**Gene expression meta-analysis of Parkinson’s disease and its relationship with Alzheimer’s disease**

Additional file 1

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S1: Information about each study used in our meta-analysis** | | | | | | | |
| **GEO Accession number** | **Platform name** | **Platform ID** |  | **Male** | **Female** | **All** | **Age range (average)** |
| GSE7621 | Affymetrix Human Genome U133 Plus 2.0 Array | GPL570 | PD | 13 | 3 | 16 | N/A |
| Control | 4 | 5 | 9 | N/A |
| GSE20141 | Affymetrix Human Genome U133 Plus 2.0 Array | GPL570 | PD | N/A | N/A | 9 | N/A |
| Control | N/A | N/A | 6 | N/A |
| GSE8397 | Affymetrix Human Genome U133A Array | GPL96 | PD | 9 | 6 | 15 | 68-89 (80) |
| Control | 5 | 1 | 6 | 46-81 (68.2) |
| GSE20292 | Affymetrix Human Genome U133A Array | GPL96 | PD | 6 | 5 | 11 | 67-84 (75.5) |
| Control | 13 | 5 | 18 | 41-94 (66.8) |
| GSE20163 | Affymetrix Human Genome U133A Array | GPL96 | PD | N/A | N/A | 8 | N/A |
| Control | N/A | N/A | 9 | N/A |
| GSE20164 | Affymetrix Human Genome U133A Array | GPL96 | PD | N/A | N/A | 6 | N/A |
| Control | N/A | N/A | 3 | N/A |
| GSE20333 | Affymetrix Human HG-Focus Target Array | GPL201 | PD | 1 | 3 | 4 | 70-87 (77.3) |
| Control | 5 | 1 | 6 | 68-88 (79) |

Table S1. Information about each study used in our meta-analysis after removal of outlier samples.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table S2: DEGs that have been previously identified as PD risk genes by GWAS** | | | | |
| **Gene name** | **Entrez ID** | **Average FC** | **metaZscore** | **FDR corrected Pval** |
| SNCA | 6622 | 0.57 | -6.00 | 1.03E-05 |
| ANK2 | 287 | 0.61 | -4.21 | 2.33E-03 |
| ALAS1 | 211 | 0.76 | -3.52 | 1.12E-02 |
| SH3GL2 | 6456 | 0.64 | -3.46 | 1.31E-02 |
| DLG2 | 1740 | 0.79 | -3.34 | 1.68E-02 |
| SCN3A | 6328 | 0.56 | -3.30 | 1.79E-02 |
| MAPT | 4137 | 1.23 | 3.15 | 2.45E-02 |
| ATP6V0A1 | 535 | 0.85 | -3.03 | 3.15E-02 |
| VPS13C | 54832 | 1.17 | 2.85 | 4.61E-02 |

Table S2: Differentially expressed genes identified in our meta-analysis that have been identified as PD risk genes in a recent GWAS meta-analysis [33].

