

A Multi-Source Profile of TSSK3: testis specific serine kinase 3 as an IDG Understudied Kinase

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Abstract

TSSK3 (testis specific serine kinase 3) is a gene classified within the Illuminating the Druggable Genome (IDG) program as a darkkinase, kinase target. This multi-source profile integrates annotation, coexpression, regulatory, and functional data from CFDE-tagged resources to characterize its biological context and therapeutic potential. Our analysis reveals 23 PubMed co-mentions, identifying top coexpressed partners including FAM229A, RP11-274B21.2, RP11-274B21.4. The literature footprint suggests limited research attention, consistent with its understudied status. Enrichr gene-set lookup identifies cellular protein modification process (GO:0006464) as a leading annotation. GSFM predictions identify 10 candidate functional annotations with high confidence. No regulatory element data were available for this locus. Multi-dataset association analysis via the Harmonizome identifies 2208 gene-set associations across multiple biological datasets. Together, these findings provide a comprehensive baseline for future investigation of TSSK3 as a druggable target.

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1. Introduction

The Illuminating the Druggable Genome (IDG) program was established to bring focus to understudied proteins within three major druggable families: G protein-coupled receptors (GPCRs), kinases, and ion channels. [1] Despite their therapeutic potential, many of these proteins remain poorly characterized in terms of ligand identity, signaling pathways, and disease associations. [1]

TSSK3 is encoded by a gene with Entrez ID 81629 (Ensembl: ENSG00000162526). According to MyGene-Info [2]: This gene encodes a kinase expressed exclusively in the testis that is thought to play a role in either germ cell differentiation or mature sperm function. [provided by RefSeq, Jul 2008].

2. Methods

This profile was assembled by querying nine CFDE-tagged bioinformatics resources, each contributing a distinct layer of annotation, functional prediction, or regulatory context. The CFDE consortium unifies data generation centers (DCCs) and knowledge resources under a common infrastructure to accelerate transla-

tional research on fibrosis. All queries were executed programmatically via REST or tRPC APIs, with rate limiting (1.2 s inter-call delay) to respect server constraints. Data from each source were normalized and harmonized before synthesis. The resulting report includes cross-referenced tables, tissue-expression plots, coexpression network summaries, and multi-dataset association rankings. Figures were rendered by matplotlib and seaborn.

Data sources used in this profile:

1. **MyGeneInfo** (<https://mygene.info>) for gene annotation, functional summary, and genomic coordinates. [2]
2. **IDG Classification API** (<https://maayanlab.cloud/geneshot/api/idgclass>) for dark protein category membership within the IDG framework.
3. **Geneshot** (<https://maayanlab.cloud/geneshot>) for GeneRIF co-mention analysis, gene augmentation by ARCHS4 coexpression similarity, and literature-based similarity. [3]
4. **Gene-Specific Functional Model** (GSFM, <https://gsfm.maayanlab.cloud>) for functional predictions via the tRPC API (model: *gsfm-rummagene*,

source: GO_Process). [4]

5. **Enrichr** (<https://maayanlab.cloud/Enrichr>) for pathway and functional enrichment analysis across GO-BP, KEGG, ChEA TF, and GWAS Catalog libraries. [5]
6. **CFDE Linked Data Hub** (<https://ldh.genome.net/work/cfde/ldh/>) for regulatory element annotation from SCREEN and xQTL evidence from GTEx and EN-TEEx.
7. **ARCHS4** (<https://maayanlab.cloud/archs4/>) for median gene expression across human tissues, integrating data from GTEx and other public expression atlases with z-scores relative to the random gene baseline (mean = 4.336, std = 3.921).
8. **Metabolomics Workbench MetGENE** (<https://www.metabolomicsworkbench.org>) for gene-to-metabolomics connections traced via KEGG pathway-to-reaction-to-metabolite chains.
9. **Harmonizome** (<https://maayanlab.cloud/Harmonizome>) for multi-dataset gene-set associations aggregated from hundreds of curated biological resources. [6]

3. Results

3.1 Literature Co-Mention Landscape

A total of 23 PubMed IDs mention TSSK3 in GeneRIF annotations [3].

Top co-mentioned genes with TSSK3:

Rank	Gene	PMIDs	Fraction
1	TSSK3	2	0.6667
2	ZBTB7C	2	0.2222
3	CARTPT	1	0.0159
4	RB1CC1	1	0.0149

Table 1. TSSK3 – Top co-mentioned genes

3.2 Coexpression Network

ARCHS4-based coexpression analysis identifies genes whose expression patterns correlate with TSSK3 across human tissues, suggesting shared biological functions or co-regulation [3].

A total of 20 genes were identified as significantly co-expressed with TSSK3. The top partners by similarity score are listed below.

