**Kidney transplantation: Transcriptomic analysis and comparisons between donor groups.**

**Pathway analysis lists.**

**Table 6.2** – REACTOME pathway analysis of upregulated DEGs in DBD and living biopsies compared at T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-Value** |
| **REACTOME Pathway** | Microtubule-dependent trafficking of connexons from Golgi to the plasma membrane | 3 | 11.5% | 6.20E-04 |
| Cilium Assembly | 3 | 11.5% | 6.80E-04 |
| Post-chaperonin tubulin folding pathway | 3 | 11.5% | 8.90E-04 |
| Formation of tubulin folding intermediates by CCT/TriC | 3 | 11.5% | 1.10E-03 |
| Recruitment of NuMA to mitotic centrosomes | 3 | 11.5% | 1.40E-03 |
| Platelet degranulation | 4 | 15.4% | 1.70E-03 |
| RHO GTPases activate IQGAPs | 3 | 11.5% | 1.80E-03 |
| Gap junction assembly | 3 | 11.5% | 2.20E-03 |
| Recycling pathway of L1 | 3 | 11.5% | 3.70E-03 |
| Intraflagellar transport | 3 | 11.5% | 4.50E-03 |
| Hedgehog 'off' state | 3 | 11.5% | 4.80E-03 |
| Kinesins | 3 | 11.5% | 6.00E-03 |
| Translocation of SLC2A4 (GLUT4) to the plasma membrane | 3 | 11.5% | 1.00E-02 |
| Integrin cell surface interactions | 3 | 11.5% | 1.10E-02 |
| COPI-mediated anterograde transport | 3 | 11.5% | 1.40E-02 |
| Mitotic Prometaphase | 3 | 11.5% | 1.70E-02 |
| Resolution of Sister Chromatid Cohesion | 3 | 11.5% | 2.10E-02 |
| MHC class II antigen presentation | 3 | 11.5% | 2.10E-02 |
| RHO GTPases Activate Formins | 3 | 11.5% | 2.60E-02 |
| GRB2:SOS provides linkage to MAPK signalling for Integrins | 2 | 7.7% | 2.80E-02 |
| Common pathway of fibrin clot formation | 2 | 7.7% | 4.0E-02 |
| Integrin signalling | 2 | 7.7% | 4.2E-02 |
| Separation of sister chromatids | 3 | 11.5% | 4.6E-02 |

**Table 6.3** – Biological process analysis of upregulated DEGs in DBD and living biopsies compared at T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category**  | **Term**  | **Count**  | **Percentage** | **P-Value** |
| **Biological Process** | Cytoskeleton-dependent intracellular transport | 3 | 11.5% | 3.20E-04 |
| Platelet degranulation | 4 | 15.4% | 4.70E-04 |
| Negative regulation of extrinsic apoptotic signalling pathway via death domain receptors | 3 | 11.5% | 1.10E-03 |
| Microtubule-based process | 3 | 11.5% | 1.30E-03 |
| Response to hydrogen peroxide | 3 | 11.5% | 2.60E-03 |
| Positive regulation of smooth muscle cell proliferation | 3 | 11.5% | 3.60E-03 |
| Induction of bacterial agglutination | 2 | 7.7% | 5.90E-03 |
| Blood coagulation, fibrin clot formation | 2 | 7.7% | 5.90E-03 |
| Positive regulation of peptide hormone secretion | 2 | 7.7% | 1.20E-02 |
| Plasminogen activation | 2 | 7.7% | 1.30E-02 |
| Positive regulation of heterotypic cell-cell adhesion | 2 | 7.7% | 1.60E-02 |
| Protein polymerization | 2 | 7.7% | 1.90E-02 |
| Innate immune response | 4 | 15.4% | 2.50E-02 |
| Cellular protein complex assembly | 2 | 7.7% | 2.60E-02 |
| Protein homooligomerization | 3 | 11.5% | 2.80E-02 |
| Positive regulation of exocytosis | 2 | 7.7% | 3.10E-02 |
| Fibrinolysis | 2 | 7.7% | 3.10E-02 |
| Extracellular matrix organization | 3 | 11.5% | 3.40E-02 |
| Negative regulation of endothelial cell apoptotic process | 2 | 7.7% | 4.10E-02 |
| Positive regulation of substrate adhesion-dependent cell spreading | 2 | 7.7% | 4.70E-02 |
| Positive regulation of vasoconstriction | 2 | 7.7% | 4.70E-02 |

**Table 8.3** – Biological process analysis of upregulated DEGs in DCD and living biopsies compared at T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-Value** |
| **Biological Process** | Platelet degranulation | 5 | 19.2% | 9.00E-06 |
| Blood coagulation, fibrin clot formation | 3 | 11.5% | 9.80E-06 |
| Positive regulation of peptide hormone secretion | 3 | 11.5% | 4.60E-05 |
| Plasminogen activation | 3 | 11.5% | 5.90E-05 |
| Positive regulation of heterotypic cell-cell adhesion | 3 | 11.5% | 8.90E-05 |
| Protein polymerization | 3 | 11.5% | 1.30E-04 |
| Cellular protein complex assembly | 3 | 11.5% | 2.50E-04 |
| Positive regulation of exocytosis | 3 | 11.5% | 3.40E-04 |
| Fibrinolysis | 3 | 11.5% | 3.40E-04 |
| Negative regulation of endopeptidase activity | 4 | 15.4% | 5.10E-04 |
| Negative regulation of endothelial cell apoptotic process | 3 | 11.5% | 6.10E-04 |
| Positive regulation of vasoconstriction | 3 | 11.5% | 7.90E-04 |
| Positive regulation of substrate adhesion-dependent cell spreading | 3 | 11.5% | 7.90E-04 |
| Negative regulation of extrinsic apoptotic signalling pathway via death domain receptors | 3 | 11.5% | 8.40E-04 |
| Positive regulation of protein secretion | 3 | 11.5% | 1.00E-03 |
| Platelet aggregation | 3 | 11.5% | 1.30E-03 |
| Response to calcium ion | 3 | 11.5% | 2.60E-03 |
| Induction of bacterial agglutination | 2 | 7.7% | 5.20E-03 |
| Cell-matrix adhesion | 3 | 11.5% | 6.10E-03 |
| Platelet activation | 3 | 11.5% | 9.80E-03 |
| Innate immune activation | 4 | 15.4% | 1.80E-02 |
| Response to lipopolysaccharide | 3 | 11.5% | 1.90E-02 |
| Positive regulation of ERK1 and ERK2 cascade | 3 | 11.5% | 2.20E-02 |
| Blood coagulation  | 3 | 11.5% | 2.40E-02 |
| Extracellular matrix organisation | 3 | 11.5% | 2.70E-02 |

**Table 9.3** – Biological process analysis of downregulated DEGs in DCD and living biopsies compared at T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category**  | **Term**  | **Count**  | **Percentage**  | **P-Value** |
| **Biological Process** | Oxidation-reduction process | 12 | 18.8% | 8.00E-06 |
| Cellular oxidant detoxification | 5 | 7.8% | 1.20E-04 |
| Xenobiotic metabolic process | 5 | 7.8% | 1.80E-04 |
| Gluconeogenesis | 4 | 6.2% | 5.40E-04 |
| Glutathione metabolic process | 4 | 6.2% | 1.10E-03 |
| Flavonoid biosynthetic process | 3 | 4.7% | 2.40E-03 |
| Flavonoid glucuronidation | 3 | 4.7% | 2.90E-03 |
| Receptor-mediated endocytosis | 5 | 7.8% | 4.70E-03 |
| Amino-acid betaine catabolic process | 2 | 3.1% | 7.30E-03 |
| Lipoprotein metabolic process | 3 | 4.7% | 8.40E-03 |
| Cellular response to heparin | 2 | 3.1% | 1.80E-02 |
| Cellular response to fructose stimulus | 2 | 3.1% | 1.80E-02 |
| Choline catabolic process | 2 | 3.1% | 2.20E-02 |
| Catecholamine biosynthetic process | 2 | 3.1% | 2.20E-02 |
| Response to lipopolysaccharide | 4 | 6.2% | 2.20E-02 |
| Response to drug | 5 | 7.8% | 2.50E-02 |
| Fatty acid alpha-oxidation | 2 | 3.1% | 2.50E-02 |
| Glycine metabolic process | 2 | 3.1% | 3.20E-02 |
| Urate metabolic process | 2 | 3.1% | 3.60E-02 |
| L-phenylalanine catabolic process | 2 | 3.1% | 3.90E-02 |
| Oxaloacetate metabolic process | 2 | 3.1% | 4.30E-02 |
| Beta-amyloid metabolic process | 2 | 3.1% | 4.60E-02 |

**Table 12.1** – KEGG pathway analysis of top 250 DEGs in living biopsies compared at T2 and T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **KEGG Pathway** | MAPK signalling pathway | 20 | 9.8% | 1.3E-09 |
| TNF signalling pathway | 13 | 6.3% | 2.30E-08 |
| Protein processing in endoplasmic reticulum | 14 | 6.8% | 5.10E-07 |
| Oestrogen signalling pathway | 11 | 5.4% | 9.80E-07 |
| Influenza A | 10 | 4.9% | 6.80E-04 |
| HTLV-I infection | 12 | 5.9% | 7.70E-04 |
| Legionellosis | 6 | 2.9% | 8.80E-04 |
| Osteoclast differentiation | 8 | 3.9% | 2.30E-03 |
| Hepatitis C | 8 | 3.9% | 2.50E-03 |
| Hepatitis B | 8 | 3.9% | 4.00E-03 |
| Antigen processing and presentation | 6 | 2.9% | 4.00E-03 |
| Toxoplasmosis | 7 | 3.4% | 4.20E-03 |
| Prostate cancer | 6 | 2.9% | 7.50E-03 |
| NOD-like receptor signalling pathway | 5 | 2.4% | 7.50E-03 |
| Amphetamine addiction | 5 | 2.4% | 1.30E-02 |
| Aldosterone synthesis and secretion | 5 | 2.4% | 2.60E-02 |
| Epstein-Barr virus | 6 | 2.9% | 2.70E-02 |
| Cell cycle | 6 | 2.9% | 2.90E-02 |
| Cocaine addiction | 4 | 2% | 3.10E-02 |
| Measles | 6 | 2.9% | 3.80E-02 |
| FoxO signalling pathway  | 6 | 2.9% | 3.90E-02 |
| Pathways in cancer | 11 | 5.4% | 4.70E-02 |

