# Using mechanistic models for the clinical interpretation of complex genomic variation

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**Additional Table 1.Gene expression values of 30 non-diseased tissues**. The 30 non-diseased tissue sites used in the current version of Hipathia, taken from the GTEx Portal

| Tissue name | Samples |
|---|---|
| **Adipose Tissue** | 797 |
| **Adrenal Gland** | 190 |
| **Bladder** | 11 |
| **Blood** | 537 |
| **Blood Vessel** | 913 |
| **Brain** | 1671 |
| **Breast** | 290 |
| **Cervix Uteri** | 11 |
| **Colon** | 507 |
| **Esophagus** | 1021 |
| **Fallopian Tube** | 7 |
| **Heart** | 600 |
| **Kidney** | 45 |
| **Liver** | 175 |
| **Lung** | 427 |
| **Muscle** | 564 |
| **Nerve** | 414 |
| **Ovary** | 133 |
| **Pancreas** | 248 |
| **Pituitary** | 183 |
| **Prostate** | 152 |
| **Salivary Gland** | 97 |
| **Skin** | 1203 |
| **Small Intestine** | 137 |
| **Spleen** | 162 |
| **Stomach** | 262 |
| **Testis** | 259 |
| **Thyroid** | 446 |
| **Uterus** | 111 |
| **Vagina** | 115 |

**Additional Table 2. Effect of LoF mutations in the genes within the FA pathway over the activity of signaling circuits**. The table contains the effect of a LoF mutations in the genes comprising the FA pathway and the corresponding effect on circuits of the FA pathways and circuits of other pathways, along with the occurrence of this type of mutations in the healthy population (1000 genomes)

| Gene Symbol | FA-association | pLI | % homozygotes | Total circuits affected | FA circuits affected | p-value |
|---|---|---|---|---|---|---|
| **FAAP100** | NP | 0.08826 | 0.039936102 | 1 | 1 | 0.00529 |
| **BLM** | NP | 4.139E-11 | 0.519169329 | 1 | 1 | 0.00529 |
| **RMI1** | NP | 0.003097 | 0.039936102 | 1 | 1 | 0.00529 |
| **RMI2** | NP | 0.0246 | 13.21884984 | NA | NA | NA |
| **TOP3A** | NP | 2.636E-08 | 2.076677316 | 0 | 0 | NA |
| **TOP3B** | NP | 0.1145 | 0.039936102 | 0 | 0 | NA |
| **ATRIP** | NP | 0.001487 | 0.878594249 | 5 | 5 | 0.00106 |
| **ATR** | NP | 0.7013 | 0.159744409 | 38 | 5 | 0.00016 |
| **RPA4** | NP | 0.274 | 0 | 1 | 1 | 0.00529 |
| **RPA1** | NP | 0.3087 | 0 | 1 | 1 | 0.00529 |
| **RPA2** | NP | 0.8885 | 0 | 1 | 1 | 0.00529 |
| **RPA3** | NP | 0.00007563 | 0 | 1 | 1 | 0.00529 |
| **TELO2** | NP | 4.842E-07 | 0.159744409 | 5 | 5 | 0.00106 |
| **MLH1** | NP | 0.7396 | 0.439297125 | 1 | 1 | 0.00529 |
| **FAN1** | NP | 1.468E-15 | 0 | 1 | 1 | 0.00529 |
| **USP1** | NP | 0.9932 | 0.039936102 | 3 | 3 | 0.00176 |
| **WDR48** | NP | 0.9998 | 25.79872204 | 3 | 3 | 0.00176 |
| **REV1** | NP | 0.997 | 1.277955272 | 1 | 1 | 0.00529 |
| **CENPX** | NP | 0.592 | 0 | NA | NA | NA |
| **CENPS** | NP | 0.008521 | 29.23322684 | 0 | 0 | NA |
| **POLH** | NP | 0.003591 | 0 | 0 | 0 | NA |
| **POLK** | NP | 5.999E-07 | 0 | NA | NA | NA |
| **REV3L** | NP | 1 | 1.837060703 | 0 | 0 | NA |
| **POLI** | NP | 4.27E-09 | 0.039936102 | 0 | 0 | NA |
| **PMS2** | NP | 1.139E-13 | 0.559105431 | 1 | 1 | 0.00529 |
| **MUS81** | NP | 0.00000157 | 41.014377 | 0 | 0 | NA |
| **EME1** | NP | 7.067E-11 | 0.638977636 | NA | NA | NA |
| **EME2** | NP | 9.501E-14 | 0 | NA | NA | NA |
| **ERCC1** | NP | 0.0002869 | 0 | 0 | 0 | NA |
| **SLX1A** | NP | 0.6255 | 0.079872205 | 0 | 0 | NA |
| **SLX1B** | NP | 0.5168 | 0 | 0 | 0 | NA |
| **FAAP24** | NP | 0.00002662 | 0 | 2 | 2 | 0.00265 |
| **HES1** | NP | 0.6441 | 0 | 5 | 1 | 0.00106 |
| **POLN** | NP | 2.997E-32 | 13.77795527 | NA | NA | NA |
| **FANCM** | P | 6.245E-12 | 0.039936102 | NA | NA | NA |
| **FANCA** | P | 2.081E-34 | 1.517571885 | 1 | 1 | 0.00529 |
| **FANCB** | P | 0.9884 | 0 | NA | NA | NA |
| **FANCC** | P | 5.88E-10 | 0.279552716 | 1 | 1 | 0.00529 |
| **FANCD2** | P | 2.479E-14 | 0.479233227 | NA | NA | NA |
| **FANCI** | P | 5.165E-19 | 9.265175719 | 3 | 3 | 0.00176 |
| **FANCE** | P | 0.003139 | 0 | 1 | 1 | 0.00529 |

