**Supplementary Tables.-**

**Table S1.** Data retrieval and read information of used datasets

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***Experiment Run*** | ***Sample type*** | ***Assay type*** | ***Bio Project*** | ***Database*** | ***Library Layout*** | ***Library Source*** | ***Platform*** | ***Cell type*** | ***Organism*** |
| SRR1791305 | CONTROL | RNA-Seq | PRJNA274708 | GEO | PAIRED | TRANSCRIPTOMIC | ILLUMIA | Sperm | Homo sapiens |
| SRR1791309 |
| SRR1791310 |
| SRR1791311 | TIC |
| SRR1791324 |
| SRR1791330 |
| SRR1791342 | IUI |
| SRR1791347 |
| SRR1791350 |
| SRR1791358 | ART |
| SRR1791361 |
| SRR1791366 |

Control, Normal samples; TIC, Timed Intercourse; IUI, Intrauterine Insemination; ART, Assisted Reproductive Technology.

**Table S2.** Characteristics of the population selected

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristics | Control | TIC | IUI | ART |
| Male Age | 35 | 34.6 | 33.6 | 34.2 |
| Female Age | 32.3 | 32 | 31.1 | 33.6 |
| Total Million sperm | 193.4 | 172.9 | 235.8 | 159 |
| Sperm Motility (%) | 54 | 52.3 | 50 | 50 |
| Sperm Morphology (Normal forms %) | 10.8 | 10.6 | 5.7 | 9.2 |
| TMC | 113.9 | 93.9 | 125.5 | 83.8 |

Control, Normal samples; TIC, Timed Intercourse; IUI, Intrauterine Insemination; ART, Assisted Reproductive Technology, TMC, Total Motile count.

**Table S3.** Alignment rate of all the samples using HISAT2

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Sample*** | ***Type*** | ***Read*** | ***Input Read Count*** | ***Overall read mapping rate*** |
| SRR1791305 | Control | Left read | 13034367 | **82.32%** |
| Right read |
| SRR1791309 | Left read | 9493416 | **90.72%** |
| Right read |
| SRR1791310 | Left read | 18055937 | **75.05%** |
| Right read |
| SRR1791311 | TIC | Left read | 11831017 | **91.13%** |
| Right read |
| SRR1791324 | Left read | 20178320 | **84.84%** |
| Right read |
| SRR1791330 | Left read | 12283033 | **88.67%** |
| Right read |
| SRR1791342 | IUI | Left read | 19708862 | **80.28%** |
| Right read |
| SRR1791347 | Left read | 13196795 | **77.99%** |
| Right read |
| SRR1791350 | Left read | 25563142 | **80.91%** |
| Right read |
| SRR1791358 | ART | Left read | 16954762 | **84.97%** |
| Right read |
| SRR1791361 | Left read | 13429725 | **76.48%** |
| Right read |
| SRR1791366 | Left read | 19517936 | **80.06%** |
| Right read |

Control, Normal samples; TIC, Timed Intercourse; IUI, Intrauterine Insemination; ART, Assisted Reproductive Technology.