**Table 12.3** – Biological process analysis of top 250 DEGs in living biopsies compared at T2 and T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **Biological Process** | Response to unfolded protein | 11 | 5.4% | 2.00E-11 |
| Negative regulation of transcription from RNA polymerase II promoter | 31 | 15.1% | 2.30E-10 |
| Positive regulation of transcription from RNA polymerase II promoter | 36 | 17.6% | 4.10E-10 |
| Transcription from RNA polymerase II promoter | 23 | 11.2% | 4.40E-08 |
| Positive regulation of transcription, DNA-templated | 22 | 10.7% | 2.10E-07 |
| Response to stress | 9 | 4.4% | 3.10E-07 |
| Protein refolding | 6 | 2.9% | 4.00E-07 |
| Negative regulation of apoptotic process RT | 20 | 9.8% | 5.80E-07 |
| Regulation of cellular response to heat | 9 | 4.4% | 1.50E-06 |
| Negative regulation of ERK1 and ERK2 cascade | 8 | 3.9% | 3.10E-06 |
| Regulation of cell death RT | 5 | 2.4% | 4.20E-06 |
| Cellular response to hormone stimulus | 7 | 3.4% | 8.80E-06 |
| Response to cAMP | 7 | 3.4% | 1.00E-05 |
| Positive regulation of apoptotic process | 14 | 6.8% | 2.60E-05 |
| Negative regulation of transcription, DNA-templated | 18 | 8.8% | 3.40E-05 |
| Response to mechanical stimulus | 7 | 3.4% | 4.30E-05 |
| Regulation of cell cycle | 9 | 4.4% | 6.40E-05 |
| Regulation of mitotic cell cycle | 6 | 2.9% | 7.00E-05 |
| Negative regulation of cell proliferation | 15 | 7.3% | 1.20E-04 |
| Negative regulation of inclusion body assembly | 4 | 2% | 1.40E-04 |
| Apoptotic process | 18 | 8.8% | 1.60E-04 |
| Protein folding | 10 | 4.9% | 1.60E-04 |
| Circadian rhythm | 7 | 3.4% | 1.70E-04 |
| Skeletal muscle cell differentiation | 6 | 2.9% | 1.90E-04 |
| Positive regulation of transcription from RNA polymerase II promoter in response to endoplasmic reticulum stress | 4 | 2% | 2.60E-04 |
| Transcription, DNA-templated | 39 | 19% | 2.60E-04 |
| Cellular response to cycloheximide | 3 | 1.5% | 3.50E-04 |
| Positive regulation of gene expression | 11 | 5.4% | 6.10E-04 |
| Regulation of protein ubiquitination | 4 | 2% | 6.40E-04 |
| Positive regulation of p38MAPK cascade | 4 | 2% | 6.40E-04 |
| Positive regulation of cell differentiation | 5 | 2.4% | 6.80E-04 |
| Negative regulation of extrinsic apoptotic signalling pathway in absence of ligand | 5 | 2.4% | 6.80E-04 |
| Cellular heat acclimation | 3 | 1.5% | 7.00E-04 |
| Protein stabilization | 8 | 3.9% | 7.30E-04 |
| Regulation of cell proliferation | 9 | 4.4% | 9.80E-04 |
| Fat cell differentiation | 6 | 2.9% | 1.20E-03 |
| Positive regulation of nitric oxide biosynthetic process | 5 | 2.4% | 1.20E-03 |
| Cellular response to corticotropin-releasing hormone stimulus | 3 | 1.5% | 1.70E-03 |
| Signal transduction | 25 | 12.2% | 1.80E-03 |
| Negative regulation of cell growth | 7 | 3.4% | 2.10E-03 |
| Response to lipopolysaccharide | 8 | 3.9% | 2.10E-03 |
| Cellular response to calcium ion | 5 | 2.4% | 2.30E-03 |
| Inactivation of MAPK activity | 4 | 2% | 2.50E-03 |
| Response to cytokine | 5 | 2.4% | 2.50E-03 |
| Response to hypoxia | 8 | 3.9% | 2.80E-03 |
| Regulation of type B pancreatic cell proliferation | 3 | 1.5% | 3.20E-03 |
| Regulation of transcription from RNA polymerase II promoter | 13 | 6.3% | 3.30E-03 |
| Transforming growth factor beta receptor signalling pathway | 6 | 2.9% | 3.30E-03 |
| Platelet-derived growth factor receptor signalling pathway | 4 | 2% | 3.80E-03 |
| Cellular response to organic cyclic compound | 5 | 2.4% | 3.90E-03 |
| Negative regulation of gene expression | 7 | 3.4% | 3.90E-03 |
| Branching involved in labyrinthine layer morphogenesis | 3 | 1.5% | 4.00E-03 |
| Negative regulation of sequence-specific DNA binding transcription factor activity | 5 | 2.4% | 4.10E-03 |
| Face morphogenesis | 4 | 2% | 4.20E-03 |
| DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest | 5 | 2.4% | 4.70E-03 |
| Response to wounding | 5 | 2.4% | 4.90E-03 |
| ATP metabolic process | 4 | 2% | 5.00E-03 |
| Skeletal system morphogenesis | 4 | 2% | 5.00E-03 |
| Chaperone mediated protein folding requiring cofactor | 3 | 1.5% | 5.00E-03 |
| Cellular response to epidermal growth factor stimulus | 4 | 2% | 5.50E-03 |
| Intrinsic apoptotic signalling pathway in response to endoplasmic reticulum stress | 4 | 2% | 5.50E-03 |
| Cellular response to peptide | 3 | 1.5% | 6.10E-03 |
| Positive regulation of nuclear-transcribed mRNA poly(A) tail shortening | 3 | 1.5% | 6.10E-03 |
| Activation of MAPKKK activity | 3 | 1.5% | 6.10E-03 |
| Response to drug | 10 | 4.9% | 6.20E-03 |
| Activation of MAPK activity | 6 | 2.9% | 6.30E-03 |
| Response to starvation | 4 | 2% | 6.50E-03 |
| Negative regulation of MAP kinase activity | 4 | 2% | 7.00E-03 |
| PERK-mediated unfolded protein response | 3 | 1.5% | 7.30E-03 |
| Cellular response to interleukin-1 | 5 | 2.4% | 7.50E-03 |
| Negative regulation of cell cycle | 4 | 2% | 7.50E-03 |
| Cellular response to heat | 4 | 2% | 7.50E-03 |
| Cellular response to DNA damage stimulus | 8 | 3.9% | 7.90E-03 |
| Mitotic cell cycle arrest | 3 | 1.5% | 8.50E-03 |
| Regulation of apoptotic process | 8 | 3.9% | 8.90E-03 |
| Negative regulation of protein ubiquitination | 4 | 2% | 1.00E-02 |
| Response to muscle stretch | 3 | 1.5% | 1.30E-02 |
| Response to light stimulus | 3 | 1.5% | 1.40E-02 |
| Positive regulation of fat cell differentiation | 4 | 2% | 1.50E-02 |
| Organ regeneration | 4 | 2% | 1.50E-02 |
| Negative regulation of neuron apoptotic process | 6 | 2.9% | 1.50E-02 |
| Positive regulation of NF-kappaB transcription factor activity | 6 | 2.9% | 1.50E-02 |
| Response to heat | 4 | 2% | 1.50E-02 |
| Cellular response to extracellular stimulus | 3 | 1.5% | 1.60E-02 |
| Response to corticosterone | 3 | 1.5% | 1.60E-02 |
| G2/M transition of mitotic cell cycle | 6 | 2.9% | 1.70E-02 |
| Cell cycle arrest | 6 | 2.9% | 1.90E-02 |
| Positive regulation of pri-miRNA transcription from RNA polymerase II promoter | 3 | 1.5% | 2.00E-02 |
| Entrainment of circadian clock by photoperiod | 3 | 1.5% | 2.00E-02 |
| Negative regulation of establishment of protein localization to mitochondrion | 2 | 1% | 2.20E-02 |
| Positive regulation of endoribonuclease activity | 2 | 1% | 2.20E-02 |
| Positive regulation of mRNA endonucleolytic cleavage involved in unfolded protein response | 2 | 1% | 2.20E-02 |
| Peptidyl-tyrosine dephosphorylation | 5 | 2.4% | 2.30E-02 |
| Vasculogenesis | 4 | 2% | 2.30E-02 |
| Circadian regulation of gene expression | 4 | 2% | 2.40E-02 |
| Cellular response to hydrogen peroxide | 4 | 2% | 2.40E-02 |
| Steroid hormone mediated signalling pathway | 4 | 2% | 2.40E-02 |
| MAPK cascade | 8 | 3.9% | 2.50E-02 |
| Regulation of mRNA stability | 5 | 2.4% | 2.60E-02 |
| Positive regulation of smooth muscle cell proliferation | 4 | 2% | 2.80E-02 |
| Positive regulation of osteoblast differentiation | 4 | 2% | 2.80E-02 |
| Protein phosphorylation | 11 | 5.4% | 2.80E-02 |
| Regulation of sequence-specific DNA binding transcription factor activity | 3 | 1.5% | 3.00E-02 |
| Cellular response to amino acid starvation | 3 | 1.5% | 3.00E-02 |
| SMAD protein signal transduction | 4 | 2% | 3.00E-02 |
| Positive regulation of nucleotide-binding oligomerization domain containing 2 signalling pathway | 2 | 1% | 3.20E-02 |
| Chaperone-mediated autophagy | 2 | 1% | 3.20E-02 |
| Positive regulation of interleukin-8 production | 3 | 1.5% | 3.20E-02 |
| Response to oestrogen | 4 | 2% | 3.40E-02 |
| Somatic stem cell population maintenance | 4 | 2% | 3.40E-02 |
| Cellular response to lipopolysaccharide | 5 | 2.4% | 3.50E-02 |
| Angiogenesis | 7 | 3.4% | 3.50E-02 |
| Protein import into nucleus, translocation | 3 | 1.5% | 3.70E-02 |
| Response to radiation | 3 | 1.5% | 3.70E-02 |
| Positive regulation of angiogenesis | 5 | 2.4% | 3.70E-02 |
| Notch signalling pathway | 5 | 2.4% | 3.70E-02 |
| Regulation of transcription, DNA-templated | 25 | 12.2% | 3.70E-02 |
| Negative regulation of smooth muscle cell proliferation | 3 | 1.5% | 4.00E-02 |
| Liver regeneration | 3 | 1.5% | 4.00E-02 |
| Protein autophosphorylation | 6 | 2.9% | 4.00E-02 |
| Cellular response to fibroblast growth factor stimulus | 3 | 1.5% | 4.20E-02 |
| Protein localization to nucleus | 3 | 1.5% | 4.20E-02 |
| Cellular response to mechanical stimulus | 4 | 2% | 4.20E-02 |
| Regulation of NF-kappaB import into nucleus | 2 | 1% | 4.30E-02 |
| Negative regulation of interleukin-8 biosynthetic process | 2 | 1% | 4.30E-02 |
| Post-embryonic camera-type eye development | 2 | 1% | 4.30E-02 |
| Cellular response to ionizing radiation | 3 | 1.5% | 4.50E-02 |
| Post-embryonic development | 4 | 2% | 4.50E-02 |
| Brown fat cell differentiation | 3 | 1.5% | 4.70E-02 |
| Response to endoplasmic reticulum stress | 4 | 2% | 4.90E-02 |

**Table 14.1** – KEGG pathway analysis of top 250 DEGs in DBD biopsies compared at T2 and T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-Value** |
| **KEGG Pathway** | TNF signalling pathway | 16 | 8% | 1.70E-11 |
| MAPK signalling pathway | 20 | 10.1% | 1.80E-09 |
| Legionellosis | 9 | 4.5% | 7.70E-07 |
| NOD-like receptor signalling pathway | 9 | 4.5% | 1.00E-06 |
| Toll-like receptor signalling pathway | 11 | 5.5% | 2.20E-06 |
| Oestrogen signalling pathway | 10 | 5% | 1.00E-05 |
| Chagas disease (American trypanosomiasis) | 10 | 5% | 1.50E-05 |
| Salmonella infection | 9 | 4.5% | 2.10E-05 |
| Influenza A | 12 | 6% | 3.30E-05 |
| Hepatitis B | 11 | 5.5% | 3.60E-05 |
| Protein processing in endoplasmic reticulum | 11 | 5.5% | 1.30E-04 |
| Osteoclast differentiation | 9 | 4.5% | 5.20E-04 |
| Transcriptional misregulation in cancer | 10 | 5% | 5.80E-04 |
| Hepatitis C | 9 | 4.5% | 5.80E-04 |
| Antigen processing and presentation | 7 | 3.5% | 7.00E-04 |
| HTLV-I infection | 12 | 6% | 9.10E-04 |
| Toxoplasmosis | 8 | 4% | 9.20E-04 |
| Chemokine signalling pathway | 10 | 5% | 1.30E-03 |
| NF-κB signalling pathway | 7 | 3.5% | 1.40E-03 |
| Rheumatoid arthritis | 7 | 3.5% | 1.50E-03 |
| Cytokine-cytokine receptor interaction | 11 | 5.5% | 2.30E-03 |
| Pertussis | 6 | 3% | 4.20E-03 |
| Viral carcinogenesis | 9 | 4.5% | 8.60E-03 |
| Measles | 7 | 3.5% | 1.20E-02 |
| T cell receptor signalling pathway | 6 | 3% | 1.40E-02 |
| p53 signalling pathway | 5 | 2.5% | 1.50E-02 |
| Herpes simplex infection | 8 | 4% | 1.50E-02 |
| Bladder cancer | 4 | 2% | 2.00E-02 |
| Epstein-Barr virus infection | 6 | 3% | 3.00E-02 |
| Prostate cancer | 5 | 2.5% | 3.60E-02 |
| FoxO signalling pathway | 6 | 3% | 4.20E-02 |

**Table 14.2** – REACTOME pathway analysis of top 250 DEGs in DBD biopsies compared at T2 and T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **REACTOME Pathway** | Chemokine receptors bind chemokines | 9 | 3% | 1.5E-07 |
| Attenuation phase | 6 | 3% | 2.10E-07 |
| HSF1-dependent transactivation | 6 | 3% | 1.20E-06 |
| Senescence-Associated Secretory Phenotype (SASP) | 10 | 5% | 2.00E-06 |
| Oxidative Stress-Induced Senescence | 8 | 4% | 2.90E-04 |
| RAF-independent MAPK1/3 activation | 4 | 2% | 2.90E-04 |
| SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription | 5 | 2.5% | 3.20E-04 |
| Negative regulation of the MAPK pathway | 5 | 2.5% | 6.30E-04 |
| Regulation of HSF1-mediated heat shock response | 6 | 3% | 8.00E-04 |
| MAL1: CLOCK, NPAS2 activates circadian gene expression | 5 | 2.5% | 1.00E-03 |
| Uptake and function of diphtheria toxin | 3 | 1.5% | 1.60E-03 |
| Activation of anterior HOX genes in hindbrain development during early embryogenesis | 7 | 3.5% | 1.70E-03 |
| AUF1 (hnRNP D0) binds and destabilizes mRNA | 5 | 2.5% | 2.70E-03 |
| NFR1-induced NFκB signalling pathway | 4 | 2% | 3.70E-03 |
| Regulation of TNFR1 signalling | 4 | 2% | 4.80E-03 |
| Cyclin E associated events during G1/S transition | 3 | 1.5% | 9.10E-03 |
| AUF1 (hnRNP D0) binds and destabilizes mRNA | 5 | 2.5% | 9.30E-03 |
| Cyclin A: Cdk2-associated events at S phase entry | 3 | 1.5% | 1.00E-02 |
| MAPK6/MAPK4 signalling | 5 | 2.5% | 1.30E-02 |
| Amyloid fibre formation | 5 | 2.5% | 1.90E-02 |
| Viral RNA Complexes in the Host Cell Nucleus | 2 | 1% | 2.10E-02 |
| Transcriptional regulation by small RNAs | 5 | 2.5% | 2.50E-02 |
| ATF4 activates gene in response to endoplasmic reticulum stress | 3 | 1.5% | 2.80E-02 |
| Signalling by ERBB2 | 3 | 1.5% | 2.80E-02 |
| RNA Polymerase I promoter opening | 4 | 2% | 2.80E-02 |
| IKK complex recruitment mediated by RIP1 | 3 | 1.5% | 3.00E-02 |
| DNA methylation | 4 | 2% | 3.00E-02 |
| DNA damage/Telomere stress induced senescence | 4 | 2% | 3.20E-02 |
| Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3 | 4 | 2% | 3.30E-02 |
| SIRT1 negatively regulates rRNA expression | 4 | 2% | 3.40E-02 |
| PRC2 methylates histones and DNA | 4 | 2% | 4.10E-02 |
| Condensation of prophase chromosomes | 4 | 2% | 4.20E-02 |