3.3 Literature-Based Gene Similarity

GeneRIF-based similarity identifies genes that share biological context with TSSK3 in curated gene-relation-inference statements compiled from the biomedical literature [3].

Rank	Gene	Similarity
1	FAM229A	0.6280
2	RP11-274B21.2	0.5585
3	RP11-274B21.4	0.5576
4	RP4-816N1.8	0.5373
5	TSSK4	0.5326
6	RP11-384K6.6	0.5217
7	PHBP9	0.5110
8	DUSP8P5	0.4988
9	AC093162.5	0.4792
10	LENG8	0.4771

Table 2. Top 10 genes coexpressed with TSSK3 across human tissues, ranked by similarity score (Source: ARCHS4)

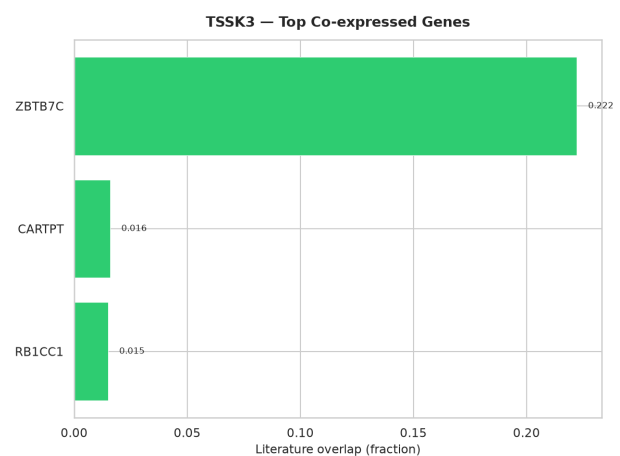


Figure 1. Bar chart showing the top coexpressed genes for TSSK3, with similarity scores derived from ARCHS4 cross-tissue correlation analysis. (Source: ARCHS4 via Geneshot)

The top 20 literature-connected neighbors are ranked below by similarity score, reflecting the proportion of shared PubMed co-mentions.

Rank	Gene	Similarity
1	IFNE	0.0417
2	RNA5-8SN3	0.0002
3	PER2	0.0000
4	PER3	0.0000
5	PERM1	0.0000
6	PERP	0.0000
7	PES1	0.0000
8	PFAS	0.0000
9	PFDN1	0.0000
10	PFDN2	0.0000

Table 3. Top 10 literature-similar genes for TSSK3, ranked by GeneRIF similarity score

3.4 Regulatory Element Landscape (CFDE Linked Data Hub)

The CFDE Linked Data Hub integrates regulatory element data from SCREEN, GTEx, and EN-TEx to map regulatory elements and quantitative trait loci associated with TSSK3. Regulatory elements include enhancers, promoters, and insulators whose activity profiles overlap or target the TSSK3 locus.

No regulatory elements or xQTL evidence were identified for the TSSK3 locus, which may reflect incomplete annotation for this genomic region.

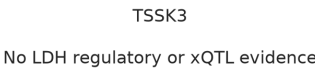


Figure 2. Summary of regulatory elements and xQTL evidence linked to the TSSK3 locus, as reported by the CFDE Linked Data Hub. (Source: CFDE Linked Data Hub)

3.5 Tissue Expression Profile (ARCHS4)

ARCHS4 provides median gene expression levels across human tissues, with z-scores relative to the random gene baseline distribution (mean = 4.336, std = 3.921). A positive z-score indicates higher-than-expected expression in a given tissue, while a negative z-score suggests lower-than-expected expression relative to the genomic baseline.

Top tissues by absolute z-score:

3.6 Functional Predictions (GSFM)

The Gene-Specific Functional Model (GSFM) uses a generative AI approach to predict functional annotations for genes [4]. The model (gsfm-rummagene) was queried for GO Biological Process predictions for TSSK3, returning predicted terms with associated probabilities, z-scores, and known-annotation status.

A total of 10 GO-BP predictions were returned. The top predictions by probability are listed below, with known annotations marked to distinguish established knowledge from novel predictions.

Rank	Tissue	Median	Z-Score
1	System	0.00	-1.11
2	System.Connective Tissue	0.00	-1.11
3	System.Connective Tissue.Bone marrow	0.00	-1.11
4	System.Connective Tissue.Bone	0.00	-1.11
5	System.Digestive System	0.00	-1.11
6	System.Digestive System.Esophagus	0.00	-1.11
7	System.Digestive System.Intestine	0.00	-1.11
8	System.Digestive System.Liver	0.00	-1.11
9	System.Digestive System.Pancreas	0.00	-1.11
10	System.Digestive System.Stomach	0.00	-1.11

Table 4. Top 10 tissues ranked by expression z-score for TSSK3, derived from ARCHS4 cross-tissue analysis (Source: ARCHS4)