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| *Table S3* | | | | | | | |
| *Ingenuity Canonical Pathways* | *DEGs* | *Genes in Pathway* | *Ratio* | *adjPval* | *AD DEGs* | *AD Ratio* | *AD adjPval* |
| Breast Cancer Regulation by Stathmin1 | 33 | 204 | 0.162 | 2.40E-06 | 47 | 0.23 | 8.51E-03 |
| Sirtuin Signaling Pathway | 40 | 284 | 0.141 | 2.40E-06 | 70 | 0.247 | 3.39E-04 |
| 14-3-3-mediated Signaling | 24 | 130 | 0.185 | 9.55E-06 | 34 | 0.262 | 5.13E-03 |
| Phagosome Maturation | 23 | 138 | 0.167 | 9.12E-05 | 34 | 0.246 | 1.15E-02 |
| Remodeling of Epithelial Adherens Junctions | 15 | 67 | 0.227 | 1.12E-04 |  |  |  |
| Mitochondrial Dysfunction | 24 | 166 | 0.145 | 4.27E-04 | 41 | 0.248 | 4.79E-03 |
| Oxidative Phosphorylation | 18 | 105 | 0.173 | 4.68E-04 |  |  |  |
| CDK5 Signaling | 17 | 99 | 0.173 | 7.24E-04 | 27 | 0.276 | 7.08E-03 |
| Huntington's Disease Signaling | 30 | 248 | 0.121 | 7.59E-04 |  |  |  |
| B Cell Receptor Signaling | 25 | 188 | 0.133 | 7.59E-04 | 50 | 0.266 | 6.92E-04 |
| Epithelial Adherens Junction Signaling | 21 | 143 | 0.147 | 7.59E-04 |  |  |  |
| Gap Junction Signaling | 24 | 191 | 0.126 | 2.51E-03 |  |  |  |
| Germ Cell-Sertoli Cell Junction Signaling | 22 | 170 | 0.130 | 2.69E-03 | 41 | 0.243 | 7.08E-03 |
| Axonal Guidance Signaling | 43 | 447 | 0.096 | 2.95E-03 | 94 | 0.211 | 2.09E-03 |
| Sertoli Cell-Sertoli Cell Junction Signaling | 22 | 174 | 0.127 | 3.31E-03 | 38 | 0.22 | 3.72E-02 |
| Rac Signaling | 17 | 116 | 0.147 | 3.31E-03 | 29 | 0.25 | 1.70E-02 |
| Synaptic Long Term Potentiation | 17 | 119 | 0.143 | 4.17E-03 | 29 | 0.244 | 2.34E-02 |
| AMPK Signaling | 25 | 216 | 0.116 | 4.17E-03 |  |  |  |
| Glycolysis I | 7 | 24 | 0.292 | 4.27E-03 |  |  |  |
| PI3K/AKT Signaling | 17 | 124 | 0.138 | 5.50E-03 | 34 | 0.276 | 2.09E-03 |
| ERK/MAPK Signaling | 23 | 199 | 0.116 | 7.08E-03 | 51 | 0.256 | 9.55E-04 |
| Iron homeostasis signaling pathway | 17 | 127 | 0.134 | 7.41E-03 |  |  |  |
| Clathrin-mediated Endocytosis Signaling | 23 | 206 | 0.112 | 1.05E-02 |  |  |  |
| Gαi Signaling | 16 | 121 | 0.133 | 1.05E-02 |  |  |  |
| Signaling by Rho Family GTPases | 26 | 250 | 0.104 | 1.38E-02 | 61 | 0.243 | 9.55E-04 |
| Neuropathic Pain Signaling In Dorsal Horn Neurons | 15 | 114 | 0.132 | 1.62E-02 |  |  |  |
| G Protein Signaling Mediated by Tubby | 7 | 31 | 0.226 | 1.62E-02 |  |  |  |
| Role of NFAT in Cardiac Hypertrophy | 23 | 217 | 0.106 | 1.62E-02 | 47 | 0.218 | 2.19E-02 |
| Reelin Signaling in Neurons | 13 | 93 | 0.141 | 1.62E-02 |  |  |  |
| Amyloid Processing | 9 | 50 | 0.180 | 1.62E-02 |  |  |  |
| Cardiac β-adrenergic Signaling | 17 | 141 | 0.121 | 1.62E-02 |  |  |  |
| TCA Cycle II (Eukaryotic) | 6 | 24 | 0.250 | 1.82E-02 |  |  |  |
| p70S6K Signaling | 16 | 132 | 0.122 | 1.95E-02 |  |  |  |
| PTEN Signaling | 15 | 120 | 0.126 | 1.95E-02 | 31 | 0.261 | 7.94E-03 |
| Sumoylation Pathway | 13 | 97 | 0.135 | 2.00E-02 | 30 | 0.312 | 9.33E-04 |
| Protein Ubiquitination Pathway | 26 | 264 | 0.099 | 2.00E-02 |  |  |  |
| Gluconeogenesis I | 6 | 25 | 0.240 | 2.00E-02 |  |  |  |
| STAT3 Pathway | 13 | 98 | 0.134 | 2.04E-02 | 20 | 0.27 | 2.63E-02 |
| HIPPO signaling | 12 | 86 | 0.140 | 2.09E-02 | 32 | 0.372 | 4.17E-05 |
| fMLP Signaling in Neutrophils | 15 | 122 | 0.123 | 2.14E-02 | 33 | 0.27 | 3.47E-03 |
| Dopamine-DARPP32 Feedback in cAMP Signaling | 18 | 161 | 0.112 | 2.14E-02 |  |  |  |
| D-myo-inositol (1,4,5)-trisphosphate Degradation | 5 | 18 | 0.278 | 2.14E-02 |  |  |  |
| Dopamine Receptor Signaling | 11 | 76 | 0.145 | 2.14E-02 |  |  |  |
| GNRH Signaling | 18 | 163 | 0.111 | 2.29E-02 | 38 | 0.235 | 1.45E-02 |
| Insulin Receptor Signaling | 16 | 137 | 0.117 | 2.34E-02 |  |  |  |
| Cardiac Hypertrophy Signaling | 23 | 233 | 0.099 | 2.63E-02 | 51 | 0.219 | 1.45E-02 |
| Cyclins and Cell Cycle Regulation | 11 | 80 | 0.138 | 3.02E-02 | 20 | 0.253 | 4.79E-02 |
| IGF-1 Signaling | 13 | 106 | 0.123 | 3.55E-02 |  |  |  |
| Protein Kinase A Signaling | 33 | 386 | 0.086 | 3.72E-02 | 82 | 0.214 | 3.24E-03 |
| Gαq Signaling | 17 | 159 | 0.107 | 3.89E-02 | 42 | 0.264 | 1.58E-03 |
| Aspartate Degradation II | 3 | 7 | 0.429 | 3.98E-02 | 5 | 0.714 | 9.55E-03 |
| Renin-Angiotensin Signaling | 14 | 121 | 0.116 | 3.98E-02 |  |  |  |
| ATM Signaling | 12 | 97 | 0.124 | 4.27E-02 |  |  |  |
| BMP signaling pathway | 10 | 75 | 0.135 | 4.47E-02 |  |  |  |