**Table S4**. Gene ontology analysis of differentially expressed genes associated with TIC

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ***Expression*** | ***Category*** | ***Term*** | ***Count*** | ***%*** | ***P-value*** | ***FDR*** |
| **Up regulated** | GOTERM\_BP\_FAT | GO:0010467 -gene expression | 22 | 24.44 | 1.72E-04 | 0.275912 |
| GOTERM\_BP\_FAT | GO:0016070 -RNA metabolic process | 20 | 22.22 | 3.31E-04 | 0.528446 |
| GOTERM\_BP\_FAT | GO:0034645 - cellular macromolecule biosynthetic process | 19 | 21.11 | 0.002906 | 4.555189 |
| GOTERM\_BP\_FAT | GO:0097190~apoptotic signaling pathway | 5 | 5.55 | 0.02724689 | 35.76167 |
| GOTERM\_BP\_FAT | GO:0001666 - response to hypoxia | 4 | 4.44 | 0.018711 | 26.11073 |
| GOTERM\_MF\_FAT | GO:0097159-organic cyclic compound binding | 19 | 21.11 | 0.016422 | 18.90228 |
| GOTERM\_MF\_FAT | GO:0003676-nucleic acid binding | 14 | 15.55 | 0.016421 | 35.25557 |
| GOTERM\_MF\_FAT | GO:0003677~DNA binding | 11 | 12.22 | 0.018731873 | 21.27989 |
| GOTERM\_MF\_FAT | GO:0043565-sequence-specific DNA binding | 7 | 7.77 | 0.0158985 | 18.35489 |
| GOTERM\_MF\_FAT | GO:0002039~p53 binding | 3 | 3.33 | 0.007425917 | 9.000334 |
| GOTERM\_CC\_FAT | GO:0030529-intracellular ribonucleoprotein complex | 6 | 6.66 | 0.0211569 | 22.73523 |
| GOTERM\_CC\_FAT | GO:1990904-ribonucleoprotein complex | 6 | 6.66 | 0.0212614 | 22.83466 |
| **Down regulated** | GOTERM\_BP\_FAT | GO:0010467-gene expression | 28 | 28.86 | 0.013527 | 20.49379 |
| GOTERM\_BP\_FAT | GO:0007049-cell cycle | 14 | 14.43 | 0.004273 | 6.956394 |
| GOTERM\_BP\_FAT | GO:0006605-protein targeting | 6 | 6.18 | 0.096483 | 81.88715 |
| GOTERM\_BP\_FAT | GO:0043933~macromolecular complex subunit organization | 15 | 15.46 | 0.040135 | 49.83196 |
| GOTERM\_BP\_FAT | GO:0006936~muscle contraction | 5 | 5.15 | 0.028093342 | 38.11235497 |
| GOTERM\_MF\_FAT | GO:0003723-RNA binding | 11 | 11.34 | 0.032339 | 34.00838 |
| GOTERM\_MF\_FAT | GO:0042803-protein homo dimerization activity | 7 | 7.21 | 0.026872 | 29.13595 |
| GOTERM\_MF\_FAT | GO:0044822-poly(A) RNA binding | 9 | 9.27 | 0.032845 | 34.44324 |
| GOTERM\_MF\_FAT | GO:0005198-structural molecule activity | 7 | 7.21 | 0.035944 | 37.05016 |
| GOTERM\_CC\_FAT | GO:1990904-ribonucleoprotein complex | 7 | 7.21 | 0.0439 | 44.76581 |
| GOTERM\_CC\_FAT | GO:0030055-cell-substrate junction | 5 | 5.15 | 0.042276 | 43.5127 |
| GOTERM\_CC\_FAT | GO:0048471-perinuclear region of cytoplasm | 8 | 8.24 | 0.004722 | 6.066214 |
| GOTERM\_CC\_FAT | GO:0005925~focal adhesion | 5 | 5.15 | 0.039720367 | 41.48646 |

GO, Gene Ontology; BP, Biological Process; MF, Molecular Function; CC, Cellular Component.

**Table S5.** Gene ontology analysis of differentially expressed genes associated with IUI

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ***Expression*** | ***Category*** | ***Term*** | ***Count*** | ***%*** | ***P-value*** | ***FDR*** |
| **Down regulated** | GOTERM\_BP\_FAT | GO:0007049~cell cycle | 37 | 11.07 | 0.004796699 | 8.420902 |
| GOTERM\_BP\_FAT | GO:0070887-cellular response to chemical stimulus | 51 | 15.26 | 0.011635 | 19.2747 |
| GOTERM\_BP\_FAT | GO:0033554-cellular response to stress | 42 | 12.57 | 6.56E-04 | 1.193898 |
| GOTERM\_BP\_FAT | GO:0034599-cellular response to oxidative stress | 13 | 3.89 | 8.08E-05 | 0.147748 |
| GOTERM\_BP\_FAT | GO:0034645~cellular macromolecule biosynthetic process | 91 | 27.24 | 0.002026 | 3.643051 |
| GOTERM\_MF\_FAT | GO:0003723-RNA binding | 73 | 21.85 | 2.57E-19 | 3.85E-16 |
| GOTERM\_MF\_FAT | GO:0003676~nucleic acid binding | 89 | 26.64 | 4.86E-06 | 0.007282 |
| GOTERM\_MF\_FAT | GO:0045296-cadherin binding | 16 | 4.79 | 3.08E-05 | 0.046129 |
| GOTERM\_MF\_FAT | GO:0043566~structure-specific DNA binding | 9 | 2.69 | 9.52E-04 | 1.416076 |
| GOTERM\_MF\_FAT | GO:0005198-structural molecule activity | 37 | 11.07 | 2.88E-10 | 4.32E-07 |
| GOTERM\_CC\_FAT | GO:0005739-mitochondrion | 51 | 15.26 | 2.19E-06 | 0.003148 |
| GOTERM\_CC\_FAT | GO:0005912-adherens junction | 38 | 11.37 | 1.60E-11 | 2.30E-08 |
| GOTERM\_CC\_FAT | GO:0005681-spliceosomal complex | 10 | 2.99 | 0.001588 | 2.261168 |
| GOTERM\_CC\_FAT | GO:0030054~cell junction | 42 | 12.57 | 1.72E-05 | 0.024773 |
| GOTERM\_CC\_FAT | GO:0005576~extracellular region | 104 | 31.13 | 1.61E-06 | 0.002318 |