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|---|---|---|---|---|---|---|
| **FANCF** | P | 0.003815 | 0.079872205 | 1 | 1 | 0.00529 |
| **FANCG** | P | 9.753E-09 | 0 | 1 | 1 | 0.00529 |
| **FANCL** | P | 0.00000002 | 4.552715655 | 1 | 1 | 0.00529 |
| **PALB2** | P | 1.326E-10 | 0 | 1 | 1 | 0.00529 |
| **BRCA2** | P | 2.213E-15 | 0.079872205 | 2 | 2 | 0.00265 |
| **BRIP1** | P | 5.378E-13 | 0 | 1 | 1 | 0.00529 |
| **BRCA1** | P | 3.287E-20 | 13.57827476 | 0 | 0 | NA |
| **RAD51C** | P | 4.278E-09 | 0 | 1 | 1 | 0.00529 |
| **UBE2T** | P | 0.0003692 | 0 | NA | NA | NA |
| **ERCC4** | P | 3.332E-10 | 0.239616613 | 0 | 0 | NA |
| **SLX4** | P | 0.00000008 | 1.277955272 | NA | NA | NA |
| **RAD51** | P | 0.9904 | 0 | 1 | 1 | 0.00529 |
| **MAD2L2** | P | 0.2025 | 0 | NA | NA | NA |
| **XRCC2** | P | 0.00000423 | 0 | 0 | 0 | NA |
| **RFWD3** | P | 0.5253 | 0 | 0 | 0 | NA |

**Additional Table 3.** Comparison of Inflammation-related circuit activities between human pancreatic islets with Type 2 diabetes and normal ones. The last column shows the circuit functionalities according Uniprot.

| Circuit | Log Fold Change | t | P-value | FDR-adj. p-value | Function (Uniprot) |
|---|---|---|---|---|---|
| **Rap1 signaling pathway: PRKCI PARD6A PARD3** | 0.001003 | 3.835813 | 0.000297 | 0.008921 | Inflammatory response, Cell cycle, Cell division, Differentiation |
| **NF-kappa B signaling pathway: CCL19** | 0.01209 | 3.374508 | 0.001285 | 0.016761 | Inflammatory response. Chemotaxis |
| **NF-kappa B signaling pathway: CCL21** | 0.02025 | 3.287014 | 0.001676 | 0.016761 | Inflammatory response. Chemotaxis |
| **NF-kappa B signaling pathway: CCL13** | 0.007066 | 2.71083 | 0.008687 | 0.065155 | Inflammatory response. Chemotaxis |
| **NF-kappa B signaling pathway: CXCL8** | 0.004867 | 2.12408 | 0.037692 | 0.18395 | Inflammatory response. Chemotaxis |
| **PPAR signaling pathway: OLR1** | 0.00917 | 2.117447 | 0.038273 | 0.18395 | Inflammatory response. Cell adhesion. Immunity |
| **Ras signaling pathway: PIK3R5*** | 0.00924 | 2.067291 | 0.042922 | 0.18395 | Angiogenesis. Endocytosis. Autophagy. Cell adhesion. Chemotaxis. Adaptive immunity. Inflammatory response. Innate immunity. Differentiation. Immunity. Stress response. Host-virus interaction. Protein transport. Transport |
| **NF-kappa B signaling pathway: IL1B*** | 0.002005 | 1.833731 | 0.071533 | 0.268251 | Inflammatory response. Pyrogen |
| **NF-kappa B signaling pathway: TNFAIP3** | 0.002549 | 1.585311 | 0.118025 | 0.393415 | Inflammatory response. Apoptosis.Ubl conjugation pathway |
| **Toll-like receptor signaling pathway: CXCL8** | 0.005751 | 1.136375 | 0.260208 | 0.780625 | Chemotaxis. Inflammatory response |
| **Toll-like receptor signaling pathway: CCL4L1** | -0.00104 | -0.88544 | 0.37937 | 0.872459 | Chemotaxis. Inflammatory response |
| **Toll-like receptor signaling pathway: IL1B** | 0.002036 | 0.858897 | 0.393733 | 0.872459 | Inflammatory response. Pyrogen |
| **NOD-like receptor signaling pathway: NLRP3 PYCARD** | -0.0003 | -0.84108 | 0.403562 | 0.872459 | Apoptosis. Inflammatory response. Innate immunity. Immunity |
| **Complement and coagulation cascades: C4A** | -0.00259 | -0.73026 | 0.468006 | 0.872459 | Complement pathway. Innate immunity. Inflammatory response. Immunity |
| **Complement and coagulation cascades: C3** | 0.022158 | 0.727085 | 0.469933 | 0.872459 | Complement pathway. Innate immunity. Inflammatory response. Complement alternate pathway. Fatty acid |