Table S3: IPA canonical pathway analysis for significant pathways identified using all PD DEGs, included with the information for pathways shared with those identified as significant using all AD DEGs.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *Table S4:* *IPA canonical pathway analysis for significant pathways identified using down-regulated PD DEGs.* | | | | |
| Ingenuity Canonical Pathways | DEGs | Genes in Pathway | Ratio | Adj. Pval |
| Breast Cancer Regulation by Stathmin1 | 32 | 204 | 0.157 | 1.86E-09 |
| Phagosome Maturation | 23 | 138 | 0.167 | 2.19E-07 |
| Sirtuin Signaling Pathway | 34 | 284 | 0.120 | 2.19E-07 |
| Mitochondrial Dysfunction | 24 | 166 | 0.145 | 9.55E-07 |
| 14-3-3-mediated Signaling | 21 | 130 | 0.162 | 9.55E-07 |
| Remodeling of Epithelial Adherens Junctions | 15 | 67 | 0.227 | 9.55E-07 |
| Oxidative Phosphorylation | 18 | 105 | 0.173 | 2.82E-06 |
| Axonal Guidance Signaling | 39 | 447 | 0.087 | 3.39E-05 |
| Gap Junction Signaling | 22 | 192 | 0.115 | 1.17E-04 |
| CDK5 Signaling | 15 | 99 | 0.153 | 1.32E-04 |
| Huntington's Disease Signaling | 25 | 248 | 0.101 | 2.14E-04 |
| Sertoli Cell-Sertoli Cell Junction Signaling | 20 | 173 | 0.116 | 2.34E-04 |
| Germ Cell-Sertoli Cell Junction Signaling | 19 | 170 | 0.112 | 5.13E-04 |
| Cardiac β-adrenergic Signaling | 17 | 141 | 0.121 | 5.13E-04 |
| Glycolysis I | 7 | 24 | 0.292 | 5.37E-04 |
| Epithelial Adherens Junction Signaling | 17 | 143 | 0.119 | 6.03E-04 |
| Synaptic Long Term Potentiation | 15 | 120 | 0.126 | 8.51E-04 |
| PI3K/AKT Signaling | 15 | 123 | 0.122 | 1.17E-03 |
| Iron homeostasis signaling pathway | 15 | 128 | 0.118 | 1.62E-03 |
| Neuropathic Pain Signaling In Dorsal Horn Neurons | 14 | 114 | 0.123 | 1.74E-03 |
| Dopamine-DARPP32 Feedback in cAMP Signaling | 17 | 161 | 0.106 | 1.91E-03 |
| Rac Signaling | 14 | 116 | 0.121 | 1.95E-03 |
| Dopamine Receptor Signaling | 11 | 76 | 0.145 | 1.99E-03 |
| Role of NFAT in Cardiac Hypertrophy | 20 | 216 | 0.093 | 2.88E-03 |
| Signaling by Rho Family GTPases | 22 | 252 | 0.088 | 2.95E-03 |
| TCA Cycle II (Eukaryotic) | 6 | 24 | 0.250 | 3.24E-03 |
| Protein Kinase A Signaling | 29 | 386 | 0.075 | 3.80E-03 |
| Gluconeogenesis I | 6 | 25 | 0.240 | 3.80E-03 |
| HIPPO signaling | 11 | 86 | 0.128 | 4.79E-03 |
| GNRH Signaling | 16 | 162 | 0.099 | 5.01E-03 |
| p70S6K Signaling | 14 | 131 | 0.107 | 5.01E-03 |
| AMPK Signaling | 19 | 215 | 0.088 | 5.62E-03 |
| ERK/MAPK Signaling | 18 | 199 | 0.091 | 5.89E-03 |
| Amyloid Processing | 8 | 50 | 0.160 | 5.89E-03 |
| Gαi Signaling | 13 | 121 | 0.108 | 6.17E-03 |
| Opioid Signaling Pathway | 20 | 237 | 0.084 | 6.46E-03 |
| fMLP Signaling in Neutrophils | 13 | 122 | 0.107 | 6.92E-03 |