GO, Gene Ontology; BP, Biological Process; MF, Molecular Function; CC, Cellular Component.

**Table S6.** Gene ontology analysis of differentially expressed genes associated with ART

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ***Expression*** | ***Category*** | ***Term*** | ***Count*** | ***%*** | ***P-value*** | ***FDR*** |
| **Up regulated** | GOTERM\_BP\_FAT | GO:0046907~intracellular transport | 16 | 8.83 | 0.027955 | 38.61081 |
| GOTERM\_BP\_FAT | GO:0009057~macromolecule catabolic process | 13 | 7.18 | 0.032442 | 43.30945 |
| GOTERM\_BP\_FAT | GO:0016311~dephosphorylation | 7 | 3.86 | 0.030013 | 40.80913 |
| GOTERM\_BP\_FAT | GO:0016925~protein sumoylation | 4 | 2.20 | 0.037414 | 48.1192 |
| GOTERM\_BP\_FAT | GO:0010605~negative regulation of macromolecule metabolic process | 21 | 11.60 | 0.027482 | 38.09458 |
| GOTERM\_MF\_FAT | GO:0003730~mRNA 3'-UTR binding | 3 | 1.65 | 0.033817 | 37.75051 |
| GOTERM\_MF\_FAT | GO:0005543~phospholipid binding | 6 | 3.31 | 0.04718 | 48.62007 |
| GOTERM\_CC\_FAT | GO:0016604~nuclear body | 7 | 3.86 | 0.013384134 | 16.675276 |
| GOTERM\_CC\_FAT | GO:0016605-PML body | 4 | 2.20 | 0.016267 | 19.91202 |
| GOTERM\_CC\_FAT | GO:0044451~nucleoplasm part | 9 | 4.97 | 0.04775 | 48.43903 |
| GOTERM\_CC\_FAT | GO:0005652~nuclear lamina | 2 | 1.10 | 0.047905 | 48.5527 |
| **Down regulated** | GOTERM\_BP\_FAT | GO:0034645~cellular macromolecule biosynthetic process | 26 | 32.91 | 0.014909842 | 22.45957 |
| GOTERM\_BP\_FAT | GO:0010467-gene expression | 30 | 37.97 | 0.001524 | 2.549241 |
| GOTERM\_BP\_FAT | GO:0048534~hematopoietic or lymphoid organ development | 7 | 8.86 | 0.045746 | 54.74691 |
| GOTERM\_BP\_FAT | GO:0016070~RNA metabolic process | 25 | 31.64 | 0.011508405 | 17.799012 |
| GOTERM\_BP\_FAT | GO:0001892~embryonic placenta development | 3 | 3.79 | 0.036851017 | 47.048278 |
| GOTERM\_MF\_FAT | GO:0003676-nucleic acid binding | 24 | 30.37 | 0.007368 | 9.295997 |
| GOTERM\_MF\_FAT | GO:0044822-poly(A) RNA binding | 13 | 16.45 | 7.01E-04 | 0.920497 |
| GOTERM\_MF\_FAT | GO:0097159-organic cyclic compound binding | 31 | 39.24 | 0.01032 | 12.79128 |
| GOTERM\_MF\_FAT | GO:0003735~structural constituent of ribosome | 4 | 5.06 | 0.042307 | 43.46466 |
| GOTERM\_CC\_FAT | GO:1990904-ribonucleoprotein complex | 11 | 13.92 | 4.09E-04 | 0.510839 |
| GOTERM\_CC\_FAT | GO:0005912-adherens junction | 8 | 10.12 | 0.011348 | 13.31917 |
| GOTERM\_CC\_FAT | GO:0070161-anchoring junction | 8 | 10.12 | 0.012844 | 14.94662 |
| GOTERM\_CC\_FAT | GO:0005654-nucleoplasm | 19 | 24.05 | 0.013347 | 15.4884 |
| GOTERM\_CC\_FAT | GO:0016604-nuclear body | 5 | 6.329 | 0.039224 | 39.41496 |

GO, Gene Ontology; BP, Biological Process; MF, Molecular Function; CC, Cellular Component.