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|---|---|---|---|---|---|
| | | | | | metabolism. Immunity. Lipid metabolism |
| **Toll-like receptor signaling pathway: CXCL10** | 0.000774 | 0.712389 | 0.478918 | 0.872459 | Chemotaxis. Inflammatory response |
| **NF-kappa B signaling pathway: CXCL2** | 0.001214 | 0.603292 | 0.548533 | 0.872459 | Inflammatory response. Chemotaxis |
| **NF-kappa B signaling pathway: CCL4L1** | 0.000327 | 0.600263 | 0.550537 | 0.872459 | Inflammatory response. Chemotaxis |
| **NOD-like receptor signaling pathway: PYCARD CASP1** | -0.00055 | -0.56603 | 0.573434 | 0.872459 | Apoptosis. Inflammatory response. Innate immunity. Immunity |
| **Chemokine signaling pathway: PARD3 PRKCZ TIAM1** | 0.000103 | 0.540267 | 0.590964 | 0.872459 | Cell cycle. Cell division. Differentiation. Inflammatory response |
| **NOD-like receptor signaling pathway: NLRC4 PYCARD** | -0.00061 | -0.47478 | 0.636626 | 0.872459 | Apoptosis. Inflammatory response. Innate immunity. Immunity |
| **Toll-like receptor signaling pathway: CXCL9** | 0.000199 | 0.470302 | 0.639803 | 0.872459 | Inflammatory response |
| **NOD-like receptor signaling pathway: CASP1 PYCARD** | -0.00095 | -0.42411 | 0.672965 | 0.87778 | Apoptosis. Inflammatory response. Innate immunity. Immunity |
| **Progesterone-mediated oocyte maturation: PIK3R5** | -0.00217 | -0.33108 | 0.741706 | 0.916293 | Angiogenesis. Endocytosis. Autophagy. Cell adhesion. Chemotaxis. Inflammatory response. Adaptive immunity. Innate immunity. Differentiation. Immunity. Stress response. Protein transport. Host-virus interaction. Transport |
| **Toll-like receptor signaling pathway: CCL3L3** | -0.00044 | -0.29644 | 0.767893 | 0.916293 | Chemotaxis. Inflammatory response |
| **Toll-like receptor signaling pathway: CCL5** | 0.000328 | 0.224689 | 0.822966 | 0.916293 | Chemotaxis. Inflammatory response |
| **Toll-like receptor signaling pathway: CXCL11** | -0.00018 | -0.2225 | 0.824663 | 0.916293 | Chemotaxis. Inflammatory response |
| **NOD-like receptor signaling pathway: NLRP3 CARD8 CASP1** | -0.0005 | -0.12203 | 0.90327 | 0.967789 | Apoptosis. Inflammatory response. Innate immunity. Immunity |
| **FoxO signaling pathway: BCL6** | 0 | 3.37E-07 | 1 | 1 | Inflammatory response. Transcription regulation. Transcription. Immunity |
| **FoxO signaling pathway: BCL6*** | 0 | 3.37E-07 | 1 | 1 | Inflammatory response. Transcription regulation. Transcription. Immunity |

**Additional Table 4. Signaling circuits differentially activated in the comparison of human islets gene expression of healthy donors with type 2 diabetic patients**. To limit the size of the table only 183 circuits, with a significant differential activity at a nominal p-value < 0.05, are listed.

| CIRCUIT | UP / DOWN | statistic | p-value | FDR p-value | FunctionUniprot |
|---|---|---|---|---|---|
| **Adherens junction: NLK** | DOWN | -3,5159 | 0,0005 | 0,1469 | Wnt signaling pathway, Transcription regulation, Transcription |
| **Adherens junction: IQGAP1**** | DOWN | -3,4766 | 0,0005 | 0,1469 | |
| **Wnt signaling pathway: MYC** | UP | 3,3980 | 0,0007 | 0,1469 | Transcription regulation, Transcription |
| **MAPK signaling pathway: MAPT** | DOWN | -3,3784 | 0,0008 | 0,1469 | |
| **Rap1 signaling pathway: CDH1** | UP | 3,3391 | 0,0009 | 0,1469 | Cell cycle, Cell division, Cell adhesion, Mitosis, DNA repair, DNA damage, Ubl conjugation pathway |
| **Rap1 signaling pathway: PRKCI PARD6A PARD3** | UP | 3,3195 | 0,0009 | 0,1469 | Inflammatory response, Cell cycle, Cell division, Differentiation |
| **PI3K-Akt signaling pathway: MYC** | UP | 3,2802 | 0,0011 | 0,1469 | Transcription regulation, Transcription |
| **Retrograde endocannabinoid signaling: CACNA1A** | DOWN | -3,2802 | 0,0011 | 0,1469 | Ion channel, Calcium channel, Calcium transport, Voltage-gated channel, Ion transport, Transport |
| **Retrograde endocannabinoid signaling: CACNA1A*** | DOWN | -3,2802 | 0,0011 | 0,1469 | Ion channel, Calcium channel, Calcium transport, Voltage-gated channel, Ion transport, Transport |
| **Thyroid hormone signaling pathway: PFKFB2** | DOWN | -3,2605 | 0,0012 | 0,1469 | |
| **PI3K-Akt signaling pathway: BCL2L1*** | UP | 3,2409 | 0,0012 | 0,1469 | Apoptosis, Endocytosis |
| **Toll-like receptor signaling pathway: CD86** | UP | 3,2409 | 0,0012 | 0,1469 | Host-virus interaction, Adaptive immunity, Immunity |
| **AMPK signaling pathway: PFKFB1** | DOWN | -3,1820 | 0,0015 | 0,1469 | |
| **Retrograde endocannabinoid signaling: PRKACA** | DOWN | -3,1427 | 0,0017 | 0,1469 | Apoptosis, Angiogenesis, Cell adhesion |
| **Rap1 signaling pathway: ACTB** | UP | 3,1034 | 0,0020 | 0,1538 | |
| **Rap1 signaling pathway: AKT3** | UP | 3,0838 | 0,0021 | 0,1578 | Glycogen biosynthesis, Glycogen metabolism, Glucose metabolism, Apoptosis, Sugar transport, Carbohydrate metabolism, Translation regulation, Neurogenesis, |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Transport |
| **PPAR signaling pathway: CPT2** | DOWN | -3,0248 | 0,0026 | 0,1651 | Fatty acid metabolism, Lipid metabolism, Transport |
| **PI3K-Akt signaling pathway: CCND1** | UP | 3,0248 | 0,0026 | 0,1651 | Cell cycle, Cell division, DNA damage, Transcription regulation, Transcription |
| **PI3K-Akt signaling pathway: G6PC** | DOWN | -3,0052 | 0,0027 | 0,1651 | Gluconeogenesis |
| **Rap1 signaling pathway: ITGAL** | UP | 2,9659 | 0,0031 | 0,1818 | Cell adhesion, Host-virus interaction |
| **Rap1 signaling pathway: MAPK14** | UP | 2,9266 | 0,0035 | 0,1942 | Stress response, Apoptosis, Transcription regulation, Transcription, Cell cycle |
| **Regulation of actin cytoskeleton: PFN3 ACTB** | DOWN | -2,9266 | 0,0035 | 0,1942 | |
| **AMPK signaling pathway: SCD** | DOWN | -2,9070 | 0,0038 | 0,1953 | Fatty acid metabolism, Fatty acid biosynthesis, Lipid metabolism, Lipid biosynthesis |
| **Gap junction: GJA1 GJA1***** | UP | 2,9070 | 0,0038 | 0,1953 | |
| **PPAR signaling pathway: SCD** | DOWN | -2,8481 | 0,0045 | 0,2117 | Fatty acid metabolism, Lipid metabolism, Fatty acid biosynthesis, Lipid biosynthesis |
| **PPAR signaling pathway: SCP2** | DOWN | -2,8481 | 0,0045 | 0,2117 | Lipid transport, Meiosis, Cell division, Transport, Cell cycle |
| **Estrogen signaling pathway: AKT3*** | UP | 2,8481 | 0,0045 | 0,2117 | Glycogen biosynthesis, Glycogen metabolism, Glucose metabolism, Sugar transport, Carbohydrate metabolism, Translation regulation, Apoptosis, Neurogenesis, Transport |
| **Thyroid hormone signaling pathway: TBC1D4** | DOWN | -2,8481 | 0,0045 | 0,2117 | |
| **Wnt signaling pathway: CCND1** | UP | 2,8284 | 0,0048 | 0,2178 | Cell division, Cell cycle, Transcription regulation, Transcription, DNA damage |
| **MAPK signaling pathway: STK3** | UP | 2,7891 | 0,0054 | 0,2178 | Apoptosis |
| **PPAR signaling pathway: ACADM** | DOWN | -2,7499 | 0,0061 | 0,2178 | Fatty acid metabolism, Lipid metabolism |
| **Adherens junction: ACTB VCL** | UP | 2,7499 | 0,0061 | 0,2178 | Cell adhesion |
| **Regulation of actin cytoskeleton: MYL12B MYH9 ACTB** | DOWN | -2,7302 | 0,0065 | 0,2178 | Cell shape, Cell adhesion |
| **cGMP-PKG signaling pathway: PDE3A** | UP | 2,7106 | 0,0069 | 0,2178 | Angiogenesis |
| **Regulation of actin cytoskeleton: CFL1 ACTB** | DOWN | -2,7106 | 0,0069 | 0,2178 | |