| Clathrin-mediated Endocytosis Signaling | 18 | 206 | 0.087 | 7.59E-03 |
| CREB Signaling in Neurons | 18 | 211 | 0.086 | 8.91E-03 |
| Gαq Signaling | 15 | 160 | 0.094 | 8.91E-03 |
| Protein Ubiquitination Pathway | 21 | 265 | 0.080 | 8.91E-03 |
| RhoGDI Signaling | 16 | 177 | 0.091 | 8.91E-03 |
| Melatonin Signaling | 9 | 70 | 0.129 | 1.10E-02 |
| Calcium Signaling | 17 | 198 | 0.086 | 1.12E-02 |
| α-Adrenergic Signaling | 10 | 85 | 0.118 | 1.12E-02 |
| Synaptic Long Term Depression | 15 | 168 | 0.089 | 1.38E-02 |
| Actin Cytoskeleton Signaling | 18 | 222 | 0.081 | 1.38E-02 |
| BMP signaling pathway | 9 | 74 | 0.122 | 1.41E-02 |
| Aspartate Degradation II | 3 | 7 | 0.429 | 1.41E-02 |
| B Cell Receptor Signaling | 16 | 189 | 0.085 | 1.48E-02 |
| Insulin Receptor Signaling | 13 | 137 | 0.095 | 1.48E-02 |
| Regulation of eIF4 and p70S6K Signaling | 14 | 155 | 0.091 | 1.48E-02 |
| IGF-1 Signaling | 11 | 106 | 0.104 | 1.55E-02 |
| Reelin Signaling in Neurons | 10 | 92 | 0.109 | 1.70E-02 |
| Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes | 10 | 93 | 0.108 | 1.82E-02 |
| Parkinson's Signaling | 4 | 16 | 0.250 | 1.86E-02 |
| Pyridoxal 5'-phosphate Salvage Pathway | 8 | 64 | 0.125 | 1.86E-02 |
| CCR3 Signaling in Eosinophils | 12 | 127 | 0.095 | 1.86E-02 |
| Cardiac Hypertrophy Signaling | 18 | 232 | 0.078 | 1.86E-02 |
| Phototransduction Pathway | 7 | 52 | 0.137 | 1.91E-02 |
| Salvage Pathways of Pyrimidine Ribonucleotides | 10 | 96 | 0.105 | 1.91E-02 |
| D-myo-inositol (1,4,5)-Trisphosphate Biosynthesis | 5 | 28 | 0.185 | 2.00E-02 |
| Cdc42 Signaling | 12 | 130 | 0.093 | 2.08E-02 |
| Tight Junction Signaling | 14 | 167 | 0.084 | 2.40E-02 |
| Chemokine Signaling | 8 | 68 | 0.118 | 2.40E-02 |
| Aldosterone Signaling in Epithelial Cells | 14 | 168 | 0.084 | 2.45E-02 |
| D-myo-inositol (1,4,5)-trisphosphate Degradation | 4 | 19 | 0.222 | 2.45E-02 |
| P2Y Purigenic Receptor Signaling Pathway | 12 | 134 | 0.090 | 2.45E-02 |
| PAK Signaling | 10 | 100 | 0.100 | 2.45E-02 |
| Role of CHK Proteins in Cell Cycle Checkpoint Control | 7 | 57 | 0.123 | 3.09E-02 |
| G Protein Signaling Mediated by Tubby | 5 | 32 | 0.161 | 3.16E-02 |
| Renin-Angiotensin Signaling | 11 | 122 | 0.091 | 3.16E-02 |
| Inhibition of Angiogenesis by TSP1 | 5 | 33 | 0.156 | 3.63E-02 |
| Xenobiotic Metabolism Signaling | 19 | 273 | 0.070 | 3.80E-02 |
| G-Protein Coupled Receptor Signaling | 19 | 275 | 0.069 | 3.98E-02 |
| GDNF Family Ligand-Receptor Interactions | 8 | 77 | 0.105 | 3.98E-02 |
| IL-1 Signaling | 9 | 93 | 0.098 | 3.98E-02 |
| Ceramide Signaling | 9 | 93 | 0.097 | 4.17E-02 |
| Arsenate Detoxification I (Glutaredoxin) | 2 | 4 | 0.500 | 4.37E-02 |
| CXCR4 Signaling | 13 | 164 | 0.079 | 4.37E-02 |
| Mevalonate Pathway I | 3 | 12 | 0.250 | 4.68E-02 |