**Table 14.3** – Biological process analysis of top 250 DEGs in DBD biopsies compared at T2 and T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **Biological Process** | Positive regulation of transcription from RNA polymerase II promoter | 38 | 19.1% | 3.40E-12 |
| Response to unfolded protein | 11 | 5.5% | 1.10E-11 |
| Negative regulation of apoptotic process | 23 | 11.6% | 1.60E-09 |
| Cellular response to interleukin-1 | 11 | 5.5% | 2.60E-09 |
| Transcription from RNA polymerase II promoter | 23 | 11.6% | 1.40E-08 |
| Negative regulation of transcription, DNA-templated | 22 | 11.1% | 4.30E-08 |
| Inflammatory response | 19 | 9.5% | 7.00E-08 |
| Negative regulation of transcription from RNA polymerase II promoter | 26 | 13.1% | 8.70E-08 |
| Cellular response to tumour necrosis factor | 11 | 5.5% | 1.90E-07 |
| Protein refolding | 6 | 3% | 2.90E-07 |
| Cellular response to fibroblast growth factor stimulus | 7 | 3.5% | 5.10E-07 |
| Skeletal muscle cell differentiation | 8 | 4% | 6.30E-07 |
| Chemokine-mediated signalling pathway | 9 | 4.5% | 6.30E-07 |
| Apoptotic process | 21 | 10.6% | 1.50E-06 |
| Positive regulation of cell differentiation | 7 | 3.5% | 1.90E-06 |
| Regulation of cell death | 5 | 2.5% | 3.30E-06 |
| Cellular response to hormone stimulus | 7 | 3.5% | 6.20E-06 |
| Response to cAMP | 7 | 3.5% | 7.10E-06 |
| Circadian rhythm | 8 | 4% | 1.20E-05 |
| Cellular response to epidermal growth factor stimulus | 6 | 3% | 2.00E-05 |
| Transcription, DNA-templated | 40 | 20.1% | 3.00E-05 |
| Cellular response to phorbol 13-acetate 12-myristate | 4 | 2% | 3.60E-05 |
| Regulation of cell cycle | 9 | 4.5% | 4.10E-05 |
| Cellular response to DNA damage stimulus | 11 | 5.5% | 5.80E-05 |
| Negative regulation of cell proliferation | 15 | 7.5% | 5.90E-05 |
| Regulation of apoptotic process | 11 | 5.5% | 7.00E-05 |
| Positive regulation of nitric oxide biosynthetic process | 6 | 3% | 7.50E-05 |
| Positive regulation of transcription, DNA-templated | 17 | 8.5% | 8.10E-05 |
| Negative regulation of gene expression | 9 | 4.5% | 8.40E-05 |
| Regulation of mRNA stability | 8 | 4% | 9.10E-05 |
| Positive regulation of inflammatory response | 7 | 3.5% | 1.00E-04 |
| Regulation of cellular response to heat | 7 | 3.5% | 1.20E-04 |
| Negative regulation of inclusion body assembly | 4 | 2% | 1.20E-04 |
| Positive regulation of interleukin-8 production | 5 | 2.5% | 1.30E-04 |
| Cellular response to lipopolysaccharide | 8 | 4% | 1.60E-04 |
| Lymphocyte chemotaxis | 5 | 2.5% | 1.80E-04 |
| Protein import into nucleus, translocation | 5 | 2.5% | 1.80E-04 |
| Response to cytokine | 6 | 3% | 1.90E-04 |
| 3'-UTR-mediated mRNA destabilization | 4 | 2% | 2.20E-04 |
| Chemotaxis | 8 | 4% | 2.60E-04 |
| Positive regulation of apoptotic process | 12 | 6% | 2.70E-04 |
| Cellular response to interferon-gamma | 6 | 3% | 2.90E-04 |
| Response to lipopolysaccharide | 9 | 4.5% | 2.90E-04 |
| Cellular response to cycloheximide | 3 | 1.5% | 3.10E-04 |
| Response to mechanical stimulus | 6 | 3% | 3.40E-04 |
| Cellular response to organic cyclic compound | 6 | 3% | 3.40E-04 |
| Positive regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay | 4 | 2% | 3.50E-04 |
| Erythrocyte development | 4 | 2% | 4.40E-04 |
| Positive regulation of ERK1 and ERK2 cascade | 9 | 4.5% | 4.50E-04 |
| Cell chemotaxis | 6 | 3% | 5.30E-04 |
| Regulation of protein ubiquitination | 4 | 2% | 5.40E-04 |
| Negative regulation of extrinsic apoptotic signalling pathway in absence of ligand | 5 | 2.5% | 5.40E-04 |
| Cellular response to heat | 5 | 2.5% | 5.40E-04 |
| Neutrophil chemotaxis | 6 | 3% | 5.70E-04 |
| Cellular heat acclimation | 3 | 1.5% | 6.20E-04 |
| Regulation of cell proliferation | 9 | 4.5% | 6.50E-04 |
| Negative regulation of protein ubiquitination | 5 | 2.5% | 8.00E-04 |
| Monocyte chemotaxis | 5 | 2.5% | 8.80E-04 |
| Fat cell differentiation | 6 | 3% | 9.10E-04 |
| Immune response | 13 | 6.5% | 1.40E-03 |
| Cellular response to corticotropin-releasing hormone stimulus | 3 | 1.5% | 1.50E-03 |
| Negative regulation of cell growth | 7 | 3.5% | 1.50E-03 |
| Positive regulation of gene expression | 10 | 5% | 1.50E-03 |
| Cellular response to calcium ion | 5 | 2.5% | 1.80E-03 |
| Inactivation of MAPK activity | 4 | 2% | 2.10E-03 |
| Positive regulation of NF-kappaB transcription factor activity | 7 | 3.5% | 2.50E-03 |
| Transforming growth factor beta receptor signalling pathway | 6 | 3% | 2.60E-03 |
| Regulation of type B pancreatic cell proliferation | 3 | 1.5% | 2.80E-03 |
| Nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay | 3 | 1.5% | 2.80E-03 |
| Negative regulation of interleukin-6 production | 4 | 2% | 2.90E-03 |
| Negative regulation of ERK1 and ERK2 cascade | 5 | 2.5% | 2.90E-03 |
| Positive regulation of protein catabolic process | 5 | 2.5% | 3.30E-03 |
| Positive regulation of smooth muscle cell proliferation | 5 | 2.5% | 3.30E-03 |
| I-kappaB kinase/NF-kappaB signalling | 5 | 2.5% | 3.30E-03 |
| Regulation of tumour necrosis factor-mediated signalling pathway | 4 | 2% | 3.50E-03 |
| Response to stress | 5 | 2.5% | 3.50E-03 |
| Response to molecule of bacterial origin | 3 | 1.5% | 3.60E-03 |
| Response to salt stress | 3 | 1.5% | 3.60E-03 |
| DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest | 5 | 2.5% | 3.70E-03 |
| Response to drug | 10 | 5% | 4.20E-03 |
| ATP metabolic process | 4 | 2% | 4.20E-03 |
| Lipopolysaccharide-mediated signalling pathway | 4 | 2% | 4.20E-03 |
| Somatic stem cell population maintenance | 5 | 2.5% | 4.40E-03 |
| Chaperone mediated protein folding requiring cofactor | 3 | 1.5% | 4.40E-03 |
| Regulation of keratinocyte differentiation | 3 | 1.5% | 4.40E-03 |
| Positive regulation of chemokine biosynthetic process | 3 | 1.5% | 4.40E-03 |
| Intrinsic apoptotic signalling pathway in response to endoplasmic reticulum stress | 4 | 2% | 4.60E-03 |
| Protein kinase B signalling | 4 | 2% | 4.60E-03 |
| Cellular response to peptide | 3 | 1.5% | 5.40E-03 |
| Positive regulation of nuclear-transcribed mRNA poly(A) tail shortening | 3 | 1.5% | 5.40E-03 |
| Activation of MAPKKK activity | 3 | 1.5% | 5.40E-03 |
| MAPK cascade | 9 | 4.5% | 5.70E-03 |
| PERK-mediated unfolded protein response | 3 | 1.5% | 6.40E-03 |
| Positive regulation of transcription from RNA polymerase II promoter in response to endoplasmic reticulum stress | 3 | 1.5% | 6.40E-03 |
| Positive regulation of angiogenesis | 6 | 3% | 6.60E-03 |
| Positive regulation of B cell proliferation | 4 | 2% | 7.40E-03 |
| Negative regulation by host of viral transcription | 3 | 1.5% | 7.60E-03 |
| Trophectodermal cell differentiation | 3 | 1.5% | 7.60E-03 |
| Positive regulation of cysteine-type endopeptidase activity involved in apoptotic process | 4 | 2% | 7.90E-03 |
| Response to hypoxia | 7 | 3.5% | 8.60E-03 |
| Positive regulation of neuron apoptotic process | 4 | 2% | 9.70E-03 |
| Cell migration involved in sprouting angiogenesis | 3 | 1.5% | 1.00E-02 |
| Protein folding | 7 | 3.5% | 1.10E-02 |
| Response to toxic substance | 5 | 2.5% | 1.10E-02 |
| Positive regulation of p38MAPK cascade | 3 | 1.5% | 1.10E-02 |
| Response to muscle stretch | 3 | 1.5% | 1.10E-02 |
| Negative regulation of neuron apoptotic process | 6 | 3% | 1.20E-02 |
| Movement of cell or subcellular component | 5 | 2.5% | 1.20E-02 |
| Positive regulation of fat cell differentiation | 4 | 2% | 1.20E-02 |
| Response to light stimulus | 3 | 1.5% | 1.30E-02 |
| Response to heat | 4 | 2% | 1.30E-02 |
| Protein stabilization | 6 | 3% | 1.30E-02 |
| Cell proliferation | 10 | 5% | 1.30E-02 |
| G2/M transition of mitotic cell cycle | 6 | 3% | 1.30E-02 |
| Cellular response to extracellular stimulus | 3 | 1.5% | 1.40E-02 |
| Response to corticosterone | 3 | 1.5% | 1.40E-02 |
| Cell cycle arrest | 6 | 3% | 1.50E-02 |
| Calcium-mediated signalling | 4 | 2% | 1.50E-02 |
| Regulation of transcription from RNA polymerase II promoter | 11 | 5.5% | 1.60E-02 |
| Positive regulation of osteoclast differentiation | 3 | 1.5% | 1.60E-02 |
| Negative regulation of cell migration | 5 | 2.5% | 1.60E-02 |
| Cellular response to glucocorticoid stimulus | 3 | 1.5% | 1.80E-02 |
| Positive regulation of pri-miRNA transcription from RNA polymerase II promoter | 3 | 1.5% | 1.80E-02 |
| Entrainment of circadian clock by photoperiod | 3 | 1.5% | 1.80E-02 |
| Positive regulation of fibroblast proliferation | 4 | 2% | 1.80E-02 |
| Negative regulation of cell death | 4 | 2% | 1.90E-02 |
| Peptidyl-tyrosine dephosphorylation | 5 | 2.5% | 1.90E-02 |
| Vasculogenesis | 4 | 2% | 2.00E-02 |
| Regulation of keratinocyte apoptotic process | 2 | 1% | 2.00E-02 |
| Positive regulation of endoribonuclease activity | 2 | 1% | 2.00E-02 |
| Nuclear-transcribed mRNA catabolic process, deadenylation-independent decay | 2 | 1% | 2.00E-02 |
| Bronchus cartilage development | 2 | 1% | 2.00E-02 |
| Lung smooth muscle development | 2 | 1% | 2.00E-02 |
| Positive regulation of mRNA endonucleolytic cleavage involved in unfolded protein response | 2 | 1% | 2.00E-02 |
| Positive regulation of intracellular mRNA localization | 2 | 1% | 2.00E-02 |
| Negative regulation of establishment of protein localization to mitochondrion | 2 | 1% | 2.00E-02 |
| Cellular response to hydrogen peroxide | 4 | 2% | 2.10E-02 |
| Positive regulation of neutrophil chemotaxis | 3 | 1.5% | 2.10E-02 |
| Osteoclast differentiation | 3 | 1.5% | 2.30E-02 |
| Negative regulation of myoblast differentiation | 3 | 1.5% | 2.30E-02 |
| Cellular response to vascular endothelial growth factor stimulus | 3 | 1.5% | 2.30E-02 |
| Positive regulation of osteoblast differentiation | 4 | 2% | 2.40E-02 |
| Negative regulation of sequence-specific DNA binding transcription factor activity | 4 | 2% | 2.40E-02 |
| Activation of MAPK activity | 5 | 2.5% | 2.40E-02 |
| Peripheral nervous system development | 3 | 1.5% | 2.50E-02 |
| ERK1 and ERK2 cascade | 3 | 1.5% | 2.50E-02 |
| Response to virus | 5 | 2.5% | 2.70E-02 |
| Regulation of inflammatory response | 4 | 2% | 2.70E-02 |
| Response to wounding | 4 | 2% | 2.70E-02 |
| Cellular response to oxidative stress | 4 | 2% | 2.80E-02 |
| Signal transduction | 20 | 10.1% | 2.90E-02 |
| Chaperone-mediated autophagy | 2 | 1% | 3.00E-02 |
| Positive regulation of nucleotide-binding oligomerization domain containing 2 signalling pathway | 2 | 1% | 3.00E-02 |
| T cell differentiation in thymus | 3 | 1.5% | 3.10E-02 |
| Positive regulation of GTPase activity | 12 | 6% | 3.10E-02 |
| Response to radiation | 3 | 1.5% | 3.30E-02 |
| TRIF-dependent toll-like receptor signalling pathway | 3 | 1.5% | 3.30E-02 |
| Cellular response to drug | 4 | 2% | 3.40E-02 |
| Liver regeneration | 3 | 1.5% | 3.50E-02 |
| Cellular response to glucose starvation | 3 | 1.5% | 3.50E-02 |
| Negative regulation of Notch signalling pathway | 3 | 1.5% | 3.50E-02 |
| Negative regulation of smooth muscle cell proliferation | 3 | 1.5% | 3.50E-02 |
| Negative regulation of NF-kappaB transcription factor activity | 4 | 2% | 3.60E-02 |
| Face morphogenesis | 3 | 1.5% | 3.80E-02 |
| Intrinsic apoptotic signalling pathway in response to DNA damage by p53 class mediator | 3 | 1.5% | 4.00E-02 |
| Regulation of NF-kappaB import into nucleus | 2 | 1% | 4.00E-02 |
| Negative regulation of interleukin-8 biosynthetic process | 2 | 1% | 4.00E-02 |
| Trachea cartilage development | 2 | 1% | 4.00E-02 |
| Negative regulation of mitotic cell cycle phase transition | 2 | 1% | 4.00E-02 |
| Circadian regulation of translation | 2 | 1% | 4.00E-02 |
| Response to endoplasmic reticulum stress | 4 | 2% | 4.20E-02 |
| Brown fat cell differentiation | 3 | 1.5% | 4.20E-02 |
| In utero embryonic development | 6 | 3% | 4.30E-02 |
| Positive regulation of cell cycle | 3 | 1.5% | 4.70E-02 |
| Negative regulation of inflammatory response | 4 | 2% | 4.70E-02 |
| Multicellular organism growth | 4 | 2% | 4.90E-02 |