**Table S7.** List of Top Significant DEGs in impaired spermatogenesis

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| ***Regulation*** | ***Gene***  ***Symbol*** | ***Description*** | ***Gene IDs*** | ***Fold change*** | ***p-value*** |
| **Up regulated** | FAM46C | Putative nucleotidyltransferase FAM46C | 25451 | 4.689298 | 2.21E-16 |
| LMAN1L | Lectin, mannose binding 1 like | 20015 | 4.509868 | 1.15E-15 |
| RNF168 | E3 ubiquitin-protein ligase RNF168 | 20404 | 4.20433 | 4.67E-15 |
| METAP1 | Methionine aminopeptidase 1 | 20205 | 3.972865 | 1.42E-15 |
| NSUN4 | 5-methylcytosine rRNA methyltransferase | 27843 | 3.705902 | 8.90E-15 |
| ATAD1 | ATPase family AAA domain-containing protein 1 | 41294 | 3.417925 | 9.70E-17 |
| PRKAA1 | 5'-AMP-activated protein kinase catalytic subunit alpha-1 | 22681 | 3.26206 | 3.04E-15 |
| MARCH7 | E3 ubiquitin-protein ligase MARCH7 | 23606 | 2.707237 | 5.15E-15 |
| C10orf90 | Fragile site associated tumor suppressor | 15486 | 2.500561 | 4.07E-16 |
| DPY19L1 | Probable C - mannosyltransferase | 26625 | 2.404213 | 1.23E-14 |
| **Down regulated** | STEAP4 | Metalloreductase | 38313 | -3.42828 | 2.63E-08 |
| PRUNE2 | Protein prune homolog 2 | 16931 | -2.89545 | 1.72E-07 |
| LPP | Lipoma-preferred partner | 33155 | -2.24093 | 1.87E-08 |
| RIN2 | Ras and Rab interactor 2 | 25579 | -2.23826 | 1.01E-07 |
| TLCD2 | TLC domain containing protein 2 | 27820 | -2.23294 | 2.76E-08 |
| SLC38A2 | Solute carrier family 38 | 28124 | -2.21444 | 2.32E-10 |
| CMYA5 | Cardiomyopathy-associated protein 5 | 37804 | -2.18749 | 6.45E-08 |
| TNFRSF14 | Tumor necrosis factor receptor superfamily member 14 | 7840 | -2.15969 | 1.86E-07 |
| LAMP2 | Lysosome-associated membrane glycoprotein 2 | 26360 | -2.06412 | 1.02E-08 |
| TBC1D9 | TBC1 domain family member 9 | 10740 | -2.0114 | 6.05E-08 |

\*Uncharacterized proteins and genes which are not found in STRING are ignored \*p-val <0.05 \*fold change (fc) >2 Up-regulated, <-2 Down-regulated