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|---|---|---|---|---|---|
| **Retrograde endocannabinoid signaling: MAPK14*** | UP | 2,6909 | 0,0073 | 0,2178 | Stress response, Apoptosis, Transcription regulation, Transcription, Cell cycle, Host-virus interaction, Biological rhythms |
| **Retrograde endocannabinoid signaling: MAPK14** | UP | 2,6909 | 0,0073 | 0,2178 | Stress response, Apoptosis, Transcription regulation, Transcription, Cell cycle, Host-virus interaction, Biological rhythms |
| **Regulation of actin cytoskeleton: ACTN4** | DOWN | -2,6909 | 0,0073 | 0,2178 | Protein transport, Transport |
| **Insulin secretion: INS** | DOWN | -2,6909 | 0,0073 | 0,2178 | Glucose metabolism, Carbohydrate metabolism |
| **Jak-STAT signaling pathway: MYC** | UP | 2,6713 | 0,0078 | 0,2178 | Transcription regulation, Transcription |
| **Fc epsilon RI signaling pathway: MAPK14** | UP | 2,6713 | 0,0078 | 0,2178 | Stress response, Apoptosis, Transcription regulation, Transcription, Cell cycle |
| **cAMP signaling pathway: AMH** | UP | 2,6517 | 0,0082 | 0,2178 | Gonadal differentiation, Differentiation |
| **Prolactin signaling pathway: CCND1**** | UP | 2,6517 | 0,0082 | 0,2178 | Cell division, Cell cycle, Transcription regulation, DNA damage, Transcription |
| **PPAR signaling pathway: GK** | UP | 2,6320 | 0,0087 | 0,2178 | Glycerol metabolism |
| **Wnt signaling pathway: MMP7** | UP | 2,6320 | 0,0087 | 0,2178 | Collagen degradation |
| **Complement and coagulation cascades: CPB2** | UP | 2,6320 | 0,0087 | 0,2178 | Blood coagulation, Hemostasis, Fibrinolysis |
| **Toll-like receptor signaling pathway: NFKB1** | UP | 2,6320 | 0,0087 | 0,2178 | Apoptosis, Transcription regulation, Transcription |
| **Cytosolic DNA-sensing pathway: NFKB1*** | UP | 2,6320 | 0,0087 | 0,2178 | Apoptosis, Transcription regulation, Transcription, Host-virus interaction |
| **Regulation of actin cytoskeleton: IQGAP2** | UP | 2,6320 | 0,0087 | 0,2178 | |
| **Estrogen signaling pathway: ESR1 C00951** | UP | 2,6320 | 0,0087 | 0,2178 | Transcription regulation, Transcription |
| **Estrogen signaling pathway: ESR1 FOS** | UP | 2,6320 | 0,0087 | 0,2178 | Transcription regulation, Transcription |
| **Estrogen signaling pathway: ESR1 C00951*** | UP | 2,6320 | 0,0087 | 0,2178 | Transcription regulation, Transcription |
| **Wnt signaling pathway: PPARD** | UP | 2,6124 | 0,0093 | 0,2178 | Transcription regulation, Transcription |
| **Hippo signaling pathway: AREG** | UP | 2,6124 | 0,0093 | 0,2178 | |
| **Hippo signaling pathway: SERPINE1** | UP | 2,6124 | 0,0093 | 0,2178 | |
| **Hippo signaling pathway: CTGF*** | UP | 2,5927 | 0,0098 | 0,2178 | DNA synthesis, Cell adhesion |
| **Progesterone-mediated oocyte maturation: ANAPC10** | UP | 2,5927 | 0,0098 | 0,2178 | Mitosis, Cell division, Cell cycle, Ubl conjugation pathway, Neurogenesis, Differentiation |