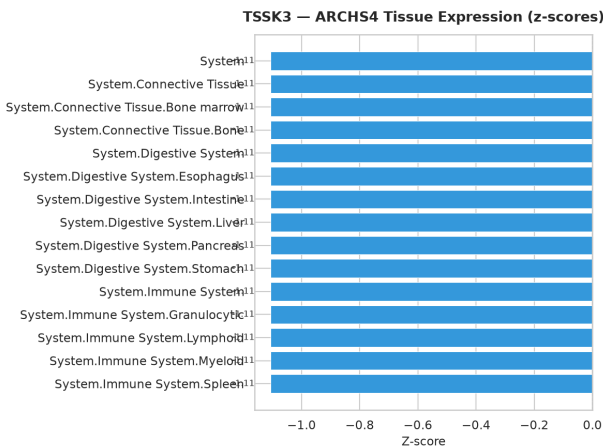


Figure 3. Bar chart of TSSK3 expression z-scores across human tissues, showing tissue-specific enrichment relative to the genomic expression baseline. (Source: ARCHS4)

3.7 Metabolomics Connections (Metabolomics Workbench MetGENE)

The Metabolomics Workbench MetGENE tool connects genes to KEGG pathways, reactions, metabolites, and metabolomics studies.

No MetGENE pathway connections were found for TSSK3. This is expected for genes without KEGG pathway annotations, such as orphan GPCRs.

3.8 Multi-Dataset Associations (Harmonizome)

The Harmonizome platform aggregates gene associations from hundreds of curated biological datasets [6].

Rank	Term	Prob	Z	Known
1	protein phosphorylation (GO:0006468)	0.7224	2.85	Yes
2	spermatogenesis (GO:0007283)	0.2139	1.92	Yes
3	protein autophosphorylation (GO:0046777)	0.1109	2.47	No
4	flagellated sperm motility (GO:0030317)	0.0671	1.85	No
5	spermatid development (GO:0007286)	0.0498	1.74	Yes
6	MAPK cascade (GO:0000165)	0.0318	1.65	No
7	peptidyl-serine phosphorylation (GO:0018105)	0.0292	2.17	No
8	male meiotic nuclear division (GO:0007140)	0.0091	1.70	No
9	protein dephosphorylation (GO:0006470)	0.0076	1.72	No
10	regulation of cell cycle phase transition (GO:1901987)	0.0061	2.03	No

Table 5. Top 10 GO-BP functional predictions for TSSK3 from the GSFM model (gsfm-rummagene), ranked by predicted probability (Source: GSFM)

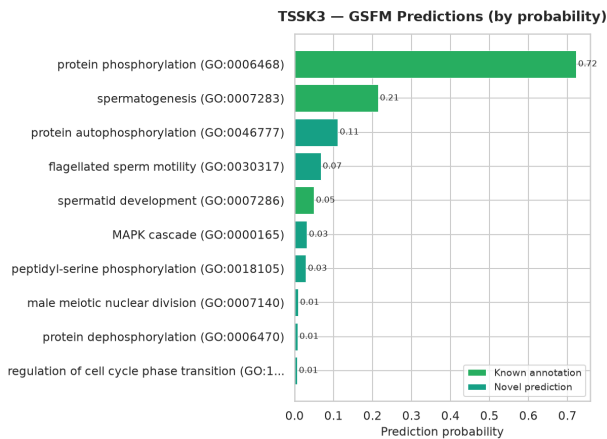


Figure 4. Hierarchical bar chart of GSFM GO-BP predictions for TSSK3, showing predicted functional terms ranked by probability with z-score shading. (Source: GSFM, Ma'ayan Lab)

A total of **2208** gene-set associations were found for TSSK3 across 2 distinct datasets.

Data sources: JASPAR Predicted Human Transcription Factor Targets 2025, JASPAR Predicted Mouse Transcription Factor Targets 2025

Rank	Gene Set	Z-Score
1	KLF5	+184.535
2	ZNF740	+174.848
3	ZNF148	+170.669
4	KLF16	+149.485
5	SP3	+142.157
6	TFAP2A	+139.919
7	MAZ	+138.743
8	RREB1	+134.727
9	KLF2	+134.421
10	SP9	+133.381

Table 6. TSSK3 – Top Harmonizome associations (Source: Harmonizome)