Table S4: IPA canonical pathway analysis for significant pathways identified using down-regulated PD DEGs.

|  |  |  |  |
| --- | --- | --- | --- |
| *Table S5: IPA upstream regulator analysis for up and down regulated PD DEGs analysed separately.* | | | |
| Upstream Regulator | Molecule type | p-value | Number of target molecules |
| **Upstream regulators for Down-regulated DEGs** | | | |
| Lh | complex | 1.21E-08 | 27 |
| FSH | complex | 7.25E-07 | 28 |
| HSP90B1 | other | 8.38E-05 | 7 |
| CUL4B | other | 2.03E-04 | 5 |
| SBDS | other | 2.67E-04 | 11 |
| REST | transcription regulator | 2.91E-04 | 6 |
| SUZ12 | enzyme | 4.01E-04 | 11 |
| LONP1 | peptidase | 6.46E-04 | 9 |
| MMP12 | peptidase | 1.51E-03 | 7 |
| INHBA | growth factor | 3.64E-03 | 10 |
| NMNAT1 | enzyme | 4.84E-03 | 3 |
| PRKAR1A | kinase | 4.84E-03 | 3 |
| RBM5 | other | 5.10E-03 | 6 |
| IL15 | cytokine | 5.16E-03 | 10 |
| HNRNPA2B1 | other | 5.42E-03 | 12 |
| CCND1 | transcription regulator | 5.87E-03 | 16 |
| TP53 | transcription regulator | 7.91E-03 | 37 |
| **Upstream regulators for Up-regulated DEGs** | | | |
| HSF1 | transcription regulator | 1.57E-04 | 8 |
| TGFBR2 | kinase | 5.16E-04 | 6 |
| miR-346 (and other miRNAs w/seed GUCUGCC) | mature microrna | 6.73E-04 | 2 |
| TP73 | transcription regulator | 8.09E-04 | 9 |
| SP4 | transcription regulator | 1.09E-03 | 3 |
| MTOR | kinase | 1.20E-03 | 5 |
| NPAT | transcription regulator | 1.33E-03 | 2 |
| AREG | growth factor | 2.60E-03 | 5 |
| COL18A1 | other | 3.18E-03 | 5 |
| ZBTB10 | other | 3.27E-03 | 2 |
| MYC | transcription regulator | 4.07E-03 | 10 |
| miR-22-3p (miRNAs w/seed AGCUGCC) | mature microrna | 4.23E-03 | 3 |
| CD24 | other | 4.50E-03 | 6 |
| ZNF652 | other | 4.53E-03 | 2 |
| CCND1 | transcription regulator | 5.50E-03 | 9 |
| GATA6 | transcription regulator | 5.86E-03 | 4 |
| Cdk | group | 6.11E-03 | 3 |
| SAFB | other | 7.26E-03 | 4 |
| mir-122 | microrna | 8.41E-03 | 5 |
| miR-155-5p (miRNAs w/seed UAAUGCU) | mature microrna | 8.42E-03 | 3 |
| E2F1 | transcription regulator | 8.87E-03 | 8 |
| KITLG | growth factor | 9.28E-03 | 3 |
| CASP8 | peptidase | 9.42E-03 | 2 |
| DDIT3 | transcription regulator | 9.42E-03 | 2 |
| CBL | transcription regulator | 9.42E-03 | 2 |