**Table S8.** Gene ontology analysis of differentially expressed genes associated with impaired spermatogenesis

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ***Expression*** | ***Category*** | ***Term*** | ***Count*** | ***%*** | ***P-value*** | ***FDR*** |
| **Up regulated** | GOTERM\_BP\_FAT | GO:0019953~sexual reproduction | 194 | 12.89 | 2.02E-75 | 1.07E-71 |
| GOTERM\_BP\_FAT | GO:0007283~spermatogenesis | 156 | 10.36 | 1.09E-73 | 2.63E-70 |
| GOTERM\_BP\_FAT | GO:0048232~male gamete generation | 156 | 10.36 | 1.50E-73 | 2.63E-70 |
| GOTERM\_BP\_FAT | GO:0007276~gamete generation | 162 | 10.76 | 9.95E-64 | 1.31E-60 |
| GOTERM\_BP\_FAT | GO:0044703~multi-organism reproductive process | 197 | 13.08 | 1.60E-62 | 1.69E-59 |
| GOTERM\_MF\_FAT | GO:0097367~carbohydrate derivative binding | 145 | 9.634551 | 7.28E-03 | 3.18E-01 |
| GOTERM\_MF\_FAT | GO:0030554~adenyl nucleotide binding | 122 | 8.10 | 5.97E-06 | 2.63E-03 |
| GOTERM\_MF\_FAT | GO:0005524~ATP binding | 118 | 7.84 | 9.91E-06 | 2.81E-03 |
| GOTERM\_MF\_FAT | GO:0035639~purine ribonucleoside triphosphate binding | 137 | 9.10 | 3.14E-05 | 4.05E-03 |
| GOTERM\_MF\_FAT | GO:0003774~motor activity | 21 | 1.39 | 4.04E-05 | 4.05E-03 |
| GOTERM\_CC\_FAT | GO:0005929~cilium | 113 | 7.508306 | 1.27E-36 | 6.24E-34 |
| GOTERM\_CC\_FAT | GO:0097223~sperm part | 63 | 4.186047 | 1.89E-36 | 6.24E-34 |
| GOTERM\_CC\_FAT | GO:0036126~sperm flagellum | 29 | 1.92691 | 1.99E-18 | 1.88E-16 |
| GOTERM\_CC\_FAT | GO:0001669~acrosomal vesicle | 40 | 2.657807 | 1.71E-22 | 2.82E-20 |
| GOTERM\_CC\_FAT | GO:0005694~chromosome | 98 | 6.511628 | 3.82E-09 | 1.80E-07 |
| **Down regulated** | GOTERM\_BP\_FAT | GO:0006952~defense response | 21 | 24.70 | 2.62E-06 | 6.20E-03 |
| GOTERM\_BP\_FAT | GO:0009605~response to external stimulus | 23 | 27.05 | 2.42E-05 | 2.87E-02 |
| GOTERM\_BP\_FAT | GO:1901700~response to oxygen-containing compound | 18 | 21.17 | 9.08E-05 | 5.62E-02 |
| GOTERM\_BP\_FAT | GO:1901701~cellular response to oxygen-containing compound | 14 | 16.47 | 9.49E-05 | 5.62E-02 |
| GOTERM\_BP\_FAT | GO:0048584~positive regulation of response to stimulus | 21 | 24.70 | 1.82E-04 | 8.01E-02 |
| GOTERM\_MF\_FAT | GO:0097367~carbohydrate derivative binding | 18 | 21.17 | 1.74E-02 | 6.06E-01 |
| GOTERM\_MF\_FAT | GO:0005509~calcium ion binding | 8 | 9.41 | 4.00E-02 | 7.46E-01 |
| GOTERM\_MF\_FAT | GO:1901681~sulfur compound binding | 7 | 8.23 | 5.93E-04 | 1.40E-01 |
| GOTERM\_MF\_FAT | GO:0008201~heparin binding | 6 | 7.058 | 7.31E-04 | 1.40E-01 |
| GOTERM\_MF\_FAT | GO:0005178~integrin binding | 5 | 5.88 | 1.28E-03 | 1.63E-01 |
| GOTERM\_CC\_FAT | GO:0005576~extracellular region | 36 | 42.35294 | 2.79E-04 | 2.18E-02 |
| GOTERM\_CC\_FAT | GO:0031988~membrane-bounded vesicle | 30 | 35.29412 | 5.39E-04 | 2.18E-02 |
| GOTERM\_CC\_FAT | GO:0043230~extracellular organelle | 25 | 29.41176 | 9.75E-04 | 2.86E-02 |
| GOTERM\_CC\_FAT | GO:0005794~Golgi apparatus | 14 | 16.47059 | 1.47E-02 | 2.52E-01 |
| GOTERM\_CC\_FAT | GO:0005783~endoplasmic reticulum | 14 | 16.47059 | 3.41E-02 | 3.89E-01 |

GO, Gene Ontology; BP, Biological Process; MF, Molecular Function; CC, Cellular Component.