**Table 15.1** – KEGG pathway analysis of upregulated DEGs in DBD biopsies compared at T2 and T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **KEGG Pathway** | TNF signalling pathway | 11 | 11.1% | 5.00E-09 |
| Oestrogen signalling pathway | 8 | 8.1% | 8.10E-06 |
| Chagas disease (American trypanosomiasis) | 8 | 8.1% | 1.10E-05 |
| MAPK signalling pathway | 11 | 11.1% | 1.50E-05 |
| Protein processing in endoplasmic reticulum | 9 | 9.1% | 3.40E-05 |
| Influenza A | 9 | 9.1% | 4.20E-05 |
| Legionellosis | 6 | 6.1% | 4.80E-05 |
| NOD-like receptor signalling pathway | 6 | 6.1% | 5.80E-05 |
| Hepatitis B | 8 | 8.1% | 9.70E-05 |
| Salmonella infection | 6 | 6.1% | 3.80E-04 |
| Osteoclast differentiation | 7 | 7.1% | 4.20E-04 |
| Rheumatoid arthritis | 6 | 6.1% | 4.90E-04 |
| HTLV-I infection | 9 | 9.1% | 5.70E-04 |
| Toll-like receptor signalling pathway | 6 | 6.1% | 1.20E-03 |
| Hepatitis C | 6 | 6.1% | 3.10E-03 |
| Bladder cancer | 4 | 4% | 3.50E-03 |
| Transcriptional misregulation in cancer | 6 | 6.1% | 8.20E-03 |
| Toxoplasmosis | 5 | 5.1% | 9.30E-03 |
| Chemokine signalling pathway | 6 | 6.1% | 1.30E-02 |
| Epstein-Barr virus infection | 5 | 5.1% | 1.30E-02 |
| Amphetamine addiction | 4 | 4.0% | 1.30E-02 |
| Epithelial cell signalling in Helicobacter pylori infection | 4 | 4.0% | 1.40E-02 |
| Measles  | 5 | 5.1% | 1.80E-02 |
| Pertussis | 4 | 4.0% | 1.90E-02 |
| Antigen processing and presentation | 4 | 4.0% | 1.90E-02 |
| ErbB signalling pathway  | 4 | 4.0% | 2.80E-02 |
| Prostate cancer | 4 | 4.0% | 2.80E-02 |
| Herpes simplex infection | 5 | 5.1% | 4.90E-02 |

**Table 15.3** – Biological process analysis of upregulated DEGs in DBD biopsies compared at T2 and T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **Biological Process** | Positive regulation of transcription from RNA polymerase II promoter | 27 | 27.3% | 1.50E-12 |
| Transcription from RNA polymerase II promoter | 19 | 19.2% | 8.90E-11 |
| Response to unfolded protein | 8 | 8.1% | 1.70E-09 |
| Cellular response to hormone stimulus | 7 | 7.1% | 1.00E-07 |
| Skeletal muscle cell differentiation | 7 | 7.1% | 1.80E-07 |
| Regulation of cell death | 5 | 5.1% | 2.10E-07 |
| Response to mechanical stimulus | 7 | 7.1% | 5.50E-07 |
| Protein refolding | 5 | 5.1% | 8.40E-07 |
| Cellular response to interleukin-1 | 7 | 7.1% | 1.70E-06 |
| Response to cAMP | 6 | 6.1% | 3.60E-06 |
| Positive regulation of transcription, DNA-templated | 13 | 13.1% | 1.20E-05 |
| Negative regulation of inclusion body assembly | 4 | 4% | 1.50E-05 |
| Cellular response to fibroblast growth factor stimulus | 5 | 5.1% | 1.60E-05 |
| Negative regulation of transcription from RNA polymerase II promoter | 15 | 15.2% | 1.60E-05 |
| Response to lipopolysaccharide | 8 | 8.1% | 2.10E-05 |
| Cellular response to tumour necrosis factor | 7 | 7.1% | 2.10E-05 |
| Inflammatory response | 11 | 11.1% | 2.30E-05 |
| PERK-mediated unfolded protein response | 4 | 4% | 2.80E-05 |
| Positive regulation of cell differentiation | 5 | 5.1% | 3.70E-05 |
| Cellular response to heat | 5 | 5.1% | 3.70E-05 |
| Negative regulation of gene expression | 7 | 7.1% | 7.30E-05 |
| Cellular response to cycloheximide | 3 | 3% | 7.80E-05 |
| Response to heat | 5 | 5.1% | 1.10E-04 |
| Negative regulation of apoptotic process | 11 | 11.1% | 1.10E-04 |
| Cellular response to calcium ion | 5 | 5.1% | 1.30E-04 |
| Response to cytokine | 5 | 5.1% | 1.40E-04 |
| Apoptotic process | 12 | 12.1% | 1.50E-04 |
| Cellular heat acclimation | 3 | 3% | 1.50E-04 |
| Vasculogenesis | 5 | 5.1% | 1.90E-04 |
| Cellular response to organic cyclic compound | 5 | 5.1% | 2.40E-04 |
| Cellular response to lipopolysaccharide | 6 | 6.1% | 2.80E-04 |
| Response to wounding | 5 | 5.1% | 3.00E-04 |
| Positive regulation of interleukin-8 production | 4 | 4% | 3.10E-04 |
| Positive regulation of gene expression | 8 | 8.1% | 3.90E-04 |
| Chemotaxis | 6 | 6.1% | 4.10E-04 |
| Regulation of cell cycle | 6 | 6.1% | 4.40E-04 |
| Chemokine-mediated signalling pathway | 5 | 5.1% | 4.80E-04 |
| Positive regulation of inflammatory response | 5 | 5.1% | 5.30E-04 |
| Regulation of cellular response to heat | 5 | 5.1% | 5.90E-04 |
| Cellular response to epidermal growth factor stimulus | 4 | 4% | 6.30E-04 |
| Response to starvation | 4 | 4% | 7.50E-04 |
| Cell cycle arrest | 6 | 6.1% | 7.80E-04 |
| Response to molecule of bacterial origin | 3 | 3% | 9.10E-04 |
| Response to drug | 8 | 8.1% | 9.40E-04 |
| Negative regulation of cell proliferation | 9 | 9.1% | 9.50E-04 |
| Negative regulation of transcription, DNA-templated | 10 | 10.1% | 1.00E-03 |
| Regulation of keratinocyte differentiation | 3 | 3% | 1.10E-03 |
| Negative regulation of protein ubiquitination | 4 | 4% | 1.20E-03 |
| Transforming growth factor beta receptor signalling pathway | 5 | 5.1% | 1.30E-03 |
| Positive regulation of transcription from RNA polymerase II promoter in response to endoplasmic reticulum stress | 3 | 3% | 1.70E-03 |
| Response to hypoxia | 6 | 6.1% | 1.90E-03 |
| MAPK cascade | 7 | 7.1% | 2.30E-03 |
| Negative regulation of cell death | 4 | 4% | 2.80E-03 |
| Response to muscle stretch | 3 | 3% | 3.00E-03 |
| Regulation of protein ubiquitination | 3 | 3% | 3.00E-03 |
| Cellular response to interferon-gamma | 4 | 4% | 3.10E-03 |
| Cellular response to hydrogen peroxide | 4 | 4% | 3.10E-03 |
| Negative regulation of ERK1 and ERK2 cascade | 4 | 4% | 3.30E-03 |
| Response to light stimulus | 3 | 3% | 3.40E-03 |
| Positive regulation of osteoblast differentiation | 4 | 4% | 3.60E-03 |
| Response to corticosterone | 3 | 3% | 3.80E-03 |
| Cellular response to extracellular stimulus | 3 | 3% | 3.80E-03 |
| Cellular response to platelet-derived growth factor stimulus | 3 | 3% | 3.80E-03 |
| Cell chemotaxis | 4 | 4% | 4.50E-03 |
| Neutrophil chemotaxis | 4 | 4% | 4.70E-03 |
| Negative regulation of neuron apoptotic process | 5 | 5.1% | 4.70E-03 |
| Angiogenesis | 6 | 6.1% | 5.80E-03 |
| Fat cell differentiation | 4 | 4% | 6.20E-03 |
| Response to endoplasmic reticulum stress | 4 | 4% | 6.70E-03 |
| Circadian rhythm | 4 | 4% | 6.70E-03 |
| Cellular response to insulin stimulus | 4 | 4% | 7.20E-03 |
| Regulation of transcription from RNA polymerase II promoter | 8 | 8.1% | 7.40E-03 |
| Negative regulation of inflammatory response | 4 | 4% | 7.80E-03 |
| Lymphocyte chemotaxis | 3 | 3% | 9.00E-03 |
| Response to radiation | 3 | 3% | 9.00E-03 |
| Liver regeneration | 3 | 3% | 9.60E-03 |
| Negative regulation of smooth muscle cell proliferation | 3 | 3% | 9.60E-03 |
| Nuclear-transcribed mRNA catabolic process, deadenylation-independent decay | 2 | 2% | 1.00E-02 |
| Positive regulation of endoribonuclease activity | 2 | 2% | 1.00E-02 |
| Negative regulation of establishment of protein localization to mitochondrion | 2 | 2% | 1.00E-02 |
| Regulation of keratinocyte apoptotic process | 2 | 2% | 1.00E-02 |
| Positive regulation of intracellular mRNA localization | 2 | 2% | 1.00E-02 |
| Positive regulation of mRNA endonucleolytic cleavage involved in unfolded protein response | 2 | 2% | 1.00E-02 |
| Aging | 5 | 5.1% | 1.00E-02 |
| ATP metabolic process | 3 | 3% | 1.20E-02 |
| Lipopolysaccharide-mediated signalling pathway | 3 | 3% | 1.20E-02 |
| Protein kinase B signalling | 3 | 3% | 1.20E-02 |
| Intrinsic apoptotic signalling pathway in response to endoplasmic reticulum stress | 3 | 3% | 1.20E-02 |
| Protein folding | 5 | 5.1% | 1.40E-02 |
| Response to cold | 3 | 3% | 1.50E-02 |
| Regulation of cell proliferation | 5 | 5.1% | 1.50E-02 |
| Positive regulation of nucleotide-binding oligomerization domain containing 2 signalling pathway | 2 | 2% | 1.50E-02 |
| Negative regulation of extrinsic apoptotic signalling pathway in absence of ligand | 3 | 3% | 1.50E-02 |
| Regulation of mRNA stability | 4 | 4% | 1.60E-02 |
| Response to progesterone | 3 | 3% | 1.70E-02 |
| Regulation of mitotic cell cycle | 3 | 3% | 1.80E-02 |
| Monocyte chemotaxis | 3 | 3% | 2.00E-02 |
| Positive regulation of nitric oxide biosynthetic process | 3 | 3% | 2.00E-02 |
| Positive regulation of neuron apoptotic process | 3 | 3% | 2.00E-02 |
| Immune response | 7 | 7.1% | 2.10E-02 |
| Positive regulation of angiogenesis | 4 | 4% | 2.10E-02 |
| Cellular response to DNA damage stimulus | 5 | 5.1% | 2.20E-02 |
| Organ regeneration | 3 | 3% | 2.40E-02 |
| Positive regulation of fat cell differentiation | 3 | 3% | 2.40E-02 |
| Negative regulation of transcription from RNA polymerase II promoter in response to endoplasmic reticulum stress | 2 | 2% | 2.50E-02 |
| Positive regulation of GTPase activity | 8 | 8.1% | 2.60E-02 |
| Calcium-mediated signalling | 3 | 3% | 2.80E-02 |
| Astrocyte cell migration | 2 | 2% | 3.00E-02 |
| Embryonic process involved in female pregnancy | 2 | 2% | 3.00E-02 |
| Regulation of DNA-templated transcription in response to stress | 2 | 2% | 3.00E-02 |
| Positive regulation of tumour necrosis factor-mediated signalling pathway | 2 | 2% | 3.00E-02 |
| Positive regulation of fibroblast proliferation | 3 | 3% | 3.10E-02 |
| Protein stabilization | 4 | 4% | 3.30E-02 |
| G2/M transition of mitotic cell cycle | 4 | 4% | 3.30E-02 |
| P38MAPK cascade | 2 | 2% | 3.50E-02 |
| Cellular response to phorbol 13-acetate 12-myristate | 2 | 2% | 3.50E-02 |
| Negative regulation of mitochondrial outer membrane permeabilization involved in apoptotic signalling pathway | 2 | 2% | 3.50E-02 |
| Chorio-allantoic fusion | 2 | 2% | 3.50E-02 |
| Negative regulation of CREB transcription factor activity | 2 | 2% | 3.50E-02 |
| Positive regulation of monocyte differentiation | 2 | 2% | 3.50E-02 |
| Positive regulation of smooth muscle cell proliferation | 3 | 3% | 3.80E-02 |
| Negative regulation of sequence-specific DNA binding transcription factor activity | 3 | 3% | 3.80E-02 |
| Response to stress | 3 | 3% | 3.90E-02 |
| SMAD protein signal transduction | 3 | 3% | 4.00E-02 |
| Regulation of response to DNA damage stimulus | 2 | 2% | 4.00E-02 |
| Negative regulation of heterotypic cell-cell adhesion | 2 | 2% | 4.00E-02 |
| Spongiotrophoblast layer development | 2 | 2% | 4.00E-02 |
| Cellular response to laminar fluid shear stress | 2 | 2% | 4.00E-02 |
| Regulation of keratinocyte proliferation | 2 | 2% | 4.00E-02 |
| Nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay | 2 | 2% | 4.00E-02 |
| Positive regulation of protein metabolic process | 2 | 2% | 4.00E-02 |
| Cellular response to oxidative stress | 3 | 3% | 4.30E-02 |
| Branching involved in labyrinthine layer morphogenesis | 2 | 2% | 4.50E-02 |
| Positive regulation of cardiac muscle contraction | 2 | 2% | 4.50E-02 |
| Negative regulation of erythrocyte differentiation | 2 | 2% | 4.50E-02 |
| Response to insulin | 3 | 3% | 4.60E-02 |

**Table 16.1** – KEGG pathway analysis of top 250 DEGs in DCD biopsies compared at T2 and T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **KEGG Pathway** | MAPK signalling pathway | 22 | 11.4% | 1.80E-11 |
| Legionellosis | 10 | 5.2% | 4.00E-08 |
| TNF signalling pathway | 12 | 6.2% | 2.00E-07 |
| Salmonella infection | 10 | 5.2% | 1.80E-06 |
| Toll-like receptor signalling pathway | 10 | 5.2% | 1.40E-05 |
| Malaria | 7 | 3.6% | 5.10E-05 |
| Oestrogen signalling pathway | 9 | 4.7% | 6.00E-05 |
| African trypanosomiasis | 6 | 3.1% | 7.90E-05 |
| Chagas disease (American trypanosomiasis) | 9 | 4.7% | 8.50E-05 |
| NOD-like receptor signalling pathway | 7 | 3.6% | 1.10E-04 |
| Influenza A | 11 | 5.7% | 1.30E-04 |
| Hepatitis B | 10 | 5.2% | 1.60E-04 |
| Rheumatoid arthritis | 8 | 4.1% | 2.00E-04 |
| Cytokine-cytokine receptor interaction | 12 | 6.2% | 4.80E-04 |
| Protein processing in endoplasmic reticulum | 10 | 5.2% | 5.10E-04 |
| HTLV-I infection | 12 | 6.2% | 7.00E-04 |
| Osteoclast differentiation | 8 | 4.1% | 2.10E-03 |
| p53 signalling pathway | 6 | 3.1% | 2.20E-03 |
| Pertussis | 6 | 3.1% | 3.60E-03 |
| Antigen processing and presentation | 6 | 3.1% | 3.90E-03 |
| Toxoplasmosis | 7 | 3.6% | 4.00E-03 |
| Cell cycle | 7 | 3.6% | 7.20E-03 |
| Transcriptional mis regulation in cancer | 8 | 4.1% | 8.10E-03 |
| Measles | 7 | 3.6% | 1.00E-02 |
| FoxO signalling pathway | 7 | 3.6% | 1.00E-02 |
| Amphetamine addiction | 5 | 2.6% | 1.30E-02 |
| Chemokine signalling pathway | 8 | 4.1% | 1.40E-02 |
| Bladder cancer | 4 | 2.1% | 1.90E-02 |
| ErbB signalling pathway | 5 | 2.6% | 3.20E-02 |
| Hepatitis C | 6 | 3.1% | 3.60E-02 |
| Pathways in cancer | 11 | 5.7% | 4.40E-02 |