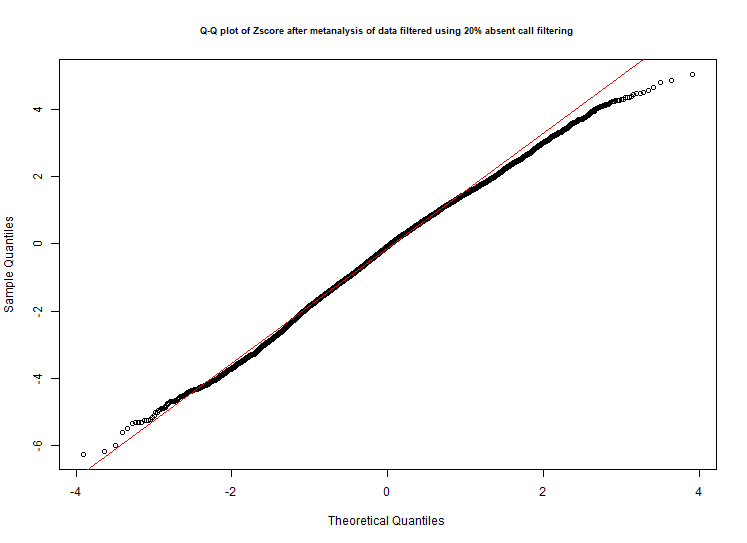
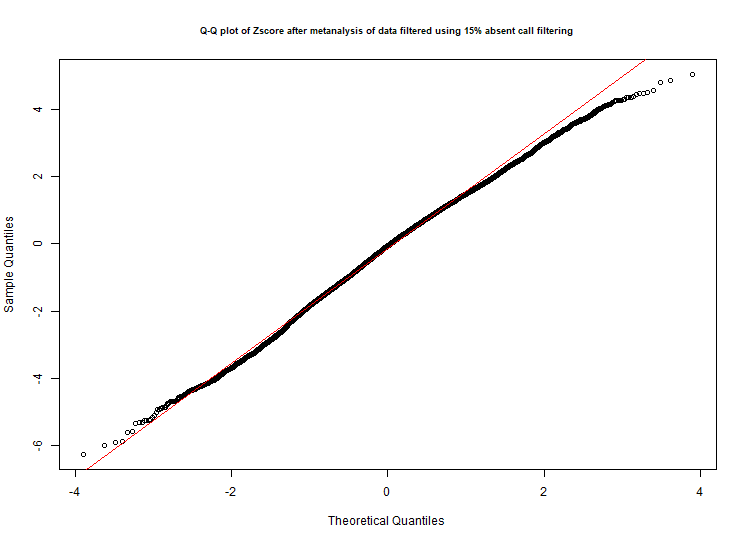
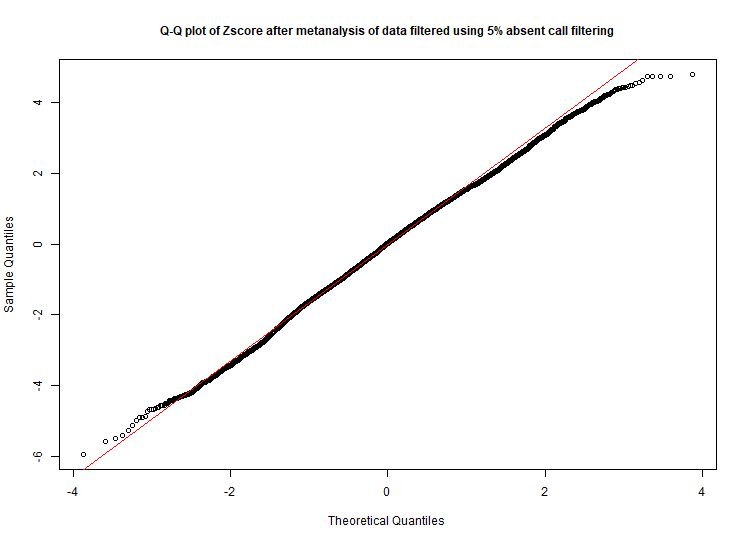
Table S5: IPA upstream regulator analysis for up and down regulated PD DEGs analyzed separately.

|  |  |
| --- | --- |
| **Table S6:** **Top 10 hubs found in the PPIN subnetwork created using the top 30 PD DEGs** | |
| **Gene name** | **Number of First neighbour nodes** |
| YWHAZ | 122 |
| YWHAB | 62 |
| YWHAG | 62 |
| YWHAE | 42 |
| YWHAQ | 39 |
| SNCA | 38 |
| YWHAH | 32 |
| TP53 | 25 |
| AKT1 | 22 |
| ABL1 | 19 |

Table S6: Top 10 hubs found in the protein-protein interaction network (PPIN) analysis subnetwork created using the top 30 PD DEGs.

|  |  |  |  |
| --- | --- | --- | --- |
| **Table S7: The direction of differential expression between the common DEGs of AD and PD.** | | | |
|  | **PD upregulated** | **PD downregulated** | **Total** |
| AD upregulated | 114 | 3 | 117 |
| AD downregulated | 1 | 318 | 319 |
| Total | 115 | 321 | 436 |

Table S7: The direction of differential expression between the common DEGs found between AD and PD.