| | | | | | |
|---|---|---|---|---|---|
| **Estrogen signaling pathway: CREB3*** ** | UP | 2,5927 | 0,0098 | 0,2178 | Unfolded protein response, Transcription regulation, Transcription, Host-virus interaction, Chemotaxis, Biological rhythms, Differentiation, DNA damage |
| **Thyroid hormone signaling pathway: WNT4** | DOWN | -2,5927 | 0,0098 | 0,2178 | Wnt signaling pathway |
| **AMPK signaling pathway: CCND1** | UP | 2,5731 | 0,0104 | 0,2200 | Cell division, Cell cycle, DNA damage, Transcription regulation, Transcription |
| **Jak-STAT signaling pathway: CDKN1A** | UP | 2,5731 | 0,0104 | 0,2200 | Cell cycle |
| **Wnt signaling pathway: FOSL1** | UP | 2,5534 | 0,0110 | 0,2276 | |
| **Regulation of actin cytoskeleton: MSN** | DOWN | -2,5534 | 0,0110 | 0,2276 | Cell shape |
| **Signaling pathways regulating pluripotency of stem cells: MYC*** | UP | 2,5338 | 0,0116 | 0,2381 | Transcription regulation, Transcription |
| **Adherens junction: SNAI1** | UP | 2,4945 | 0,0130 | 0,2417 | |
| **Regulation of actin cytoskeleton: VCL*** | DOWN | -2,4945 | 0,0130 | 0,2417 | Cell adhesion |
| **Ras signaling pathway: RAC1**** | UP | 2,4749 | 0,0137 | 0,2417 | |
| **HIF-1 signaling pathway: PFKFB3** | UP | 2,4749 | 0,0137 | 0,2417 | |
| **Hedgehog signaling pathway: PTCH1**** | DOWN | -2,4749 | 0,0137 | 0,2417 | |
| **Fc gamma R-mediated phagocytosis: PLA2G4B** | UP | 2,4749 | 0,0137 | 0,2417 | Lipid degradation, Lipid metabolism |
| **NF-kappa B signaling pathway: PLCG1** | DOWN | -2,4552 | 0,0145 | 0,2417 | Host-virus interaction, Lipid degradation, Lipid metabolism |
| **Focal adhesion: VASP ACTB** | UP | 2,4552 | 0,0145 | 0,2417 | |
| **Prolactin signaling pathway: TNFSF11** | UP | 2,4552 | 0,0145 | 0,2417 | |
| **Oxytocin signaling pathway: MYL9 ACTB** | DOWN | -2,4552 | 0,0145 | 0,2417 | |
| **Axon guidance: UNC5D PTPN11** | DOWN | -2,4356 | 0,0153 | 0,2417 | Apoptosis |
| **Hippo signaling pathway: YWHAQ YAP1** | UP | 2,4356 | 0,0153 | 0,2417 | Host-virus interaction, Transcription regulation, Transcription |
| **Hippo signaling pathway: SMAD7** | UP | 2,4356 | 0,0153 | 0,2417 | Transcription regulation, Transcription |
| **Retrograde endocannabinoid signaling: ADCY1** | DOWN | -2,4356 | 0,0153 | 0,2417 | cAMP biosynthesis, Biological rhythms, Olfaction, Sensory transduction |
| **Insulin secretion: CACNA1C** | DOWN | -2,4356 | 0,0153 | 0,2417 | Calcium channel, Calcium transport, Voltage-gated channel, Ion channel, Ion transport, Transport, Vision, |