**Table 16.2** – REACTOME pathway analysis of top 250 DEGs in DCD biopsies compared at T2 and T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **REACTOME Pathway** | Negative regulation of the MAPK pathway | 7 | 3.6% | 2.50E-06 |
| Chemokine receptors bind chemokines | 8 | 4.1% | 2.60E-06 |
| RAF-independent MAPK1/3 activation | 5 | 2.6% | 7.80E-06 |
| Regulation of HSF1-mediated heat shock response | 8 | 4.1% | 8.30E-06 |
| Attenuation phase | 5 | 2.6% | 1.10E-05 |
| HSF1-dependent transactivation | 5 | 2.6% | 4.00E-05 |
| AUF1 (hnRNP D0) binds and destabilizes mRNA | 6 | 3.1% | 3.00E-04 |
| SMAD2/SMAD3:SMAD4 heterotrimer regulates transcription | 5 | 2.6% | 3.40E-04 |
| Senescence-Associated Secretory Phenotype (SASP) | 7 | 3.6% | 1.10E-03 |
| Signalling by ERBB2 | 4 | 2.1% | 2.20E-03 |
| MAPK6/MAPK4 signalling | 6 | 3.1% | 2.30E-03 |
| TNFR1-induced NFκB signalling pathway | 4 | 2.1% | 3.80E-03 |
| Erythrocytes take up oxygen and release carbon dioxide | 3 | 1.6% | 3.80E-03 |
| Regulation of TNFR1 signalling | 4 | 2.1% | 5.00E-03 |
| Erythrocytes take up carbon dioxide and release oxygen | 3 | 1.6% | 8.00E-03 |
| Cyclin E associated events during G1/S transition | 3 | 1.6% | 9.30E-03 |
| BMAL1: CLOCK, NPAS2 activates circadian gene expression | 4 | 2.1% | 1.00E-02 |
| Cyclin A: Cdk2-associated events at S phase entry | 3 | 1.6% | 1.10E-02 |
| MAP3K8 (TPL2)-dependent MAPK1/3 activation | 3 | 1.6% | 1.20E-02 |
| Nuclear Receptor transcription pathway | 4 | 2.1% | 1.70E-02 |
| Constitutive signalling by ligand-responsive EGFR cancer variants | 3 | 1.6% | 1.70E-02 |
| Viral RNP Complexes in the host cell nucleus | 2 | 1% | 2.10E-02 |
| ATF4 activates genes in response to endoplasmic reticulum stress | 3 | 1.6% | 2.80E-02 |
| Downregulation of TFG-beta receptor signalling | 3 | 1.6% | 3.10E-02 |
| Factors involved in megakaryocyte development and platelet production | 5 | 2.6% | 3.10E-02 |
| Interferon alpha/beta signalling | 4 | 2.1% | 3.40E-02 |
| G alpha (i) signalling events | 7 | 3.6% | 4.60E-02 |
| Recruitment and ATM-mediated phosphorylation of repair and signalling proteins at DNA double strand breaks | 4 | 2.1% | 4.60E-02 |

**Table 16.3** – Biological process analysis of top 250 DEGs in DCD biopsies compared at T2 and T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **Biological Process** | Response to unfolded protein | 11 | 5.7% | 4.60E-12 |
| Positive regulation of transcription from RNA polymerase II promoter | 35 | 18.1% | 2.50E-11 |
| Negative regulation of apoptotic process | 22 | 11.4% | 1.80E-09 |
| Protein refolding | 7 | 3.6% | 2.90E-09 |
| Inflammatory response | 19 | 9.8% | 1.90E-08 |
| Positive regulation of apoptotic process | 17 | 8.8% | 2.40E-08 |
| Response to lipopolysaccharide | 13 | 6.7% | 4.80E-08 |
| Negative regulation of transcription from RNA polymerase II promoter | 25 | 13% | 6.70E-08 |
| Positive regulation of gene expression | 15 | 7.8% | 1.90E-07 |
| Cellular response to interleukin-1 | 9 | 4.7% | 3.30E-07 |
| Skeletal muscle cell differentiation | 8 | 4.1% | 3.50E-07 |
| Transcription from RNA polymerase II promoter | 20 | 10.4% | 3.70E-07 |
| Negative regulation of gene expression | 11 | 5.7% | 6.70E-07 |
| Response to drug | 15 | 7.8% | 1.10E-06 |
| Regulation of cell death | 5 | 2.6% | 2.40E-06 |
| Cellular response to hormone stimulus | 7 | 3.6% | 3.80E-06 |
| Response to cAMP | 7 | 3.6% | 4.30E-06 |
| Chemokine-mediated signalling pathway | 8 | 4.1% | 4.60E-06 |
| Negative regulation of cell proliferation | 16 | 8.3% | 5.10E-06 |
| Regulation of cellular response to heat | 8 | 4.1% | 6.60E-06 |
| Response to hydrogen peroxide | 7 | 3.6% | 8.00E-06 |
| Cellular response to tumour necrosis factor | 9 | 4.7% | 9.40E-06 |
| Positive regulation of p38MAPK cascade | 5 | 2.6% | 1.30E-05 |
| Cellular response to hydrogen peroxide | 7 | 3.6% | 1.50E-05 |
| Positive regulation of smooth muscle cell proliferation | 7 | 3.6% | 2.10E-05 |
| Regulation of cell cycle | 9 | 4.7% | 2.20E-05 |
| Positive regulation of cell differentiation | 6 | 3.1% | 2.40E-05 |
| DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest | 7 | 3.6% | 2.50E-05 |
| Positive regulation of transcription, DNA-templated | 17 | 8.8% | 2.90E-05 |
| Monocyte chemotaxis | 6 | 3.1% | 4.40E-05 |
| Response to X-ray | 5 | 2.6% | 4.80E-05 |
| Positive regulation of nitric oxide biosynthetic process | 6 | 3.1% | 5.00E-05 |
| Positive regulation of inflammatory response | 7 | 3.6% | 6.40E-05 |
| Fat cell differentiation | 7 | 3.6% | 6.40E-05 |
| Circadian rhythm | 7 | 3.6% | 7.40E-05 |
| Negative regulation of transcription, DNA-templated | 16 | 8.3% | 7.50E-05 |
| Inactivation of MAPK activity | 5 | 2.6% | 8.20E-05 |
| Response to heat | 6 | 3.1% | 8.60E-05 |
| Negative regulation of inclusion body assembly | 4 | 2.1% | 9.30E-05 |
| Chaperone mediated protein folding requiring cofactor | 4 | 2.1% | 9.30E-05 |
| Cellular response to lipopolysaccharide | 8 | 4.1% | 9.60E-05 |
| Positive regulation of interleukin-8 production | 5 | 2.6% | 9.60E-05 |
| Response to cytokine | 6 | 3.1% | 1.30E-04 |
| Activation of MAPKKK activity | 4 | 2.1% | 1.30E-04 |
| Positive regulation of cell death | 5 | 2.6% | 1.50E-04 |
| Cellular response to fibroblast growth factor stimulus | 5 | 2.6% | 1.70E-04 |
| Negative regulation of ERK1 and ERK2 cascade | 6 | 3.1% | 2.10E-04 |
| Response to hypoxia | 9 | 4.7% | 2.30E-04 |
| Response to mechanical stimulus | 6 | 3.1% | 2.30E-04 |
| Transforming growth factor beta receptor signalling pathway | 7 | 3.6% | 2.30E-04 |
| Positive regulation of ERK1 and ERK2 cascade | 9 | 4.7% | 2.50E-04 |
| Cellular response to cycloheximide | 3 | 1.6% | 2.60E-04 |
| Apoptotic process | 16 | 8.3% | 3.00E-04 |
| Oxygen transport | 4 | 2.1% | 3.40E-04 |
| Negative regulation of protein kinase activity | 7 | 3.6% | 3.40E-04 |
| Peptidyl-tyrosine dephosphorylation | 7 | 3.6% | 3.40E-04 |
| Response to cold | 5 | 2.6% | 3.50E-04 |
| Cell cycle arrest | 8 | 4.1% | 3.80E-04 |
| Negative regulation of extrinsic apoptotic signalling pathway in absence of ligand | 5 | 2.6% | 3.90E-04 |
| Regulation of mRNA stability | 7 | 3.6% | 4.30E-04 |
| Cellular heat acclimation | 3 | 1.6% | 5.20E-04 |
| Activation of MAPK activity | 7 | 3.6% | 5.20E-04 |
| Positive regulation of neuron apoptotic process | 5 | 2.6% | 7.00E-04 |
| Cellular response to DNA damage stimulus | 9 | 4.7% | 8.00E-04 |
| Positive regulation of pri-miRNA transcription from RNA polymerase II promoter | 4 | 2.1% | 8.30E-04 |
| Positive regulation of fat cell differentiation | 5 | 2.6% | 9.80E-04 |
| Chemotaxis | 7 | 3.6% | 1.00E-03 |
| Response to toxic substance | 6 | 3.1% | 1.20E-03 |
| Cellular response to corticotropin-releasing hormone stimulus | 3 | 1.6% | 1.30E-03 |
| Cellular response to calcium ion | 5 | 2.6% | 1.30E-03 |
| Peripheral nervous system development | 4 | 2.1% | 1.40E-03 |
| Positive regulation of NF-kappaB transcription factor activity | 7 | 3.6% | 1.60E-03 |
| Positive regulation of fibroblast proliferation | 5 | 2.6% | 1.70E-03 |
| Protein stabilization | 7 | 3.6% | 1.80E-03 |
| Regulation of cell proliferation | 8 | 4.1% | 1.90E-03 |
| Cellular response to interferon-gamma | 5 | 2.6% | 2.00E-03 |
| Negative regulation of interleukin-6 production | 4 | 2.1% | 2.30E-03 |
| Lymphocyte chemotaxis | 4 | 2.1% | 2.30E-03 |
| Regulation of response to DNA damage stimulus | 3 | 1.6% | 2.40E-03 |
| Positive regulation of osteoblast differentiation | 5 | 2.6% | 2.40E-03 |
| Negative regulation of sequence-specific DNA binding transcription factor activity | 5 | 2.6% | 2.40E-03 |
| Regulation of tumour necrosis factor-mediated signalling pathway | 4 | 2.1% | 2.80E-03 |
| Cellular response to ionizing radiation | 4 | 2.1% | 3.00E-03 |
| Response to molecule of bacterial origin | 3 | 1.6% | 3.00E-03 |
| Cellular response to oxidative stress | 5 | 2.6% | 3.10E-03 |
| Response to glucocorticoid | 5 | 2.6% | 3.30E-03 |
| Cell chemotaxis | 5 | 2.6% | 3.30E-03 |
| ATP metabolic process | 4 | 2.1% | 3.30E-03 |
| MAPK cascade | 9 | 4.7% | 3.40E-03 |
| Neutrophil chemotaxis | 5 | 2.6% | 3.50E-03 |
| Response to starvation | 4 | 2.1% | 4.30E-03 |
| Cellular response to peptide | 3 | 1.6% | 4.60E-03 |
| Positive regulation of osteoblast proliferation | 3 | 1.6% | 4.60E-03 |
| Positive regulation of angiogenesis | 6 | 3.1% | 4.60E-03 |
| Cellular response to heat | 4 | 2.1% | 5.00E-03 |
| Negative regulation of cell cycle | 4 | 2.1% | 5.00E-03 |
| ERBB2 signalling pathway | 4 | 2.1% | 5.40E-03 |
| Extrinsic apoptotic signalling pathway via death domain receptors | 4 | 2.1% | 5.40E-03 |
| Endoderm formation | 3 | 1.6% | 5.50E-03 |
| PERK-mediated unfolded protein response | 3 | 1.6% | 5.50E-03 |
| Positive regulation of cysteine-type endopeptidase activity involved in apoptotic process | 4 | 2.1% | 6.30E-03 |
| Mitotic cell cycle arrest | 3 | 1.6% | 6.40E-03 |
| Trophectodermal cell differentiation | 3 | 1.6% | 6.40E-03 |
| Negative regulation by host of viral transcription | 3 | 1.6% | 6.40E-03 |
| Immune response | 11 | 5.7% | 6.60E-03 |
| Negative regulation of protein ubiquitination | 4 | 2.1% | 6.70E-03 |
| Protein folding | 7 | 3.6% | 7.20E-03 |
| Negative regulation of fat cell differentiation | 4 | 2.1% | 7.20E-03 |
| Erythrocyte development | 3 | 1.6% | 8.50E-03 |
| Cell migration involved in sprouting angiogenesis | 3 | 1.6% | 8.50E-03 |
| G2/M transition of mitotic cell cycle | 6 | 3.1% | 9.60E-03 |
| Regulation of protein ubiquitination | 3 | 1.6% | 9.70E-03 |
| Organ regeneration | 4 | 2.1% | 9.80E-03 |
| Response to light stimulus | 3 | 1.6% | 1.10E-02 |
| JNK cascade | 4 | 2.1% | 1.10E-02 |
| Response to corticosterone | 3 | 1.6% | 1.20E-02 |
| Cellular response to extracellular stimulus | 3 | 1.6% | 1.20E-02 |
| Calcium-mediated signalling | 4 | 2.1% | 1.20E-02 |
| Signal transduction | 20 | 10.4% | 1.30E-02 |
| Positive regulation of osteoclast differentiation | 3 | 1.6% | 1.40E-02 |
| Peptidyl-tyrosine phosphorylation | 6 | 3.1% | 1.50E-02 |
| Hydrogen peroxide catabolic process | 3 | 1.6% | 1.50E-02 |
| Entrainment of circadian clock by photoperiod | 3 | 1.6% | 1.50E-02 |
| Negative regulation of cell death | 4 | 2.1% | 1.50E-02 |
| Regulation of apoptotic process | 7 | 3.6% | 1.60E-02 |
| Cellular response to gamma radiation | 3 | 1.6% | 1.60E-02 |
| Stress-activated MAPK cascade | 3 | 1.6% | 1.60E-02 |
| Steroid hormone mediated signalling pathway | 4 | 2.1% | 1.70E-02 |
| Positive regulation of neutrophil chemotaxis | 3 | 1.6% | 1.80E-02 |
| Positive regulation of I-kappaB kinase/NF-kappaB signalling | 6 | 3.1% | 1.80E-02 |
| Positive regulation of mRNA endonucleolytic cleavage involved in unfolded protein response | 2 | 1% | 1.90E-02 |
| Positive regulation of endoribonuclease activity | 2 | 1% | 1.90E-02 |
| Negative regulation of establishment of protein localization to mitochondrion | 2 | 1% | 1.90E-02 |
| Cellular response to vascular endothelial growth factor stimulus | 3 | 1.6% | 2.00E-02 |
| Cellular senescence | 3 | 1.6% | 2.00E-02 |
| Response to stress | 4 | 2.1% | 2.00E-02 |
| SMAD protein signal transduction | 4 | 2.1% | 2.10E-02 |
| Associative learning | 3 | 1.6% | 2.10E-02 |
| Positive regulation of epidermal growth factor receptor signalling pathway | 3 | 1.6% | 2.10E-02 |
| Positive regulation of proteasomal ubiquitin-dependent protein catabolic process | 4 | 2.1% | 2.20E-02 |
| Nucleotide-binding oligomerization domain containing signalling pathway | 3 | 1.6% | 2.30E-02 |
| Notch signalling pathway | 5 | 2.6% | 2.30E-02 |
| Positive regulation of JNK cascade | 4 | 2.1% | 2.30E-02 |
| Response to insulin | 4 | 2.1% | 2.50E-02 |
| Transcription, DNA-templated | 28 | 14.5% | 2.60E-02 |
| Positive regulation of endothelial cell proliferation | 4 | 2.1% | 2.70E-02 |
| Negative regulation of tyrosine phosphorylation of Stat1 protein | 2 | 1% | 2.80E-02 |
| Chaperone-mediated autophagy | 2 | 1% | 2.80E-02 |
| Cellular response to prolactin | 2 | 1% | 2.80E-02 |
| Positive regulation of nucleotide-binding oligomerization domain containing 2 signalling pathway | 2 | 1% | 2.80E-02 |
| Positive regulation of intrinsic apoptotic signalling pathway by p53 class mediator | 2 | 1% | 2.80E-02 |
| Negative regulation of endothelial cell apoptotic process | 3 | 1.6% | 2.80E-02 |
| Regulation of transcription from RNA polymerase II promoter in response to hypoxia | 3 | 1.6% | 2.80E-02 |
| Response to radiation | 3 | 1.6% | 2.80E-02 |
| Negative regulation of smooth muscle cell proliferation | 3 | 1.6% | 3.00E-02 |
| Cellular response to glucose starvation | 3 | 1.6% | 3.00E-02 |
| Receptor-mediated endocytosis | 6 | 3.1% | 3.10E-02 |
| In utero embryonic development | 6 | 3.1% | 3.20E-02 |
| Positive regulation of protein phosphorylation | 5 | 2.6% | 3.20E-02 |
| Negative regulation of type I interferon production | 3 | 1.6% | 3.20E-02 |
| Positive regulation of reactive oxygen species metabolic process | 3 | 1.6% | 3.20E-02 |
| Cell-cell signalling | 7 | 3.6% | 3.30E-02 |
| Response to endoplasmic reticulum stress | 4 | 2.1% | 3.40E-02 |
| Negative regulation of neuron apoptotic process | 5 | 2.6% | 3.60E-02 |
| Intracellular signal transduction | 9 | 4.7% | 3.70E-02 |
| B-1 B cell homeostasis | 2 | 1% | 3.70E-02 |
| MyD88-dependent toll-like receptor signalling pathway | 3 | 1.6% | 3.80E-02 |
| Intrinsic apoptotic signalling pathway in response to endoplasmic reticulum stress | 3 | 1.6% | 3.80E-02 |
| Negative regulation of inflammatory response | 4 | 2.1% | 3.80E-02 |
| Regulation of protein phosphorylation | 3 | 1.6% | 4.10E-02 |
| Bone mineralization | 3 | 1.6% | 4.10E-02 |
| Positive regulation of cell cycle | 3 | 1.6% | 4.10E-02 |
| Reactive oxygen species metabolic process | 3 | 1.6% | 4.30E-02 |
| Positive regulation of protein kinase B signalling | 4 | 2.1% | 4.50E-02 |
| DNA damage response, detection of DNA damage | 3 | 1.6% | 4.50E-02 |
| Granulocyte chemotaxis | 2 | 1% | 4.60E-02 |
| Negative regulation of transcription from RNA polymerase II promoter in response to endoplasmic reticulum stress | 2 | 1% | 4.60E-02 |
| Negative regulation of steroid biosynthetic process | 2 | 1% | 4.60E-02 |
| Movement of cell or subcellular component | 4 | 2.1% | 4.70E-02 |

