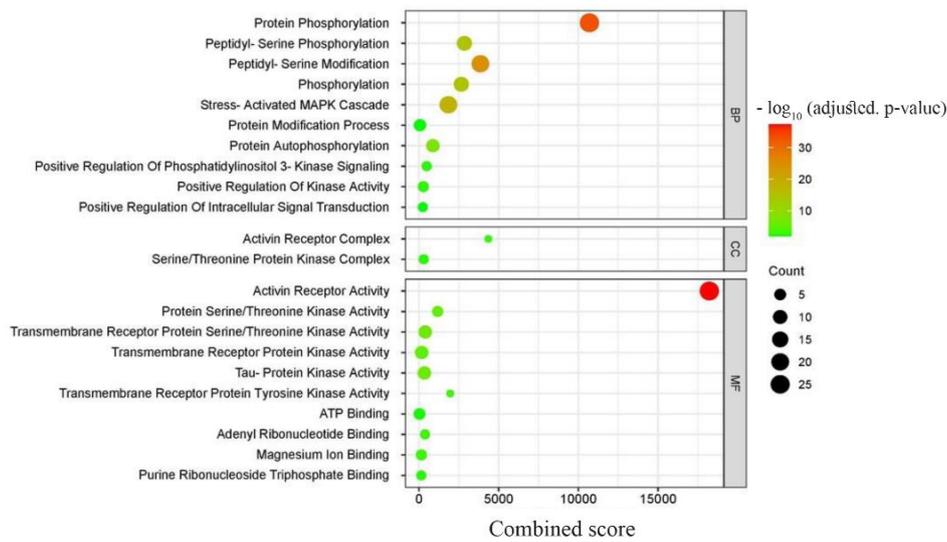
Figure 3. Bubble plot of the functional enrichment analysis (top GO terms) of the DEG kinases. This bubble plot displays the most significantly enriched GO terms, including biological processes (BP), cellular components (CC), and molecular functions (MF) related to important phosphorylation processes. The size of the bubbles represents the number of genes associated with each GO term, while the color indicates the adjusted p-value

Figure 4. Chord plot of enriched KEGG pathways for 34 DEG kinases in teratozoospermia versus normozoospermia. Genes (outer ring) link to pathways (inner ring) by ribbon thickness (gene count) and color: red (oocyte meiosis), blue (GnRH signaling), cyan (Hedgehog), dark red (TRP regulation), green (stem cell pluripotency), yellow (TGF-β), light green (MAPK), and pink (Wnt). LogFC gradient (blue: down; red: up) highlights key kinases like ROR1 (up in Wnt) and STK39 (down in MAPK), revealing signaling disruptions in sperm defects

Discussion

The main goal of this study was to identify kinases potentially involved in teratozoospermia by integrating multiple gene expression datasets. Generally, 34 differentially expressed kinases linked to critical signaling pathways were identified that regulate spermatogenesis and sperm function. Spermatogenesis is a complex process requiring the coordinated expression of numerous genes; disruptions in these genes can lead to morphological sperm abnormalities and male infertility (16-18). Phosphorylation serves as a key regulatory mechanism within many signaling pathways, including transcription, cell cycle progression, and apoptosis (6, 19). Several kinases are known to play essential roles in sperm development and function. For instance, TSSK3 is involved in spermiogenesis and sperm tail formation, FYN kinase affects sperm head and acrosome shaping, and mutations in TSSK1B have been linked to asthenoteratozoospermia (20-23). Understanding how kinase-mediated signaling pathways influence sperm morphology could open avenues for novel diagnostic and personalized therapeutic strategies.

The 34 kinases identified in our study participate in major biological pathways, notably GnRH, Hedgehog, TGF-β, MAPK, and Wnt signaling. These pathways collaboratively regulate critical stages of spermatogenesis. For example, GnRH signaling via ERK1/2 is vital for gonadotrope differentiation, Hedgehog signaling controls germline development, and MAPK governs spermatogonial renewal and sperm maturation. Wnt signaling also contributes to post-transcriptional regulation of sperm maturation, with disruptions leading to infertility characterized by malformed and immotile sperm (24-30). Our findings enhance understanding of the complex signaling disruptions underlying teratozoospermia. By mapping dysregulated kinases to these pathways, a framework for future research is provided to explore the regulation of gene expression and functional consequences for sperm development. These insights may guide the development of targeted diagnostics or personalized treatments. Despite new insights, this study has key limitations. The small sample size may limit statistical power and generalizability. Using public datasets and different microarray platforms introduces variability and potential confounding. mRNA levels may not reflect the actual protein function, requiring proteomic validation. Functional roles of kinases need experimental confirmation. Also, transcript data from testicular biopsies may not perfectly represent mature sperm function. Future larger, proteomic, and functional studies are needed to validate and build on these findings.

Conclusion

This study identified 34 differentially expressed kinases associated with teratozoospermia, implicating major signaling pathways such as GnRH, Hedgehog, TGF-β, MAPK, and Wnt in the pathogenesis of abnormal sperm morphology. While these findings provide promising candidates for understanding molecular mechanisms, their clinical utility remains to be validated through rigorous experimental and clinical studies. Future research should focus on validating our integrative transcriptomic findings by using immunohistochemistry, qPCR, and Western blot analyses in human testicular tissue samples. These methodologies will enable the assessment of protein expression, localization, and phosphorylation status, providing critical functional insights into kinase involvement in teratozoospermia and translating these insights into diagnostic or therapeutic applications.

Conflict of Interest

The authors declare that they have no competing interests.

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