**Table S9.** Pathway analysis of differentially expressed genes associated with impaired spermatogenesis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ***Group*** | ***Category*** | ***Term*** | ***Count*** | ***%*** | ***P-value*** | ***Genes*** | ***FDR*** |
| **Up regulated** | KEGG\_  PATHWAY | HSA-04110: Cell cycle | 17 | 1.12 | 2.02E-05 | CDKN2D, BUB1B, TTK, CDC25C, SMC1B, RBL2, CCNA1, CCNB2, WEE1, FZR1, CDC45, PTTG1, PTTG2, ORC2, CDK1, MCM4, BUB1 | 4.62E-03 |
| KEGG\_  PATHWAY | HSA-04114: Oocyte meiosis | 14 | 0.93 | 3.26E-04 | CDC25C, AURKA, SMC1B, CCNB2, PLCZ1, STAG3, PPP2R1B, PTTG1, PTTG2, PRKACG, CDK1, CALM3, PGR, BUB1 | 3.73E-02 |
| KEGG\_  PATHWAY | HSA-05016: Huntington’s disease | 18 | 1.19 | 1.16E-03 | DNAI2, DNAH2, DNAH10, HIP1, DNAH7, DNAH17, COX7A2, DNAH9, AP2B1, COX6B2, COX7B2, DNALI1, CLTCL1, TBPL1, SLC25A31, IFT57, DNAI1, DNAL1 | 8.87E-02 |
| KEGG\_  PATHWAY | HSA-05034: Alcoholism | 16 | 1.06 | 3.43E-03 | HDAC4, H2AFB2, HIST1H2AH, HIST1H2AK, HIST1H2BL, HDAC11, PDYN, GNG3, GNG2, CAMK4, GNAS, CALM3, HIST1H2AG, HIST1H2AA, HIST1H3C, HIST1H2BA | 1.86E-01 |
| KEGG\_  PATHWAY | HSA-00010: Glycolysis / Gluconeogenesis | 9 | 0.59 | 4.06E-03 | LDHC, ADH4, PDHA2, PGAM2, GAPDHS, PGK2, PFKP, LDHAL6B, HK1 | 1.86E-01 |
| **Down regulated** | KEGG\_  PATHWAY | HSA-04913: Ovarian steroidogenesis | 6 | 7.05 | 3.55E-06 | SCARB1, HSD3B1, ADCY3, IGF1, LDLR, PRKACB | 4.86E-04 |
| KEGG\_  PATHWAY | HSA-04925: Aldosterone synthesis and secretion | 6 | 7.05 | 4.26E-05 | SCARB1, HSD3B1, ADCY3, PRKCA, LDLR, PRKACB | 2.91E-03 |
| KEGG\_  PATHWAY | HSA-04974: Protein digestion and absorption | 5 | 5.88 | 8.65E-04 | COL3A1, KCNE3, KCNQ1, COL12A1, SLC38A2 | 3.36E-02 |
| KEGG\_  PATHWAY | HSA-05032: Morphine addiction | 5 | 5.88 | 9.81E-04 | GRK5, ADCY3, PRKCA, PDE8B, PRKACB | 3.36E-02 |
| KEGG\_  PATHWAY | HSA-05110: Vibrio cholerae infection | 4 | 4.70 | 2.07E-03 | KCNQ1, ADCY3, PRKCA, PRKACB | 5.26E-02 |

**Table S10.** Topological parameters for Protein-protein interaction network

|  |  |  |  |
| --- | --- | --- | --- |
| ***Topological parameters*** | ***TIC*** | ***IUI*** | ***ART*** |
| ***Comprehended values*** | | |
| Clustering coefficient | 0.346 | 0.541 | 0.284 |
| Connected components | 8 | 10 | 11 |
| Network diameter | 4 | 14 | 4 |
| Network radius | 1 | 1 | 1 |
| Network centralization | 0.337 | 0.124 | 0.124 |
| Shortest paths | 200 (24%) | 35624 (73%) | 210 (12%) |
| Characteristic path length | 1.93 | 5.120 | 1.781 |
| Avg. number of neighbors | 2.207 | 9.145 | 2.143 |
| Number of nodes | 29 | 220 | 42 |
| Network density | 0.079 | 0.042 | 0.052 |
| Network heterogeneity | 0.955 | 1.102 | 0.831 |

TIC, Timed Intercourse; IUI, Intrauterine Insemination; ART, Assisted Reproductive Technology,