**Table 17.1** – KEGG pathway analysis of upregulated DEGs in DCD biopsies compared at T2 and T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **KEGG Pathway** | MAPK signalling pathway | 12 | 14.8% | 5.70E-07 |
| Protein processing in endoplasmic reticulum | 9 | 11.1% | 1.30E-05 |
| Malaria | 6 | 7.4% | 1.60E-05 |
| Oestrogen signalling pathway | 7 | 8.6% | 4.50E-05 |
| TNF signalling pathway | 7 | 8.6% | 7.00E-05 |
| Influenza A | 8 | 9.9% | 1.40E-04 |
| Legionellosis | 5 | 6.2% | 4.30E-04 |
| African trypanosomiasis | 4 | 4.9% | 1.30E-03 |
| HTLV-I infection | 8 | 9.9% | 1.30E-03 |
| Osteoclast differentiation | 6 | 7.4% | 1.70E-03 |
| Bladder cancer | 4 | 4.9% | 2.50E-03 |
| Hepatitis B | 6 | 7.4% | 2.70E-03 |
| NOD-like receptor signalling pathway | 4 | 4.9% | 6.10E-03 |
| Hepatitis C | 5 | 6.2% | 1.20E-02 |
| Pertussis | 4 | 4.9% | 1.40E-02 |
| Antigen processing and presentation | 4 | 4.9% | 1.40E-02 |
| Salmonella infection | 4 | 4.9% | 1.80E-02 |
| ErbB signalling pathway | 4 | 4.9% | 2.00E-02 |
| Rheumatoid arthritis | 4 | 4.9% | 2.10E-02 |
| Transcriptional misregulation in cancer | 5 | 6.2% | 2.50E-02 |
| Chagas disease  | 4 | 4.9% | 3.20E-02 |
| Toxoplasmosis | 4 | 4.9% | 3.70E-02 |

**Table 17.3** – Biological process analysis of upregulated DEGs in DCD biopsies compared at T2 and T1.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **Biological Process** | Response to unfolded protein | 9 | 11.1% | 7.20E-12 |
| Positive regulation of transcription from RNA polymerase II promoter | 20 | 24.7% | 1.50E-08 |
| Regulation of cell death | 5 | 6.2% | 9.50E-08 |
| Protein refolding | 5 | 6.2% | 3.90E-07 |
| Response to lipopolysaccharide | 9 | 11.1% | 4.40E-07 |
| Cellular response to hormone stimulus | 6 | 7.4% | 1.30E-06 |
| Response to cAMP | 6 | 7.4% | 1.40E-06 |
| Transcription from RNA polymerase II promoter | 13 | 16% | 1.40E-06 |
| Skeletal muscle cell differentiation | 6 | 7.4% | 1.90E-06 |
| Response to mechanical stimulus | 6 | 7.4% | 4.90E-06 |
| Negative regulation of inclusion body assembly | 4 | 4.9% | 8.50E-06 |
| PERK-mediated unfolded protein response | 4 | 4.9% | 1.60E-05 |
| Regulation of cellular response to heat | 6 | 7.4% | 1.60E-05 |
| Positive regulation of cell differentiation | 5 | 6.2% | 1.70E-05 |
| Negative regulation of apoptotic process | 11 | 13.6% | 2.00E-05 |
| Oxygen transport | 4 | 4.9% | 3.20E-05 |
| Negative regulation of transcription from RNA polymerase II promoter | 13 | 16% | 4.40E-05 |
| Response to heat | 5 | 6.2% | 5.00E-05 |
| Cellular response to cycloheximide | 3 | 3.7% | 5.30E-05 |
| Response to hydrogen peroxide | 5 | 6.2% | 6.30E-05 |
| Cellular response to calcium ion | 5 | 6.2% | 6.30E-05 |
| Response to cytokine | 5 | 6.2% | 6.80E-05 |
| Cellular heat acclimation | 3 | 3.7% | 1.10E-04 |
| Cellular response to interleukin-1 | 5 | 6.2% | 2.30E-04 |
| Cellular response to fibroblast growth factor stimulus | 4 | 4.9% | 2.70E-04 |
| Response to drug | 8 | 9.9% | 2.90E-04 |
| Positive regulation of transcription, DNA-templated | 10 | 12.3% | 3.10E-04 |
| Cell cycle arrest | 6 | 7.4% | 3.20E-04 |
| Response to starvation | 4 | 4.9% | 4.30E-04 |
| Cellular response to heat | 4 | 4.9% | 5.10E-04 |
| Aging | 6 | 7.4% | 6.70E-04 |
| Positive regulation of nitric oxide biosynthetic process | 4 | 4.9% | 7.90E-04 |
| Protein folding | 6 | 7.4% | 9.80E-04 |
| Receptor-mediated endocytosis | 6 | 7.4% | 1.10E-03 |
| Cellular response to tumour necrosis factor | 5 | 6.2% | 1.20E-03 |
| Negative regulation of cell proliferation | 8 | 9.9% | 1.40E-03 |
| Negative regulation of cell death | 4 | 4.9% | 1.60E-03 |
| Chemotaxis | 5 | 6.2% | 1.80E-03 |
| Regulation of cell cycle | 5 | 6.2% | 1.90E-03 |
| Regulation of protein ubiquitination | 3 | 3.7% | 2.00E-03 |
| Response to light stimulus | 3 | 3.7% | 2.30E-03 |
| Response to wounding | 4 | 4.9% | 2.40E-03 |
| Response to corticosterone | 3 | 3.7% | 2.60E-03 |
| Cellular response to extracellular stimulus | 3 | 3.7% | 2.60E-03 |
| Protein stabilization | 5 | 6.2% | 2.60E-03 |
| Response to insulin | 4 | 4.9% | 2.90E-03 |
| Hydrogen peroxide catabolic process | 3 | 3.7% | 3.20E-03 |
| Cellular response to retinoic acid | 4 | 4.9% | 3.20E-03 |
| Positive regulation of interleukin-8 production | 3 | 3.7% | 5.40E-03 |
| Response to hypoxia | 5 | 6.2% | 6.10E-03 |
| Response to radiation | 3 | 3.7% | 6.20E-03 |
| Positive regulation of cell death | 3 | 3.7% | 6.60E-03 |
| Transforming growth factor beta receptor signalling pathway | 4 | 4.9% | 7.00E-03 |
| ATP metabolic process | 3 | 3.7% | 8.10E-03 |
| Positive regulation of endoribonuclease activity | 2 | 2.5% | 8.40E-03 |
| Negative regulation of establishment of protein localization to mitochondrion | 2 | 2.5% | 8.40E-03 |
| Positive regulation of mRNA endonucleolytic cleavage involved in unfolded protein response | 2 | 2.5% | 8.40E-03 |
| Negative regulation of protein kinase activity | 4 | 4.9% | 8.50E-03 |
| Regulation of mRNA stability | 4 | 4.9% | 9.50E-03 |
| Response to cold | 3 | 3.7% | 1.00E-02 |
| Negative regulation of extrinsic apoptotic signalling pathway in absence of ligand | 3 | 3.7% | 1.10E-02 |
| Regulation of transcription from RNA polymerase II promoter | 7 | 8.6% | 1.10E-02 |
| Cellular response to DNA damage stimulus | 5 | 6.2% | 1.20E-02 |
| Response to progesterone | 3 | 3.7% | 1.20E-02 |
| Cellular response to potassium ion starvation | 2 | 2.5% | 1.30E-02 |
| Positive regulation of nucleotide-binding oligomerization domain containing 2 signalling pathway | 2 | 2.5% | 1.30E-02 |
| Positive regulation of angiogenesis | 4 | 4.9% | 1.30E-02 |
| Negative regulation of protein ubiquitination | 3 | 3.7% | 1.30E-02 |
| Response to activity | 3 | 3.7% | 1.40E-02 |
| Angiogenesis | 5 | 6.2% | 1.50E-02 |
| Bicarbonate transport | 3 | 3.7% | 1.50E-02 |
| Organ regeneration | 3 | 3.7% | 1.70E-02 |
| Negative regulation of neuron apoptotic process | 4 | 4.9% | 1.80E-02 |
| Negative regulation of gene expression | 4 | 4.9% | 2.00E-02 |
| Negative regulation of transcription from RNA polymerase II promoter in response to endoplasmic reticulum stress | 2 | 2.5% | 2.10E-02 |
| Positive regulation of fibroblast proliferation | 3 | 3.7% | 2.20E-02 |
| Inflammatory response | 6 | 7.4% | 2.20E-02 |
| Cellular response to hydrogen peroxide | 3 | 3.7% | 2.40E-02 |
| MAPK cascade | 5 | 6.2% | 2.50E-02 |
| Positive regulation of gene expression | 5 | 6.2% | 2.50E-02 |
| Negative regulation of ERK1 and ERK2 cascade | 3 | 3.7% | 2.50E-02 |
| Positive regulation of tumour necrosis factor-mediated signalling pathway | 2 | 2.5% | 2.50E-02 |
| Negative regulation of sequence-specific DNA binding transcription factor activity | 3 | 3.7% | 2.70E-02 |
| Positive regulation of smooth muscle cell proliferation | 3 | 3.7% | 2.70E-02 |
| SMAD protein signal transduction | 3 | 3.7% | 2.80E-02 |
| Negative regulation of mitochondrial outer membrane permeabilization involved in apoptotic signalling pathway | 2 | 2.5% | 2.90E-02 |
| Positive regulation of proteasomal ubiquitin-dependent protein catabolic process | 3 | 3.7% | 3.00E-02 |
| Cellular response to oxidative stress | 3 | 3.7% | 3.00E-02 |
| Cell chemotaxis | 3 | 3.7% | 3.10E-02 |
| Apoptotic process | 7 | 8.6% | 3.30E-02 |
| Protein heterooligomerization | 3 | 3.7% | 3.30E-02 |
| Glucose metabolic process | 3 | 3.7% | 3.30E-02 |
| Regulation of response to DNA damage stimulus | 2 | 2.5% | 3.30E-02 |
| Positive regulation of protein metabolic process | 2 | 2.5% | 3.30E-02 |
| Negative regulation of heterotypic cell-cell adhesion | 2 | 2.5% | 3.30E-02 |
| Cellular response to laminar fluid shear stress | 2 | 2.5% | 3.30E-02 |
| Cellular oxidant detoxification | 3 | 3.7% | 3.50E-02 |
| Chemokine-mediated signalling pathway | 3 | 3.7% | 3.60E-02 |
| Vascular endothelial growth factor receptor signalling pathway | 3 | 3.7% | 3.70E-02 |
| Positive regulation of cardiac muscle contraction | 2 | 2.5% | 3.70E-02 |
| Response to molecule of bacterial origin | 2 | 2.5% | 3.70E-02 |
| Branching involved in labyrinthine layer morphogenesis | 2 | 2.5% | 3.70E-02 |
| Positive regulation of apoptotic process | 5 | 6.2% | 3.80E-02 |
| Fat cell differentiation | 3 | 3.7% | 3.80E-02 |
| Response to endoplasmic reticulum stress | 3 | 3.7% | 4.00E-02 |
| Chaperone mediated protein folding requiring cofactor | 2 | 2.5% | 4.10E-02 |
| Cellular response to insulin stimulus | 3 | 3.7% | 4.20E-02 |
| Blood coagulation | 4 | 4.9% | 4.30E-02 |
| Regulation of cell proliferation | 4 | 4.9% | 4.40E-02 |
| Negative regulation of inflammatory response | 3 | 3.7% | 4.40E-02 |
| Viral entry into host cell | 3 | 3.7% | 4.50E-02 |
| Leukocyte migration involved in inflammatory response | 2 | 2.5% | 4.60E-02 |
| Cellular response to peptide | 2 | 2.5% | 4.60E-02 |
| Positive regulation of nuclear-transcribed mRNA poly(A) tail shortening | 2 | 2.5% | 4.60E-02 |
| Peptidyl-threonine dephosphorylation | 2 | 2.5% | 4.60E-02 |
| Canonical Wnt signalling pathway | 3 | 3.7% | 4.80E-02 |