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|---|---|---|---|---|---|
| | | | | | Sensory transduction |
| **Insulin secretion: CAMK2A** | DOWN | -2,4356 | 0,0153 | 0,2417 | Neurogenesis, Differentiation |
| **Estrogen signaling pathway: CREB3** | UP | 2,4356 | 0,0153 | 0,2417 | Unfolded protein response, Transcription regulation, Transcription, Host-virus interaction, Chemotaxis, Biological rhythms, Differentiation, DNA damage |
| **Glutamatergic synapse: GRM3** | DOWN | -2,4258 | 0,0157 | 0,2462 | |
| **PPAR signaling pathway: MMP1** | UP | 2,4159 | 0,0161 | 0,2470 | Collagen degradation, Host-virus interaction |
| **NF-kappa B signaling pathway: PLAU** | UP | 2,3963 | 0,0170 | 0,2470 | Fibrinolysis, Plasminogen activation, Blood coagulation, Hemostasis |
| **Regulation of actin cytoskeleton: ACTB ARPC5** | UP | 2,3963 | 0,0170 | 0,2470 | |
| **Regulation of actin cytoskeleton: GSN** | DOWN | -2,3963 | 0,0170 | 0,2470 | Cilium biogenesis/degradation |
| **Insulin secretion: RAB3A** | DOWN | -2,3963 | 0,0170 | 0,2470 | Exocytosis, Transport, Protein transport |
| **Axon guidance: ROCK1*** | UP | 2,3767 | 0,0179 | 0,2470 | Apoptosis, Biological rhythms |
| **TNF signaling pathway: CEBPB** | UP | 2,3767 | 0,0179 | 0,2470 | Transcription regulation, Transcription, Differentiation |
| **Thyroid hormone signaling pathway: NOTCH1** | DOWN | -2,3767 | 0,0179 | 0,2470 | Notch signaling pathway, Transcription regulation, Transcription, Differentiation, Angiogenesis |
| **Aldosterone-regulated sodium reabsorption: ATP1B4** | DOWN | -2,3767 | 0,0179 | 0,2470 | Ion transport, Transport, Transcription regulation, Transcription, Sodium/potassium transport, Potassium transport, Sodium transport, Cell adhesion |
| **PPAR signaling pathway: FADS2** | DOWN | -2,3570 | 0,0189 | 0,2470 | Fatty acid metabolism, Lipid metabolism, Fatty acid biosynthesis, Lipid biosynthesis, Transport, Electron transport |
| **Rap1 signaling pathway: RALA** | DOWN | -2,3570 | 0,0189 | 0,2470 | Cell cycle, Cell division, Host-virus interaction, Exocytosis, Apoptosis |
| **MAPK signaling pathway: ECSIT TRAF6** | UP | 2,3374 | 0,0199 | 0,2515 | Innate immunity, Immunity, Osteogenesis, Ubl conjugation pathway |
| **Axon guidance: UNC5D DCC** | DOWN | -2,3374 | 0,0199 | 0,2515 | Apoptosis |
| **HIF-1 signaling pathway: HMOX1** | UP | 2,2981 | 0,0221 | 0,2597 | Apoptosis |
| **Focal adhesion: BAD** | DOWN | -2,2981 | 0,0221 | 0,2597 | Apoptosis |
| **Jak-STAT signaling pathway: MCL1** | UP | 2,2981 | 0,0221 | 0,2597 | Apoptosis, Differentiation |

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| **PI3K-Akt signaling pathway: BCL2*** | UP | 2,2785 | 0,0233 | 0,2597 | Apoptosis |
| **Antigen processing and presentation: CD4 HLA-DMA** | UP | 2,2785 | 0,0233 | 0,2597 | Immunity, Adaptive immunity, Host-virus interaction, MHC II, MHC I |
| **Fc gamma R-mediated phagocytosis: ARPC5** | UP | 2,2785 | 0,0233 | 0,2597 | |
| **Inflammatory mediator regulation of TRP channels: TRPV2** | UP | 2,2785 | 0,0233 | 0,2597 | Ion channel, Ion transport, Calcium transport, Calcium channel, Transport |
| **GnRH signaling pathway: JUN** | UP | 2,2785 | 0,0233 | 0,2597 | Transcription regulation, Transcription |
| **PPAR signaling pathway: DBI** | DOWN | -2,2588 | 0,0245 | 0,2597 | Transport |
| **Ras signaling pathway: STK4 STK4** | UP | 2,2588 | 0,0245 | 0,2597 | Apoptosis |
| **HIF-1 signaling pathway: LDHA** | UP | 2,2588 | 0,0245 | 0,2597 | |
| **Thyroid hormone signaling pathway: CTNNB1** | UP | 2,2588 | 0,0245 | 0,2597 | Transcription regulation, Transcription, Wnt signaling pathway, Cell adhesion, Neurogenesis |
| **NF-kappa B signaling pathway: CCL19** | UP | 2,2392 | 0,0258 | 0,2597 | Inflammatory response, Chemotaxis |
| **Sphingolipid signaling pathway: PRKCA** | DOWN | -2,2392 | 0,0258 | 0,2597 | Apoptosis, Angiogenesis, Cell adhesion, Transcription regulation, Transcription, Adaptive immunity, Immunity, Biological rhythms |
| **PI3K-Akt signaling pathway: GYS1** | UP | 2,2392 | 0,0258 | 0,2597 | Glycogen biosynthesis |
| **Jak-STAT signaling pathway: BCL2L1** | UP | 2,2392 | 0,0258 | 0,2597 | Apoptosis, Endocytosis |
| **cGMP-PKG signaling pathway: PDE2A** | DOWN | -2,2195 | 0,0271 | 0,2597 | |
| **Hippo signaling pathway: SOX2** | DOWN | -2,2195 | 0,0271 | 0,2597 | Transcription regulation, Transcription |
| **Adherens junction: ACTB** | UP | 2,2195 | 0,0271 | 0,2597 | |
| **Tight junction: IGSF5 TJP1 MLLT4** | UP | 2,2195 | 0,0271 | 0,2597 | Host-virus interaction, Cell adhesion, Angiogenesis |
| **RIG-I-like receptor signaling pathway: NFKB1** | UP | 2,2195 | 0,0271 | 0,2597 | Transcription regulation, Transcription, Apoptosis, Host-virus interaction |
| **Jak-STAT signaling pathway: GFAP** | UP | 2,2195 | 0,0271 | 0,2597 | |
| **Estrogen signaling pathway: CREB3*** | DOWN | -2,2195 | 0,0271 | 0,2597 | Unfolded protein response, Transcription regulation, Transcription, Host-virus interaction, Chemotaxis, Biological rhythms, Differentiation, DNA damage |
| **Oxytocin signaling pathway: CDKN1A** | UP | 2,2195 | 0,0271 | 0,2597 | Cell cycle |