**Table S11.** Top genes with higher degree of connectivity in impaired spermatogenesis data

|  |  |  |  |
| --- | --- | --- | --- |
| ***Gene*** | ***Description*** | ***Degree*** | ***P-value*** |
| CDK1 | Cyclin-dependent kinase 1 | 53 | 2.18E-06 |
| BUB1 | Mitotic checkpoint serine/threonine-protein kinase BUB1 | 34 | 2.93E-05 |
| CCNB2 | G2/mitotic-specific cyclin-B2 | 34 | 7.26E-08 |
| TOP2A | DNA topoisomerase 2-alpha | 33 | 1.47E-04 |
| BUB1B | Mitotic checkpoint serine/threonine-protein kinase BUB1 beta | 30 | 8.05E-05 |
| CDCA8 | Cell division cycle associated 8 | 29 | 4.45E-05 |
| AURKA | Aurora kinase A | 28 | 1.25E-09 |
| NCAPG | Condensin complex subunit 3 | 27 | 3.29E-04 |
| KIF11 | Kinesin-like protein KIF11 | 27 | 7.45E-06 |
| TTK | Serine/threonine-protein kinase ttk/mps1 | 25 | 2.30E-06 |
| DLGAP5 | Disks large-associated protein 5 | 25 | 1.66E-06 |
| CEP55 | Centrosomal protein of 55 kDa | 24 | 4.32E-07 |
| BIRC5 | Baculoviral iap repeat-containing protein 5 | 24 | 5.09E-07 |
| PBK | Lymphokine-activated killer T-cell-originated protein kinase | 23 | 1.87E-08 |
| KIF2C | Kinesin-like protein KIF2C | 23 | 6.02E-05 |
| CENPF | Centromere protein F | 22 | 1.93E-06 |
| PTTG1 | Securin, Regulatory protein | 22 | 7.59E-09 |
| NUF2 | Kinetochore protein Nuf2 | 21 | 9.95E-07 |
| SPAG5 | Sperm-associated antigen 5 | 20 | 1.15E-07 |
| CDC45 | Cell division control protein 45 homolog | 19 | 2.65E-04 |

**Table S12.** Top hub genes rank in cytoHubba for idiopathic infertility

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Top hub genes for TIC** | | | | | | | | |
| **Degree** | | **Stress** | | **Closeness** | | **MNC** | | **Radiality** |
| AURKAIP1 | | ATP5D | | BTBD6 | | AURKAIP1 | | BTBD6 |
| BTBD6 | | ATP5I | | DCUN1D1 | | BTBD6 | | DCUN1D1 |
| EIF3A | | BTBD6 | | EIF3A | | EIF3A | | EIF3A |
| EIF4E | | EIF3A | | EIF4E | | EIF4E | | EIF4E |
| MRPL18 | | EIF4E | | PSMD6 | | MRPL18 | | PSMD6 |
| MRPS21 | | MRPS21 | | RBBP6 | | MRPS21 | | RBBP6 |
| RPL4 | | NUP160 | | RPL4 | | RPL4 | | RPL4 |
| RPL7 | | RPL4 | | RPL7 | | RPL7 | | RPL7 |
| UBA52 | | RPL7 | | UBA52 | | UBA52 | | UBA52 |
| **Top hub genes for IUI** | | | | | | | | |
| RPL18A | ACTB | | ACTB | | RPL18A | | ACTB | |
| RPL23 | CCT7 | | EIF3A | | RPL23 | | CCT7 | |
| RPL27 | CHTOP | | GNB2L1 | | RPL27 | | EIF3A | |
| RPL4 | EIF3A | | POLR2L | | RPL4 | | GNB2L1 | |
| RPL9 | HNRNPA1 | | RPL23 | | RPL9 | | GTF3A | |
| RPLP0 | HNRNPK | | RPL27 | | RPLP0 | | HNRNPA1 | |
| RPS11 | HSPA9 | | RPL9 | | RPS11 | | HNRNPK | |
| RPS13 | NUP155 | | RPLP0 | | RPS13 | | POLR2L | |
| RPS16 | POLR2L | | RPS11 | | RPS16 | | PTBP1 | |
| **Top hub genes for ART** | | | | | | | | |
| CDC26 | BMI1 | | CDC26 | | EIF1 | | BMI1 | |
| EIF2S3 | CDC26 | | EIF1 | | EIF2S3 | | CDC26 | |
| EIF4E | EIF2S3 | | EIF2S3 | | EIF4E | | EIF2S3 | |
| HIST1H2BK | EIF4E | | EIF4E | | GOLM1 | | EIF4E | |
| PSMA6 | GNAS | | RPL13 | | RPL13 | | MEX3C | |
| RPL13 | HIST1H2BK | | RPS15 | | RPS15 | | PSMA6 | |
| RPS15 | PSMA6 | | RPS19 | | RPS19 | | RPL13 | |
| RPS19 | RPL13 | | SERBP1 | | SERBP1 | | RPS15 | |
| SMG7 | RPS15 | | SMG7 | | SMG7 | | RPS19 | |

