Statistically Relevant Pathways obtained using S2B and SAPDSB in Diabetes- Carcinoma

In order to quantify the significance of pathways associated with the unique genes, the common genes from top 500 ranked candidates belonging to final rank list of SAPDSB and S2B are excluded. As a result, 97 common genes are identified and are removed from top 500 ranked gene list produced by both SAPDSB and S2B. By querying GO using those 403 genes, 12 and 18 statistically relevant pathways are obtained in S2B and SAPDSB respectively and is listed in Table 1. Comparing the pathways obtained in SAPDSB and S2B, the unique pathways in both cases are identified. Thus, a total number of unique pathways obtained for SAPDSB and S2B are 10 and 4 respectively. These unique pathways highlighted in the Table 1 are further investigated via clinical literature analysis for confirming their significance and role in ALS-SMA.

|  |  |  |  |
| --- | --- | --- | --- |
| Table 1. PANTHER pathways obtained using top 403 unique genes of SAPDSB and S2B | | | |
| SAPDSB | **PANTHER Pathways** | **Raw P-value** | **FDR** |
| [**Axon guidance mediated by Slit/Robo**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00008');) | **2.11E-03** | **1.96E-02** |
| [**Angiogenesis**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00005');) | **2.44E-16** | **2.04E-14** |
| [Apoptosis signaling pathway](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00006');) | 8.50E-10 | 4.73E-08 |
| [**Toll receptor signaling pathway**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00054');) | **2.33E-04** | **3.24E-03** |
| [**VEGF signaling pathway**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00056');) | **9.85E-05** | **2.06E-03** |
| [**T cell activation**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00053');) | **1.48E-05** | **3.53E-04** |
| [Ras Pathway](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P04393');) | 1.55E-04 | 2.87E-03 |
| [CCKR signaling map](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P06959');) | 1.38E-07 | 5.78E-06 |
| [Ubiquitin proteasome pathway](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00060');) | 1.73E-03 | 1.70E-02 |
| [FGF signaling pathway](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00021');) | 1.09E-05 | 3.04E-04 |
| [Parkinson disease](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00049');) | 1.95E-04 | 2.96E-03 |
| [**p53 pathway**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00059');) | **5.34E-04** | **6.37E-03** |
| [**Cytoskeletal regulation by Rho GTPase**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00016');) | **1.56E-03** | **1.63E-02** |
| [EGF receptor signaling pathway](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00018');) | 1.64E-04 | 2.74E-03 |
| [**Inflammation mediated by chemokine and cytokine signaling pathway**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00031');) | **1.45E-06** | **4.86E-05** |
| [Huntington disease](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00029');) | 2.44E-04 | 3.13E-03 |
| [**PDGF signaling pathway**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00047');) | **3.09E-03** | **2.72E-02** |
| [**Wnt signaling pathway**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00057');) | **7.06E-04** | **7.86E-03** |
| [Apoptosis signaling pathway](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00006');) | 8.50E-10 | 4.73E-08 |
| S2B | [**FAS signaling pathway**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00020');) | **9.34E-07** | **3.12E-05** |
| [**Interferon-gamma signaling pathway**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00035');) | **4.54E-04** | **6.88E-03** |
| [Ubiquitin proteasome pathway](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00060');) | 6.01E-06 | 1.67E-04 |
| [Apoptosis signaling pathway](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00006');) | 4.43E-09 | 3.70E-07 |
| [Parkinson disease](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00049');) | 1.43E-07 | 5.95E-06 |
| [CCKR signaling map](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P06959');) | 1.96E-08 | 1.09E-06 |
| [**Interleukin signaling pathway**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00036');) | **3.79E-04** | **6.33E-03** |
| [Huntington disease](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00029');) | 1.09E-05 | 2.60E-04 |
| [Ras Pathway](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P04393');) | 3.61E-03 | 4.64E-02 |
| [EGF receptor signaling pathway](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00018');) | 1.38E-04 | 2.57E-03 |
| [FGF signaling pathway](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00021');) | 3.25E-03 | 4.52E-02 |
| [**Gonadotropin-releasing hormone receptor pathway**](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P06664');) | **6.52E-05** | **1.36E-03** |

For corroborating the results, a clinical literature review showing the evidences of comorbidities are collected. As per the evidences obtained, 6 out of 10 in SAPDSB pathways are leading to both diseases and comorbidities. A brief description of the evidences is included based on the six pathways obtained in SAPDSB.

* [Axon guidance mediated by Slit/Robo](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00008');): The role of [Axon guidance mediated by Slit/Robo](javascript:openDiagramWindow('/pathway/pathwayDiagram.jsp?color=1&catsInfo=true&catAccession=P00008');) is critical in different neurodevelopmental diseases including dyslexia and autism etc. *(Y Gonda et al.,2020)*
* Toll receptor signaling pathway: The involvement of Toll receptor signaling pathway is indicated in the pathogenesis of Cerebral vascular diseases, inflammatory diseases etc. *(Ahmadabad et al.,2020; Lin et al.,2011)*.
* VEGF signaling pathway: VEGF signaling pathways play significant roles in Carcinoma (Apte et al.,2019), neurological disorders *(Shim et al.,2018),* retinal neovascularization *(Apte et al.,2019)* etc.
* T cell activation: T cell activation pathway has important roles in autoimmune diseases as it affects the autoimmune response *(Tai et al.,2018)*.
* p53 pathway: The role of p53 pathway in diseases such as neuro degenerative diseases, human cancers *(Royds et al.,2009)*, neurological disorders etc. *(Chang et al.,2012)*.
* Cytoskeletal regulation by Rho GTPase: This pathway is involved with disease like apoptosis *(Coleman et al., 2002),* cancer *(Clayton & Ridley et al.,2020)* etc.
* Inflammation mediated by chemokine and cytokine signaling pathway: Dysregulation of cytokines and chemokines leads to neuronal inflammation, degeneration, and demyelination neuropathic pain etc. *(G Ramesh et al.,2013)*.
* PDGF signaling pathway: Clinical interventions controlling PDGF signaling pathway is used in different diseases like systemic sclerosis *(Trojanowska,2008)* vascular diseases *(Folestad et al.,2018)*, tumor treatment *(Heldin, 2013)* etc.
* Wnt signaling pathway: Mutations in modulators of this pathway leads to the pathogenesis of diseases like Alzheimer’s *(Ng et al.,2019)*, ageing *(Palomer et al.,2019)* etc.

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