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| **Aldosterone synthesis and secretion: ITPR1** | DOWN | -2,2195 | 0,0271 | 0,2597 | Ion channel, Calcium channel, Ligand-gated ion channel, Calcium transport, Ion transport, Transport, Apoptosis |
| **Axon guidance: NFATC2** | DOWN | -2,1999 | 0,0285 | 0,2649 | Transcription regulation, Transcription, Differentiation |
| **Dopaminergic synapse: CAMK2A** | DOWN | -2,1999 | 0,0285 | 0,2649 | Neurogenesis, Differentiation |
| **Glucagon signaling pathway: GYS1** | UP | 2,1999 | 0,0285 | 0,2649 | Glycogen biosynthesis |
| **Adherens junction: CTNND1** | DOWN | -2,1802 | 0,0300 | 0,2649 | Wnt signaling pathway, Cell adhesion, Transcription regulation, Transcription |
| **Jak-STAT signaling pathway: BCL2** | UP | 2,1802 | 0,0300 | 0,2649 | Apoptosis |
| **Natural killer cell mediated cytotoxicity: KLRC4-KLRK1** | UP | 2,1802 | 0,0300 | 0,2649 | Adaptive immunity, Innate immunity, Differentiation, Immunity |
| **GABAergic synapse: CACNA1A*** | DOWN | -2,1802 | 0,0300 | 0,2649 | Ion channel, Ion transport, Calcium channel, Calcium transport, Voltage-gated channel, Transport, Vision, Sensory transduction |
| **Regulation of actin cytoskeleton: ARPC5 ACTB** | UP | 2,1802 | 0,0300 | 0,2649 |  |
| **Regulation of actin cytoskeleton: ARPC5 ACTB*** | UP | 2,1802 | 0,0300 | 0,2649 |  |
| **Insulin secretion: PRKCA** | DOWN | -2,1802 | 0,0300 | 0,2649 | Angiogenesis, Apoptosis, Cell adhesion, Adaptive immunity, Immunity, Transcription regulation, Transcription, Biological rhythms |
| **Ras signaling pathway: PIK3R5*** | UP | 2,1606 | 0,0315 | 0,2649 | Angiogenesis, Endocytosis, Autophagy, Cell adhesion, Chemotaxis, Adaptive immunity, Inflammatory response, Innate immunity, Differentiation, Immunity, Stress response, Host-virus interaction, Protein transport, Transport |
| **Rap1 signaling pathway: THBS1** | UP | 2,1606 | 0,0315 | 0,2649 | Cell adhesion, Unfolded protein response |
| **Tight junction: TJP1 YBX3 CDK4** | UP | 2,1606 | 0,0315 | 0,2649 | Transcription regulation, Transcription, Cell division, Cell cycle |
| **Jak-STAT signaling pathway: CCND1** | UP | 2,1606 | 0,0315 | 0,2649 | Cell cycle, Cell division, DNA damage, Transcription regulation, Transcription |
| **T cell receptor signaling pathway: CD3E** | UP | 2,1606 | 0,0315 | 0,2649 |  |
| **B cell receptor signaling pathway: RAC1** | UP | 2,1606 | 0,0315 | 0,2649 | Transcription regulation, Transcription |

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| **Adipocytokine signaling pathway: AGRP** | UP | 2,1606 | 0,0315 | 0,2649 | |
| **Adipocytokine signaling pathway: POMC** | DOWN | -2,1606 | 0,0315 | 0,2649 | |
| **NF-kappa B signaling pathway: CXCL12** | UP | 2,1410 | 0,0331 | 0,2673 | Chemotaxis |
| **PI3K-Akt signaling pathway: BCL2L1** | UP | 2,1410 | 0,0331 | 0,2673 | Apoptosis, Endocytosis |
| **Toll-like receptor signaling pathway: CASP8** | UP | 2,1410 | 0,0331 | 0,2673 | Host-virus interaction, Apoptosis |
| **Natural killer cell mediated cytotoxicity: TNFRSF10D** | UP | 2,1410 | 0,0331 | 0,2673 | Apoptosis |
| **NF-kappa B signaling pathway: TNFSF13B*** | UP | 2,1213 | 0,0347 | 0,2679 | Immunity |
| **HIF-1 signaling pathway: EDN1** | UP | 2,1213 | 0,0347 | 0,2679 | |
| **Apoptosis: TNFRSF10D*** | UP | 2,1213 | 0,0347 | 0,2679 | Apoptosis |
| **Wnt signaling pathway: JUN** | UP | 2,1213 | 0,0347 | 0,2679 | Transcription regulation, Transcription |
| **TNF signaling pathway: BAG4** | UP | 2,1213 | 0,0347 | 0,2679 | |
| **NF-kappa B signaling pathway: CCL13** | UP | 2,1017 | 0,0365 | 0,2679 | Inflammatory response, Chemotaxis |
| **Adipocytokine signaling pathway: PTPN11** | DOWN | -2,1017 | 0,0365 | 0,2679 | |
| **MAPK signaling pathway: JUND** | DOWN | -2,0820 | 0,0382 | 0,2715 | Transcription regulation, Transcription |
| **ErbB signaling pathway: MYC** | UP | 2,0820 | 0,0382 | 0,2715 | Transcription regulation, Transcription |
| **Ras signaling pathway: NFKB1** | UP | 2,0820 | 0,0382 | 0,2715 | Apoptosis, Transcription regulation, Transcription, Host-virus interaction |
| **Sphingolipid signaling pathway: RAC1** | UP | 2,0820 | 0,0382 | 0,2715 | Transcription regulation, Transcription |
| **Complement and coagulation cascades: F2RL2** | UP | 2,0820 | 0,0382 | 0,2715 | Blood coagulation, Hemostasis |
| **Endocrine and other factor-regulated calcium reabsorption: TRPV5*** | UP | 2,0820 | 0,0382 | 0,2715 | Calcium transport, Ion transport, Calcium channel, Transport, Ion channel |
| **cAMP signaling pathway: CACNA1C** | DOWN | -2,0624 | 0,0401 | 0,2746 | Ion transport, Ion channel, Calcium transport, Calcium channel, Voltage-gated channel, Transport, Vision, Sensory transduction |
| **Melanogenesis: TYRP1** | UP | 2,0624 | 0,0401 | 0,2746 | Melanin biosynthesis |
| **Sphingolipid signaling pathway: SMPD1** | DOWN | -2,0428 | 0,0421 | 0,2746 | |
| **Axon guidance: GSK3B** | DOWN | -2,0428 | 0,0421 | 0,2746 | Neurogenesis, Differentiation, Glycogen metabolism, Biological rhythms, Carbohydrate metabolism, Wnt signaling pathway |