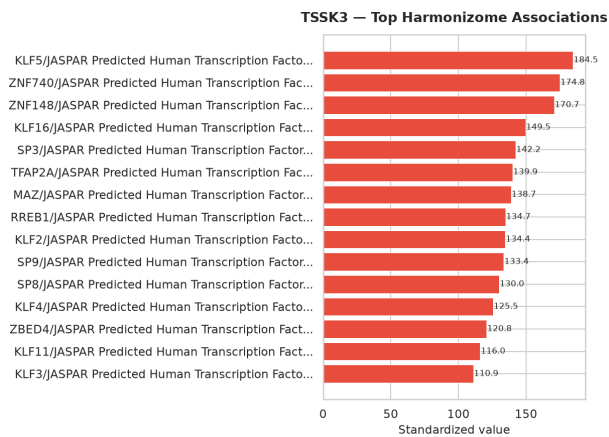


Figure 5. Top 10 Harmonizome gene-set associations for TSSK3, ranked by standardized z-score across multiple curated biological datasets. Data: JASPAR TF Target predictions. (Source: Harmonizome)

3.9 Gene Annotation Lookup

The Enrichr genemap service was used to identify all curated gene sets and pathway terms that include TSSK3. Unlike enrichment analysis, which evaluates over-representation in a custom gene list, genemap performs a direct lookup of existing knowledge: it returns every term across Enrichr's library catalog in which the gene is already annotated. [5].

GO Biological Process terms:

Term
cellular protein modification process (GO:0006464)
phosphorylation (GO:0016310)
protein phosphorylation (GO:0006468)

Table 7. TSSK3 – GO Biological Process terms containing this gene

ChEA Transcription Factor terms:

GWAS Catalog associations:

Term
POU5F1 CHEA
SOX2 CHEA

Table 8. TSSK3 – ChEA TF targets containing this gene

Trait
Pre-treatment Viral Load In HIV-1 Infection

Table 9. TSSK3 – GWAS Catalog entries containing this gene

4. Discussion

The literature footprint of TSSK3 consists of 23 PubMed co-mentions, indicating limited research attention. Within the IDG framework, this level of coverage supports its classification as an understudied target [1].

4.1 Therapeutic Context

As a member of the protein family family, TSSK3 represents a potentially druggable target. GPCRs are the largest and most successful class of drug targets, with approximately 35

4.2 Coexpression Insights

Coexpression analysis reveals that TSSK3 shares expression patterns with FAM229A, RP11-274B21.2, RP11-274B21.4, suggesting potential shared biological functions or tissue-specific co-regulation. These coexpression partners form a functional neighborhood that may point to upstream regulators or downstream effectors relevant to TSSK3 activity. Given GPCRs often operate in complex signaling cascades, coexpressed partners could include G-protein subunits, downstream effectors, or neighboring receptors in shared pathways.

4.3 Literature Network Insights

GeneRIF-based similarity identifies IFNE as the most literature-connected neighbor, though similarity scores were low across the board, reflecting the sparse annotation landscape around TSSK3.

4.4 Knowledge Gaps and Priorities

Key priorities for future investigation of TSSK3 include:

1. Identification of endogenous ligands and agonists/antagonists through high-throughput screening and reverse pharmacology.
2. Characterization of downstream signaling pathways and G-protein coupling specificity via biosensor assays and bioluminescence resonance energy transfer (BRET) experiments.

3. Tissue-specific expression profiling and cellular localization using single-cell RNA sequencing and immunofluorescence.
4. Genetic association studies to link TSSK3 variants to disease phenotypes using GWAS meta-analysis and Mendelian randomization.
5. Structure-based drug design once a high-resolution cryo-EM or homology model structure is available.
6. Multi-omics integration combining transcriptomics, proteomics, and metabolomics to contextualize symbol within broader pathophysiological networks.

5. Supplementary Information

This section provides quick-reference summaries and resource links for TSSK3. The GSFM model page can be revisited for up-to-date functional predictions as the model is retrained:

GSFM predictions for TSSK3: <https://gsfm.maayanlab.cloud/gene/TSSK3>

5.1 Data Summary

Key identifiers and annotation counts for TSSK3 are summarized below.

Field	Value
Symbol	TSSK3
Entrez Gene ID	81629
Ensembl	ENSG00000162526
IDG classification	darkkinase, kinase
PubMed co-mentions	23

Table 10. Data summary for TSSK3

References

1. Oprea, T. I. *et al.* Illuminating the druggable genome one target at a time. *Nature Reviews Drug Discovery* **17**, 597–598 (2018).
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3. Wang, Z. *et al.* Geneshot: a web-based platform for the analysis of gene sets. *Nucleic Acids Research* **48**, D397–D402 (2020).
4. Luo, J. *et al.* Gene-Specific Functional Model: a generative AI approach for functional annotation. *bioRxiv* (2025).
5. Rehfuess, M. *et al.* Enrichr: a cloud-based platform for genomic data analysis. *Nucleic Acids Research* (2023).
6. Liberles, D. A. *et al.* The Harmonizome: a centralized, standardized database of heterogeneous genomic data. *Nucleic Acids Research* **48**, D371–D379 (2020).