A

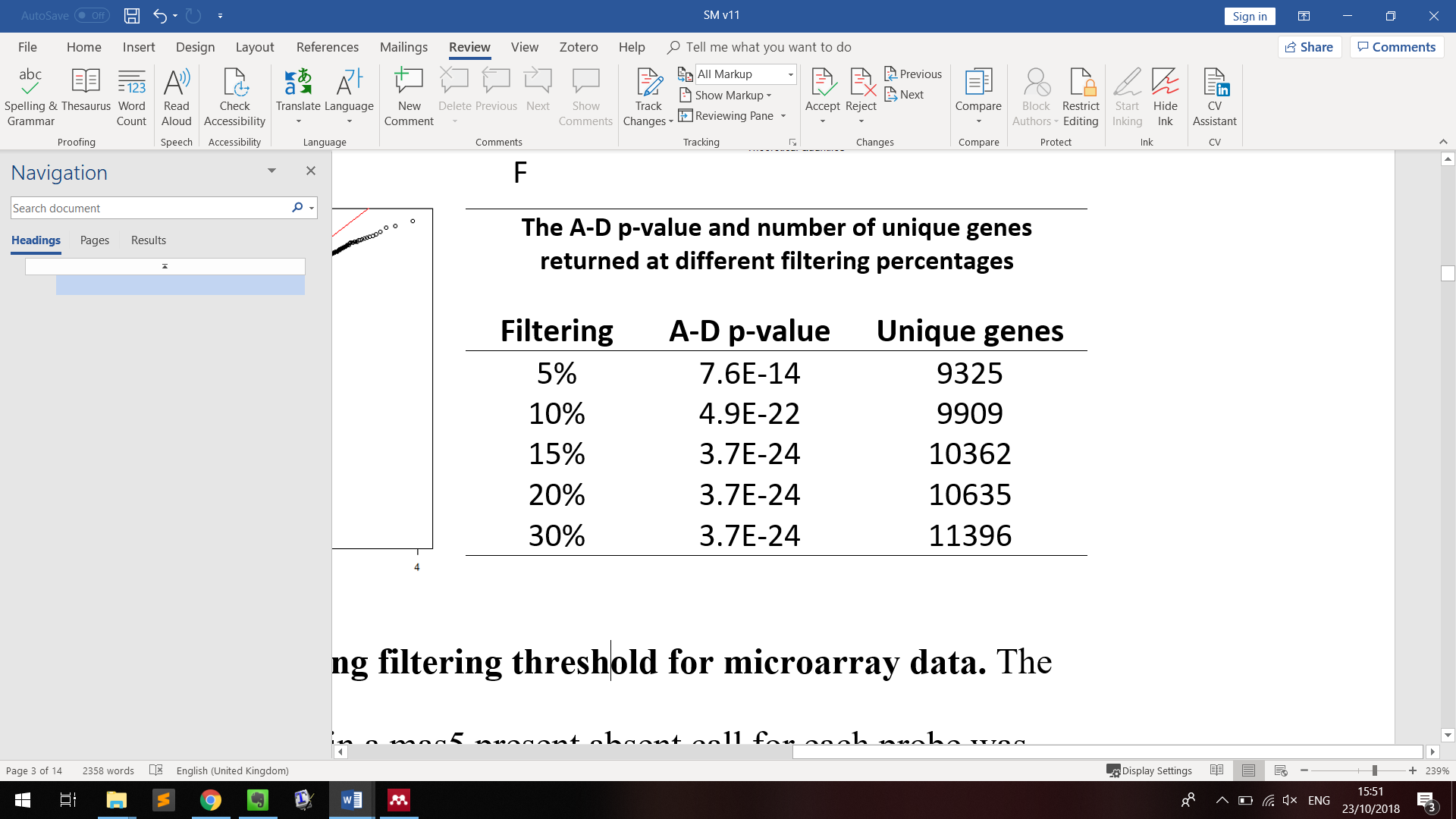
B

D

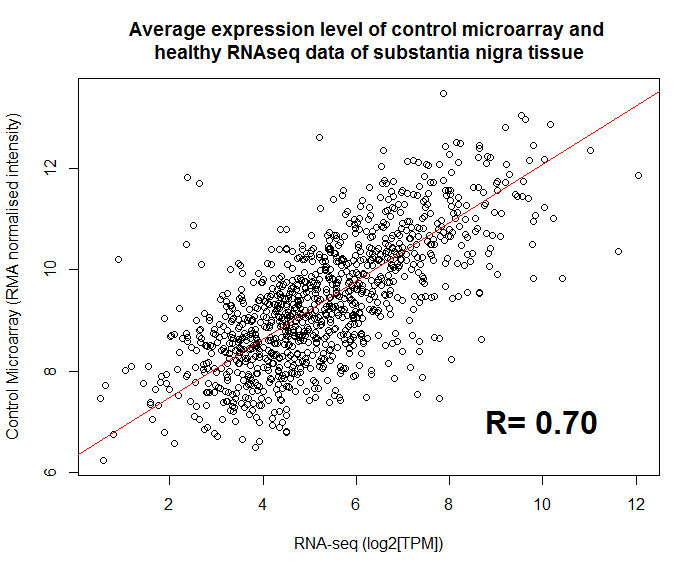
C

E

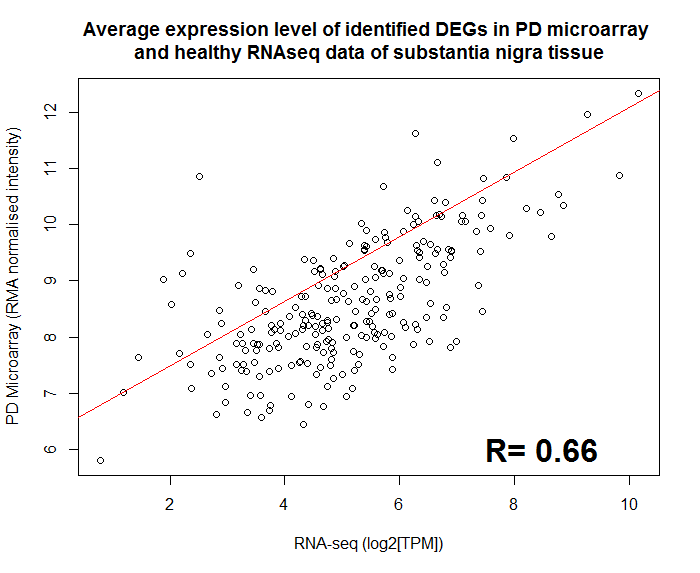
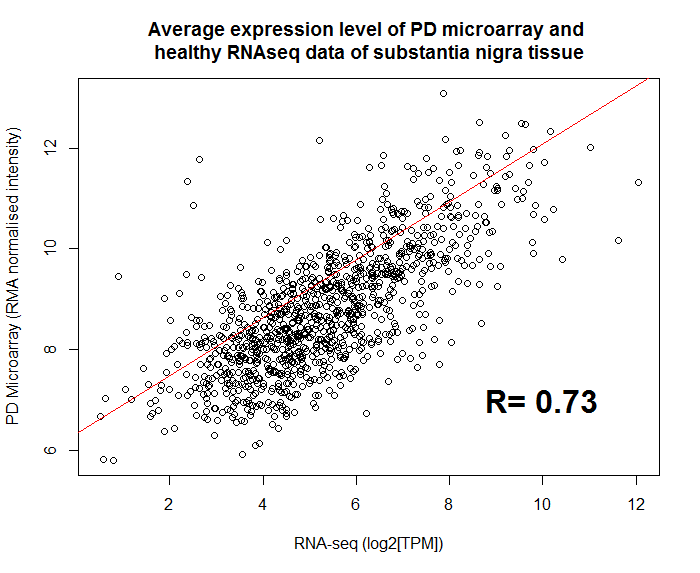
F



**Figure S1: Selecting filtering threshold for microarray data.** The percentage of studies called absent in a mas5 present absent call for each probe was calculated, and threshold determined by minimizing Anderson-Darling normality tests and giving optimal Q-Q plot of the Z-scores after meta-analysis. The Q-Q plot for (A) 5%, (B) 10%, (C) 15%, (D) 20% and (E) 30% filtering. After 15% filtering A-D p-values were minimized (F) and the 15% Q-Q plot gave closest values to normality. A-D is Anderson-Darling normality test.

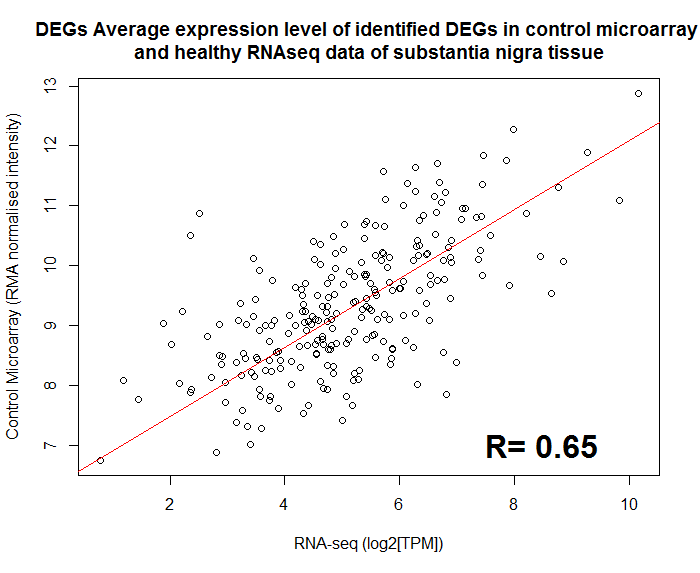


A



D

B



C

**Figure S2. RNA-seq vs microarray.** Average absolute expression level of RNA-seq log2(TPM) of SN tissue from GTEx database plotted against RMA normalised and filtered intensity of microarray control and PD data used in this meta-analysis**.** The Pearson correlation coefficient between the control microarray data and healthy RNA-seq data (A) is 0.70 (pvalue < 2.2e-16) showing that the expression values of genes between microarray and RNA-seq are correlated and expression data distribution is similar. The Pearson correlation between the healthy RNA-seq and PD microarray data (B) is actually higher than between RNA-seq and control microarray at 0.73 (pvalue < 2.2e-16), when it would be expected to be lower due to some genes being differentially expressed. When using only DEGs, correlation between healthy RNA-seq and control microarray (C) and PD microarray (D) data this difference in correlation is minimised to 0.65 (pvalue < 2.2e-16) and 0.66 (pvalue < 2.2e-16) respectively, suggesting that the difference in correlation could be due to the larger sample size of the PD data.