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| **Tight junction: OCLN OCLN** | UP | 2,0428 | 0,0421 | 0,2746 | |
| **Signaling pathways regulating pluripotency of stem cells: AKT3*** | UP | 2,0428 | 0,0421 | 0,2746 | Glycogen biosynthesis, Glycogen metabolism, Glucose metabolism, Sugar transport, Carbohydrate metabolism, Apoptosis, Translation regulation, Neurogenesis, Transport |
| **Circadian entrainment: PRKCA** | DOWN | -2,0428 | 0,0421 | 0,2746 | Angiogenesis, Apoptosis, Cell adhesion, Adaptive immunity, Transcription regulation, Transcription, Immunity, Biological rhythms |
| **Insulin signaling pathway: G6PC** | DOWN | -2,0428 | 0,0421 | 0,2746 | Gluconeogenesis |
| **Melanogenesis: CAMK2A** | UP | 2,0428 | 0,0421 | 0,2746 | Neurogenesis, Differentiation |
| **Thyroid hormone signaling pathway: MYC** | UP | 2,0428 | 0,0421 | 0,2746 | Transcription regulation, Transcription |
| **PPAR signaling pathway: EHHADH** | DOWN | -2,0231 | 0,0441 | 0,2746 | Fatty acid metabolism, Lipid metabolism |
| **HIF-1 signaling pathway: PDHA1** | UP | 2,0231 | 0,0441 | 0,2746 | Glucose metabolism, Tricarboxylic acid cycle, Carbohydrate metabolism |
| **Apoptosis: PMAIP1** | UP | 2,0231 | 0,0441 | 0,2746 | Apoptosis |
| **Leukocyte transendothelial migration: RAC2** | UP | 2,0231 | 0,0441 | 0,2746 | |
| **Aldosterone synthesis and secretion: KCNK3** | UP | 2,0231 | 0,0441 | 0,2746 | Ion channel, Ion transport, Potassium channel, Potassium transport, Voltage-gated channel, Transport |
| **Adherens junction: CDH1*** | UP | 2,0035 | 0,0462 | 0,2746 | Cell adhesion, Cell division, Cell cycle, Mitosis, DNA repair, DNA damage, Ubl conjugation pathway |
| **PPAR signaling pathway: ME1** | DOWN | -2,0035 | 0,0462 | 0,2746 | |
| **MAPK signaling pathway: STMN1** | DOWN | -2,0035 | 0,0462 | 0,2746 | Neurogenesis, Differentiation |
| **Rap1 signaling pathway: RAC1** | DOWN | -2,0035 | 0,0462 | 0,2746 | Transcription regulation, Transcription |
| **FoxO signaling pathway: IL7R** | UP | 2,0035 | 0,0462 | 0,2746 | |
| **Hedgehog signaling pathway: SMO** | UP | 2,0035 | 0,0462 | 0,2746 | |
| **Cytosolic DNA-sensing pathway: NFKB1** | UP | 2,0035 | 0,0462 | 0,2746 | Apoptosis, Transcription regulation, Transcription, Host-virus interaction |
| **TNF signaling pathway: MAPK14*** | UP | 2,0035 | 0,0462 | 0,2746 | Transcription regulation, Transcription, Stress response, Apoptosis, Cell cycle |
| **Serotonergic synapse: CACNA1C** | DOWN | -2,0035 | 0,0462 | 0,2746 | Ion channel, Calcium channel, Ion transport, Calcium |

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| | | | | | transport, Voltage-gated channel, Transport, Vision, Sensory transduction |
| **Oxytocin signaling pathway: C00219** | UP | 2,0035 | 0,0462 | 0,2746 | |
| **HIF-1 signaling pathway: TFRC** | UP | 1,9838 | 0,0484 | 0,2823 | Endocytosis, Host-virus interaction |
| **p53 signaling pathway: PMAIP1** | UP | 1,9838 | 0,0484 | 0,2823 | Apoptosis |
| **Signaling pathways regulating pluripotency of stem cells: MAPK1*** | UP | 1,9838 | 0,0484 | 0,2823 | Transcription regulation, Transcription, Apoptosis, Cell cycle, Host-virus interaction |

**Additional Figure 1. Correlation between LoF simulation effects on the circuits and the population frequency of LoF mutations**. LoF mutations were simulated in all the genes of circuits (from left to right) Rap1 signaling pathway:PRKCI-PARD6A-PARD3, Chemokynes pathway:PARD3-PRKCZ-TIAM1 and TNF signaling pathway:CREB3 and the -log(p-value) of the differential activity caused in the corresponding circuit is plotted against the population frequency at which this gene appear in the healthy population (1000 genomes) with a LoF mutation.