\*MNC- Maximum Neighborhood Component

**Table S13.** Top hub genes rank in cytoHubba for impaired spermatogenesis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Degree** | **Stress** | **Closeness** | **MNC** | **Radiality** |
| AURKA | BUB1B | AURKA | AURKA | AURKA |
| BUB1 | CDK1 | BIRC5 | BUB1 | BIRC5 |
| BUB1B | GNAS | BUB1 | BUB1B | BUB1 |
| CCNB2 | GNG2 | BUB1B | CCNB2 | BUB1B |
| CDCA8 | KIF2C | CCNB2 | CDCA8 | CCNB2 |
| CDK1 | NUP155 | CDCA8 | CDK1 | CDCA8 |
| DLGAP5 | NUP98 | CDK1 | DLGAP5 | CDK1 |
| KIF11 | NUPL1 | KIF11 | KIF11 | PRKACB |
| NCAPG | PRKACB | NCAPG | NCAPG | PRKACG |

\*MNC- Maximum Neighborhood Component

**Table S14.** Top GO functions and KEGG pathways enriched for the genes in module 1

|  |  |  |  |
| --- | --- | --- | --- |
| **Description** | **Gene symbol** | **Count** | **P value** |
| GO:0000280~nuclear division (BP) | TOP2A, SPAG5, CDCA8, NCAPG, BUB1B, TTK, KIF11, KIF15, AURKA, CCNB2, CENPF, PTTG1, NUF2, PBK, CDK1, BIRC5, KIF2C, BUB1, DLGAP5, CEP55 | 20 | 1.65E-28 |
| GO:0051276~chromosome organization (BP) | TOP2A, SPAG5, CDCA8, NCAPG, BUB1B, TTK, AURKA, CENPF, PTTG1, NUF2, CDK1, BIRC5, KIF2C, BUB1, DLGAP5, CEP55 | 16 | 1.64E-14 |
| GO:0022402~cell cycle process (BP) | TOP2A, SPAG5, CDCA8, NCAPG, BUB1B, TTK, KIF11, KIF15, AURKA, CCNB2, CENPF, PTTG1, NUF2, PBK, CDK1, BIRC5, KIF2C, BUB1, DLGAP5, CEP55 | 20 | 1.83E-21 |
| GO:0000166~nucleotide binding (MF) | TOP2A, PBK, CDK1, BUB1B, TTK, KIF2C, KIF11, BUB1, KIF15, AURKA | 10 | 4.68E-05 |
| GO:0016301~kinase activity (MF) | CCNB2, PBK, CDK1, BUB1B, TTK, BUB1, AURKA | 7 | 8.83E-05 |
| GO:0016887~ATPase activity (MF) | TOP2A, KIF2C, KIF11, KIF15 | 4 | 6.53E-03 |
| GO:0015630~microtubule cytoskeleton (CC) | TOP2A, SPAG5, CDCA8, NCAPG, BUB1B, TTK, KIF11, KIF15, AURKA, CCNB2, CENPF, CDK1, BIRC5, KIF2C, DLGAP5, CEP55 | 16 | 9.24E-15 |
| GO:0005829~cytosol (CC) | CDCA8, NCAPG, BUB1B, KIF11, KIF15, AURKA, CCNB2, CENPF, PTTG1, NUF2, CDK1, BIRC5, KIF2C, BUB1 | 14 | 1.57E-05 |
| GO:0030496~midbody (CC) | CENPF, SPAG5, CDK1, CDCA8, BIRC5, CEP55, AURKA | 7 | 8.92E-09 |
| HSA 04110: Cell cycle | CCNB2, PTTG1, CDK1, BUB1B, TTK, BUB1 | 6 | 3.58E-08 |
| HSA 04114: Oocyte meiosis | CCNB2, PTTG1, CDK1, BUB1, AURKA | 5 | 2.17E-06 |
| HSA 04115: p53 signaling pathway | CCNB2, CDK1 | 2 | 6.62E-02 |

GO, Gene Ontology; BP, Biological Process; MF, Molecular Function; CC, Cellular Component.