**Table 19.3** – Biological process pathway analysis of top 250 DEGs at T2 in living, DBD and DCD biopsies.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **Biological Process** | Oxidation-reduction process | 17 | 8.3% | 3.70E-04 |
| Protein refolding | 4 | 2% | 4.30E-04 |
| Cellular heat acclimation | 3 | 1.5% | 6.10E-04 |
| Response to interferon-beta | 3 | 1.5% | 3.50E-03 |
| Type I interferon signalling pathway | 5 | 2.4% | 4.10E-03 |
| Regulation of blood pressure | 5 | 2.4% | 4.30E-03 |
| Negative regulation of inclusion body assembly | 3 | 1.5% | 4.40E-03 |
| Regulation of catalytic activity | 5 | 2.4% | 4.60E-03 |
| Regulation of cell death | 3 | 1.5% | 5.30E-03 |
| Cellular response to heat | 4 | 2% | 6.30E-03 |
| Xenobiotic metabolic process | 5 | 2.4% | 8.30E-03 |
| Negative regulation of viral entry into a host cell | 3 | 1.5% | 1.40E-02 |
| Response to hydrogen peroxide | 4 | 2% | 1.50E-02 |
| Negative regulation of apoptotic process | 11 | 5.4% | 1.80E-02 |
| Positive regulation of mRNA endonucleolytic cleavage involved in unfolded protein response | 2 | 1% | 2.00E-02 |
| Phytol metabolic process | 2 | 1% | 2.00E-02 |
| Positive regulation of endoribonuclease activity | 2 | 1% | 2.00E-02 |
| Regulation of apoptotic process | 7 | 3.4% | 2.20E-02 |
| Response to mechanical stimulus | 4 | 2% | 2.20E-02 |
| Response to virus | 5 | 2.4% | 2.60E-02 |
| Response to cadmium ion  | 3 | 1.5% | 2.70E-02 |
| Positive regulation of mesenchymal cell proliferation  | 3 | 1.5% | 2.90E-02 |
| Positive regulation of nucleotide-binding oligomerization domain containing 2 signalling pathway | 2 | 1% | 3.00E-02 |
| Negative regulation of endopeptidase activity | 5 | 2.4% | 3.50E-02 |
| Triglyceride metabolic process | 3 | 1.5% | 4.90E-02 |

**Table 20.3** – Biological process analysis of co-expressed DEGs at T2 in living, DBD and DCD biopsies.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **Biological Process** | Response to unfolded protein | 7 | 2.3% | 3.70E-05 |
| Type I interferon signalling pathway | 8 | 2.7% | 4.80E-05 |
| Response to oestrogen | 8 | 2.7% | 5.40E-05 |
| Protein refolding | 4 | 1.3% | 1.30E-03 |
| Protein kinase C signalling | 4 | 1.3% | 1.60E-03 |
| Interferon-gamma-mediated signalling pathway | 6 | 2% | 4.30E-03 |
| Platelet degranulation | 7 | 2.3% | 4.70E-03 |
| Response to heat | 5 | 1.7% | 5.80E-03 |
| Negative regulation of cell proliferation | 14 | 4.7% | 7.20E-03 |
| Response to interferon-beta | 3 | 1% | 7.60E-03 |
| Negative regulation of inclusion body assembly | 3 | 1% | 9.40E-03 |
| Chaperone mediated protein folding requiring cofactor | 3 | 1% | 9.40E-03 |
| JAK-STAT cascade | 4 | 1.3% | 1.20E-02 |
| Positive regulation of smooth muscle cell proliferation | 5 | 1.7% | 1.30E-02 |
| Response to stress | 5 | 1.7% | 1.30E-02 |
| Response to cold | 4 | 1.3% | 1.70E-02 |
| Response to zinc ion | 4 | 1.3% | 1.70E-02 |
| Response to drug | 11 | 3.7% | 1.70E-02 |
| Cellular response to heat | 4 | 1.3% | 1.80E-02 |
| Acute-phase response | 4 | 1.3% | 2.10E-02 |
| JAK-STAT cascade involved in growth hormone signalling pathway | 3 | 1% | 2.10E-02 |
| response to ethanol | 6 | 2% | 2.10E-02 |
| Positive regulation of cAMP biosynthetic process | 4 | 1.3% | 2.20E-02 |
| Positive regulation of inflammatory response | 5 | 1.7% | 2.40E-02 |
| Lactation | 4 | 1.3% | 2.50E-02 |
| Response to oxidative stress | 6 | 2% | 2.50E-02 |
| Mammary gland alveolus development | 3 | 1% | 2.60E-02 |
| Extracellular matrix disassembly | 5 | 1.7% | 2.80E-02 |
| Blood coagulation, intrinsic pathway | 3 | 1% | 3.00E-02 |
| Cytoskeleton-dependent intracellular transport | 3 | 1% | 3.00E-02 |
| Adrenergic receptor signalling pathway | 2 | 0.7% | 3.00E-02 |
| Positive regulation of I-kappaB kinase/NF-kappaB signalling | 7 | 2.3% | 3.50E-02 |
| Proteolysis involved in cellular protein catabolic process | 4 | 1.3% | 3.60E-02 |
| Respiratory electron transport chain | 3 | 1% | 3.60E-02 |
| Negative regulation of endopeptidase activity | 6 | 2% | 3.60E-02 |
| Response to lipopolysaccharide | 7 | 2.3% | 3.80E-02 |
| Positive regulation of apoptotic process | 10 | 3.4% | 3.80E-02 |
| Defense response to virus | 7 | 2.3% | 3.90E-02 |
| Aging | 7 | 2.3% | 3.90E-02 |
| Movement of cell or subcellular component | 5 | 1.7% | 4.10E-02 |
| Response to hydrogen peroxide | 4 | 1.3% | 4.10E-02 |
| Positive regulation of neutrophil chemotaxis | 3 | 1% | 4.30E-02 |
| Negative regulation of apoptotic process | 13 | 4.4% | 4.30E-02 |
| Vascular endothelial growth factor production | 2 | 0.7% | 4.50E-02 |
| Prolactin signalling pathway | 2 | 0.7% | 4.50E-02 |
| Response to hypoxia | 7 | 2.3% | 4.60E-02 |
| Cellular response to vascular endothelial growth factor stimulus | 3 | 1% | 4.60E-02 |

**Table 21.2** – REACTOME pathway analysis of upregulated DEGs in DBD and living biopsies compared at T2.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **REACTOME Pathway** | Interferon alpha/beta signalling | 6 | 8.6% | 2.50E-05 |
| HSF1-dependent transactivation | 4 | 5.7% | 1.30E-04 |
| Regulation of HSF1-mediated heat shock response | 5 | 7.1% | 4.90E-04 |
| Platelet degranulation | 6 | 8.6% | 5.80E-04 |
| Attenuation phase | 3 | 4.3% | 2.40E-03 |
| GRB2: SOS provides linkage to MAPK signalling for Integrins | 3 | 4.3% | 2.80E-03 |
| p130Cas linkage to MAPK signalling for integrins | 3 | 4.3% | 2.80E-03 |
| Common Pathway of Fibrin Clot Formation | 3 | 4.3% | 5.90E-03 |
| Integrin signalling | 3 | 4.3% | 6.50E-03 |
| Integrin cell surface interactions | 4 | 5.7% | 1.00E-02 |
| Viral RNP Complexes in the Host Cell Nucleus | 2 | 2.9% | 1.10E-02 |
| Interferon gamma signalling | 4 | 5.7% | 1.10E-02 |
| Amyloid fibre formation | 4 | 5.7% | 1.50E-02 |
| MAP2K and MAPK activation | 3 | 4.3% | 1.90E-02 |
| Senescence-Associated Secretory Phenotype (SASP) | 4 | 5.7% | 2.00E-02 |
| Signalling by Interleukins | 3 | 4.3% | 2.60E-02 |
| Packaging of Telomere Ends | 3 | 4.3% | 3.10E-02 |
| Chemokine receptors bind chemokines | 3 | 4.3% | 3.90E-02 |
| RNA Polymerase I Promoter Opening | 3 | 4.3% | 4.40E-02 |
| DNA methylation | 3 | 4.3% | 4.60E-02 |
| DNA damage/Telomere stress induced senescence  | 3 | 4.3% | 4.70E-02 |
| Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3 | 3 | 4.3% | 4.9E-02 |

**Table 21.3** – Biological process analysis of upregulated DEGs in DBD and living biopsies compared at T2.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **Biological Process** | Negative regulation of inclusion body assembly | 4 | 5.7% | 4.90E-06 |
| Protein refolding | 4 | 5.7% | 1.80E-05 |
| Platelet degranulation | 6 | 8.6% | 3.00E-05 |
| Cellular heat acclimation | 3 | 4.3% | 7.20E-05 |
| Blood coagulation, fibrin clot formation | 3 | 4.3% | 7.20E-05 |
| Type I interferon signalling pathway | 5 | 7.1% | 7.50E-05 |
| Regulation of cellular response to heat | 5 | 7.1% | 1.40E-04 |
| Negative regulation of extrinsic apoptotic signalling pathway via death domain receptors | 4 | 5.7% | 2.10E-04 |
| Cellular response to heat | 4 | 5.7% | 2.90E-04 |
| Positive regulation of peptide hormone secretion | 3 | 4.3% | 3.40E-04 |
| Inflammatory response | 8 | 11.4% | 3.50E-04 |
| Response to unfolded protein | 4 | 5.7% | 4.30E-04 |
| Response to interferon-beta | 3 | 4.3% | 4.30E-04 |
| Plasminogen activation | 3 | 4.3% | 4.30E-04 |
| Regulation of cell death | 3 | 4.3% | 6.50E-04 |
| Positive regulation of heterotypic cell-cell adhesion | 3 | 4.3% | 6.50E-04 |
| Immune response | 8 | 11.4% | 6.60E-04 |
| Response to hydrogen peroxide | 4 | 5.7% | 7.60E-04 |
| Negative regulation of endopeptidase activity | 5 | 7.1% | 8.60E-04 |
| Protein polymerization | 3 | 4.3% | 9.20E-04 |
| Cellular protein complex assembly | 3 | 4.3% | 1.80E-03 |
| Negative regulation of viral entry into host cell | 3 | 4.3% | 1.80E-03 |
| Cellular response to interleukin-1 | 4 | 5.7% | 2.00E-03 |
| Positive regulation of inflammatory response | 4 | 5.7% | 2.20E-03 |
| Positive regulation of exocytosis | 3 | 4.3% | 2.40E-03 |
| Fibrinolysis | 3 | 4.3% | 2.40E-03 |
| Response to lipopolysaccharide | 5 | 7.1% | 2.60E-03 |
| Positive regulation of neutrophil chemotaxis | 3 | 4.3% | 2.70E-03 |
| Defence response to virus | 5 | 7.1% | 2.70E-03 |
| Response to hypoxia | 5 | 7.1% | 3.10E-03 |
| Positive regulation of interleukin-8 production | 3 | 4.3% | 3.70E-03 |
| Blood coagulation | 5 | 7.1% | 4.00E-03 |
| Negative regulation of endothelial cell apoptotic process | 3 | 4.3% | 4.30E-03 |
| Extracellular matrix organization | 5 | 7.1% | 5.00E-03 |
| Positive regulation of vasoconstriction | 3 | 4.3% | 5.60E-03 |
| Positive regulation of substrate adhesion-dependent cell spreading | 3 | 4.3% | 5.60E-03 |
| JAK-STAT cascade | 3 | 4.3% | 5.60E-03 |
| Positive regulation of mRNA endonucleolytic cleavage involved in unfolded protein response | 2 | 2.9% | 7.00E-03 |
| Positive regulation of endoribonuclease activity | 2 | 2.9% | 7.00E-03 |
| Positive regulation of protein secretion | 3 | 4.3% | 7.10E-03 |
| Angiogenesis | 5 | 7.1% | 7.80E-03 |
| Acute-phase response | 3 | 4.3% | 8.30E-03 |
| Chemotaxis | 4 | 5.7% | 9.00E-03 |
| Platelet aggregation | 3 | 4.3% | 9.10E-03 |
| Positive regulation of nucleotide-binding oligomerization domain containing 2 signalling pathway | 2 | 2.9% | 1.10E-02 |
| Chromatin silencing | 3 | 4.3% | 1.10E-02 |
| Negative regulation of cell proliferation | 6 | 8.6% | 1.30E-02 |
| Induction of bacterial agglutination | 2 | 2.9% | 1.40E-02 |
| Response to calcium ion | 3 | 4.3% | 1.80E-02 |
| Positive regulation of smooth muscle cell proliferation | 3 | 4.3% | 1.90E-02 |
| Positive regulation of I-kappaB kinase/NF-kappaB signalling | 4 | 5.7% | 1.90E-02 |
| Positive regulation of tumour necrosis factor-mediated signalling pathway | 2 | 2.9% | 2.10E-02 |
| Regulation of transcription from RNA polymerase II promoter in response to oxidative stress | 2 | 2.9% | 2.10E-02 |
| Oxygen homeostasis | 2 | 2.9% | 2.10E-02 |
| Negative regulation of apoptotic process | 6 | 8.6% | 2.20E-02 |
| Positive regulation of ERK1 and ERK2 cascade | 4 | 5.7% | 2.40E-02 |
| Protein homooligomerization | 4 | 5.7% | 2.40E-02 |
| Negative regulation of mitochondrial outer membrane permeabilization involved in apoptotic signalling pathway | 2 | 2.9% | 2.40E-02 |
| Chemokine-mediated signalling pathway | 3 | 4.3% | 2.60E-02 |
| Interferon-gamma-mediated signalling pathway | 3 | 4.3% | 2.60E-02 |
| Low-density lipoprotein particle clearance | 2 | 2.9% | 2.80E-02 |
| Proteolysis | 6 | 8.6% | 3.10E-02 |
| Response to molecule of bacterial origin | 2 | 2.9% | 3.10E-02 |
| Viral entry into host cell | 3 | 4.3% | 3.20E-02 |
| Response to interferon-alpha | 2 | 2.9% | 3.50E-02 |
| Chaperone mediated protein folding requiring cofactor | 2 | 2.9% | 3.50E-02 |
| Complement activation | 3 | 4.3% | 3.80E-02 |
| Leukocyte migration involved in inflammatory response | 2 | 2.9% | 3.80E-02 |
| Cell-matrix adhesion | 3 | 4.3% | 4.00E-02 |
| PERK-mediated unfolded protein response | 2 | 2.9% | 4.10E-02 |
| Positive regulation of macrophage activation | 2 | 2.9% | 4.10E-02 |
| Regulation of interferon-gamma-mediated signalling pathway | 2 | 2.9% | 4.50E-02 |
| Regulation of innate immune response | 2 | 2.9% | 4.50E-02 |
| Response to biotic stimulus | 2 | 2.9% | 4.80E-02 |

**Table 22.1** – KEGG pathway analysis of downregulated DEGs in DBD and living biopsies compared at T2.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **KEGG Pathway** | Metabolic pathways | 47 | 41.6% | 1.20E-16 |
| Drug metabolism - cytochrome P450 | 8 | 7.1% | 9.40E-06 |
| Arginine and proline metabolism | 7 | 6.2% | 1.70E-05 |
| Biosynthesis of antibiotics | 12 | 10.6% | 2.10E-05 |
| Pentose and glucuronate interconversions | 6 | 5.3% | 2.90E-05 |
| Peroxisome | 8 | 7.1% | 3.50E-05 |
| Glycine, serine, and threonine metabolism | 6 | 5.3% | 6.60E-05 |
| Metabolism of xenobiotics by cytochrome P450 | 7 | 6.2% | 1.60E-04 |
| Ascorbate and aldarate metabolism | 5 | 4.4% | 2.10E-04 |
| Phenylalanine metabolism | 4 | 3.5% | 8.20E-04 |
| Glycolysis / Gluconeogenesis | 6 | 5.3% | 8.70E-04 |
| Tryptophan metabolism | 5 | 4.4% | 9.80E-04 |
| Drug metabolism - other enzymes | 5 | 4.4% | 1.70E-03 |
| Chemical carcinogenesis | 6 | 5.3% | 1.90E-03 |
| beta-Alanine metabolism | 4 | 3.5% | 4.80E-03 |
| Retinol metabolism | 5 | 4.4% | 5.50E-03 |
| PPAR signalling pathway | 5 | 4.4% | 6.50E-03 |
| Alanine, aspartate, and glutamate metabolism | 4 | 3.5% | 6.80E-03 |
| Porphyrin and chlorophyll metabolism | 4 | 3.5% | 1.10E-02 |
| Mineral absorption | 4 | 3.5% | 1.30E-02 |
| Histidine metabolism | 3 | 2.7% | 2.50E-02 |

**Table 22.3** – Biological process analysis of downregulated DEGs in DBD and living biopsies compared at T2.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **Biological Process** | Oxidation-reduction process | 21 | 18.6% | 8.70E-10 |
| Xenobiotic metabolic process | 8 | 7.1% | 6.40E-07 |
| Cellular response to cadmium ion | 4 | 3.5% | 1.60E-04 |
| Negative regulation of growth | 4 | 3.5% | 2.30E-04 |
| Cellular response to zinc ion | 4 | 3.5% | 2.30E-04 |
| Metabolic process | 7 | 6.2% | 7.20E-04 |
| Glucose metabolic process | 5 | 4.4% | 8.80E-04 |
| Urate metabolic process | 3 | 2.7% | 1.80E-03 |
| Response to toxic substance | 5 | 4.4% | 2.10E-03 |
| Gluconeogenesis | 4 | 3.5% | 2.80E-03 |
| Beta-amyloid metabolic process | 3 | 2.7% | 3.00E-03 |
| Platelet degranulation | 5 | 4.4% | 4.20E-03 |
| Glutathione metabolic process | 4 | 3.5% | 5.50E-03 |
| Flavonoid biosynthetic process | 3 | 2.7% | 7.10E-03 |
| Flavonoid glucuronidation | 3 | 2.7% | 8.60E-03 |
| Sodium-independent organic anion transport | 3 | 2.7% | 9.30E-03 |
| Cellular oxidant detoxification | 4 | 3.5% | 1.00E-02 |
| Response to cadmium ion | 3 | 2.7% | 1.10E-02 |
| Glyoxylate metabolic process | 3 | 2.7% | 1.20E-02 |
| Amino-acid betaine catabolic process | 2 | 1.8% | 1.30E-02 |
| Drug metabolic process | 3 | 2.7% | 1.30E-02 |
| Response to drug | 7 | 6.2% | 1.30E-02 |
| Glyoxylate catabolic process | 2 | 1.8% | 1.90E-02 |
| Lipoprotein metabolic process | 3 | 2.7% | 2.40E-02 |
| Carbohydrate metabolic process | 5 | 4.4% | 2.50E-02 |
| Leukotriene B4 catabolic process | 2 | 1.8% | 2.50E-02 |
| Choline metabolic process | 2 | 1.8% | 2.50E-02 |
| Proline catabolic process | 2 | 1.8% | 2.50E-02 |
| Cellular amino acid metabolic process | 3 | 2.7% | 2.70E-02 |
| Steroid metabolic process | 3 | 2.7% | 3.10E-02 |
| Cellular response to fructose stimulus | 2 | 1.8% | 3.10E-02 |
| Glucuronate catabolic process to xylulose 5-phosphate | 2 | 1.8% | 3.10E-02 |
| Fatty acid beta-oxidation | 3 | 2.7% | 3.20E-02 |
| Aspartate metabolic process | 2 | 1.8% | 3.80E-02 |
| Cellular response to copper ion | 2 | 1.8% | 3.80E-02 |
| Choline catabolic process | 2 | 1.8% | 3.80E-02 |
| Catecholamine biosynthetic process | 2 | 1.8% | 3.80E-02 |
| Cellular protein metabolic process | 4 | 3.5% | 4.00E-02 |
| Fatty acid alpha-oxidation | 2 | 1.8% | 4.40E-02 |
| Glucose-6-phosphate transport | 2 | 1.8% | 4.40E-02 |
| Response to mercury ion | 2 | 1.8% | 4.40E-02 |

**Table 23.3** – Biological process analysis of upregulated DEGs in DCD and living biopsies compared at T2.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **Biological Process** | Inflammatory response | 9 | 20.5% | 3.10E-07 |
| Negative regulation of inclusion body assembly | 4 | 9.1% | 6.80E-07 |
| Leukocyte migration involved in the inflammatory response | 4 | 9.1% | 9.30E-07 |
| Response to unfolded protein | 5 | 11.4% | 1.00E-06 |
| Protein refolding | 4 | 9.1% | 2.60E-06 |
| Cellular heat acclimation | 3 | 6.8% | 2.00E-05 |
| Neutrophil chemotaxis | 4 | 9.1% | 2.40E-04 |
| Positive regulation of inflammatory response | 4 | 9.1% | 3.20E-04 |
| Regulation of cellular response to heat | 4 | 9.1% | 3.50E-04 |
| Negative regulation of endopeptidase activity | 4 | 9.1% | 1.40E-03 |
| Positive regulation of NF-κB transcription factor activity | 4 | 9.1% | 1.90E-03 |
| Cellular response to heat | 3 | 6.8% | 2.10E-03 |
| Response to peptide hormone | 3 | 6.8% | 3.00E-03 |
| Response to lipopolysaccharide | 4 | 9.1% | 3.40E-03 |
| Response to heat | 3 | 6.8% | 3.50E-03 |
| Positive regulation of mRNA endonucleolytic cleavage involved in unfolded protein response | 2 | 4.5% | 3.70E-03 |
| Positive regulation of endoribonuclease activity | 2 | 4.5% | 3.70E-03 |
| Neutrophil aggregation | 2 | 4.5% | 3.70E-03 |
| Chemokine production | 2 | 4.5% | 5.50E-03 |
| Positive regulation of nucleotide-binding oligomerization domain containing 2 signalling pathways | 2 | 4.5% | 5.50E-03 |
| Positive regulation of peptide secretion | 2 | 4.5% | 7.40E-03 |
| Sequestering of zinc ion | 2 | 4.5% | 7.40E-03 |
| Chemokine-mediated signalling pathway | 3 | 6.8% | 7.60E-03 |
| Positive regulation of tumour necrosis factor-mediated signalling pathway | 2 | 4.5% | 1.10E-02 |
| Negative regulation of mitochondrial outer membrane permeabilization involved in apoptotic signalling pathway | 2 | 4.5% | 1.30E-02 |
| Response to molecule of bacterial origin | 2 | 4.5% | 1.60E-02 |
| Chaperone mediated protein folding requiring cofactor | 2 | 4.5% | 1.80E-02 |
| Regulation of cell death | 2 | 4.5% | 2.00E-02 |
| Chemotaxis | 3 | 6.8% | 2.10E-02 |
| PERK-mediated unfolded protein response | 2 | 4.5% | 2.20E-02 |
| Astrocyte development | 2 | 4.5% | 2.90E-02 |
| Regulation of protein ubiquitination | 2 | 4.5% | 2.90E-02 |
| Negative regulation of endoplasmic reticulum stress-induced intrinsic apoptotic signalling pathway | 2 | 4.5% | 3.50E-02 |
| Regulation of cytoskeleton organization | 2 | 4.5% | 3.50E-02 |
| Defence response to virus | 3 | 6.8% | 3.70E-02 |
| Positive regulation of neutrophil chemotaxis | 2 | 4.5% | 4.00E-02 |
| Response to hypoxia | 3 | 6.8% | 4.00E-02 |
| Protein folding | 3 | 6.8% | 4.30E-02 |
| Cytokine production | 2 | 4.5% | 4.50E-02 |
| Positive regulation of interleukin-8 production | 2 | 4.5% | 4.70E-02 |
| Defence response to fungus | 2 | 4.5% | 4.90E-02 |

**Table 24.3** – Biological process analysis of downregulated DEGs in DCD and living biopsies compared at T2.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Category** | **Term** | **Count** | **Percentage** | **P-value** |
| **Biological Process** | Cellular response to cadmium ion | 5 | 6.7% | 6.70E-07 |
| Negative regulation of growth | 5 | 6.7% | 1.10E-06 |
| Cellular response to zinc ion | 5 | 6.7% | 1.10E-06 |
| Gluconeogenesis | 5 | 6.7% | 3.50E-05 |
| Oxidation-reduction process | 12 | 16% | 3.60E-05 |
| Xenobiotic metabolic process | 5 | 6.7% | 3.30E-04 |
| Urate metabolic process | 3 | 4% | 7.80E-04 |
| Glutathione metabolic process | 4 | 5.3% | 1.70E-03 |
| Amino-acid betaine catabolic process | 2 | 2.7% | 8.40E-03 |
| Glucose homeostasis | 4 | 5.3% | 9.00E-03 |
| Lipoprotein metabolic process | 3 | 4% | 1.10E-02 |
| Cellular amino acid metabolic process | 3 | 4% | 1.20E-02 |
| Steroid metabolic process | 3 | 4% | 1.40E-02 |
| Choline metabolic process | 2 | 2.7% | 1.70E-02 |
| Cellular response to fructose stimulus | 2 | 2.7% | 2.10E-02 |
| Vitamin transport | 2 | 2.7% | 2.10E-02 |
| Catecholamine biosynthetic process | 2 | 2.7% | 2.50E-02 |
| Choline catabolic process | 2 | 2.7% | 2.50E-02 |
| Aspartate metabolic process | 2 | 2.7% | 2.50E-02 |
| Fatty acid alpha-oxidation | 2 | 2.7% | 2.90E-02 |
| Response to lipopolysaccharide | 4 | 5.4% | 3.10E-02 |
| Metabolic process | 4 | 5.4% | 3.30E-02 |
| Cellular response to drug | 3 | 4.1% | 3.40E-02 |
| Cellular oxidant detoxification | 3 | 4.1% | 3.40E-02 |
| Carbohydrate metabolic process | 4 | 5.4% | 3.60E-02 |
| Glycine metabolic process | 2 | 2.7% | 3.70E-02 |
| Vitamin D metabolic process | 2 | 2.7% | 4.10E-02 |
| L-phenylalanine catabolic process | 2 | 2.7% | 4.50E-02 |
| Sulphur amino acid metabolic process | 2 | 2.7% | 4.50E-02 |
| Oxaloacetate metabolic process | 2 | 2.7% | 4.90E-02 |