**Supplementary Table 1.** STRING assessment of the curated ARC complex for enrichment of GO processes.

Only processes revealing false discovery rate below 1.00E-04 are reported.

|  |  |  |
| --- | --- | --- |
| **Biological Process (GO)** | | |
| **pathway ID** | **pathway description** | **false discovery rate** |
| GO:0000904 | cell morphogenesis involved in differentiation | 7.00E-07 |
| GO:0031175 | neuron projection development | 7.00E-07 |
| GO:0048666 | neuron development | 7.00E-07 |
| GO:0048812 | neuron projection morphogenesis | 1.22E-06 |
| GO:0010628 | positive regulation of gene expression | 1.44E-06 |
| GO:0030182 | neuron differentiation | 1.94E-06 |
| GO:0006897 | endocytosis | 4.42E-06 |
| GO:0007417 | central nervous system development | 4.42E-06 |
| GO:0010557 | positive regulation of macromolecule biosynthetic process | 4.42E-06 |
| GO:0050890 | cognition | 4.42E-06 |
| GO:0048667 | cell morphogenesis involved in neuron differentiation | 6.50E-06 |
| GO:0031328 | positive regulation of cellular biosynthetic process | 8.59E-06 |
| GO:0051173 | positive regulation of nitrogen compound metabolic process | 9.32E-06 |
| GO:0048731 | system development | 9.45E-06 |
| GO:0007275 | multicellular organismal development | 1.38E-05 |
| GO:0048856 | anatomical structure development | 1.38E-05 |
| GO:0007611 | learning or memory | 2.25E-05 |
| GO:0048468 | cell development | 2.25E-05 |
| GO:0050803 | regulation of synapse structure or activity | 2.37E-05 |
| GO:0007409 | axonogenesis | 2.55E-05 |
| GO:0048167 | regulation of synaptic plasticity | 2.55E-05 |
| GO:0045935 | positive regulation of nucleobase-containing compound metabolic process | 2.79E-05 |
| GO:0007399 | nervous system development | 2.84E-05 |
| GO:0061564 | axon development | 3.02E-05 |
| GO:0045893 | positive regulation of transcription, DNA-templated | 3.08E-05 |
| GO:0009653 | anatomical structure morphogenesis | 4.63E-05 |
| GO:2000112 | regulation of cellular macromolecule biosynthetic process | 5.50E-05 |
| GO:0048583 | regulation of response to stimulus | 7.48E-05 |
| GO:0006417 | regulation of translation | 9.57E-05 |
| **Molecular Function (GO)** | | |
| **pathway ID** | **pathway description** | **false discovery rate** |
| GO:0005515 | protein binding | 2.28E-05 |
| GO:0019899 | enzyme binding | 9.30E-05 |
| **Cellular Component (GO)** | | |
| **pathway ID** | **pathway description** | **false discovery rate** |
| GO:0043005 | neuron projection | 2.59E-07 |
| GO:0097458 | neuron part | 2.59E-07 |
| GO:0042995 | cell projection | 3.10E-07 |
| GO:0030425 | dendrite | 6.58E-06 |
| GO:0036477 | somatodendritic compartment | 6.99E-06 |
| GO:0005654 | nucleoplasm | 7.52E-06 |
| GO:0045202 | synapse | 7.52E-06 |
| GO:0016605 | PML body | 6.77E-05 |
| GO:0014069 | postsynaptic density | 7.97E-05 |
| GO:0044427 | chromosomal part | 8.99E-05 |

**Supplementary Table 2. Summary of associations observed in ALSPAC sample for gene set and individuals genes comprising those.**

1. *Association results for ARC gene sets.*

Gene sets are defined in Table 1.

P-values below 0.05 are highlighted in bold. Bonferroni corrected significance threshold was set to 4.17E-03 (12 tests).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Sample** | | ***ARC* expression** | | **Arc function** | | **Both *ARC* expression and Arc function** | |
| Number of Genes | p-value | Number of Genes | p-value | Number of Genes | p-value |
| ALSPAC | Verbal IQ | 17 | 0.661 | 18 | **0.027** | 36 | 0.182 |
| Performance IQ | 17 | 0.865 | 18 | 0.124 | 36 | 0.635 |
| Full Scale IQ | 17 | 0.753 | 18 | **0.041** | 36 | 0.370 |

1. *Association results for individual genes comprising the ARC gene sets.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **ARC Gene Set** | **Gene** | **Number of SNPs** | **p-value** | | |
| **Verbal IQ** | **Performance IQ** | **Full Scale IQ** |
| ARC expression | CREB1 | 25 | 0.600 | 0.461 | 0.461 |
| MEF2A | 58 | 0.426 | 0.094 | 0.277 |
| SRF | 6 | 0.651 | 0.110 | 0.252 |
| HNF4A | 83 | 0.909 | 0.570 | 0.792 |
| HNRNPAB | 8 | 0.276 | 0.315 | 0.265 |
| HNRNPA2B1 | 6 | 0.803 | 0.783 | 0.675 |
| UPF1 | 14 | 0.354 | 0.648 | 0.560 |
| EIF4A3 | 10 | 0.233 | 0.410 | 0.267 |
| MIR34A | 1 | 0.240 | 0.698 | 0.603 |
| MIR193A | no SNPs present | NA | NA | NA |
| MIR326 | 1 | 0.091 | 0.183 | 0.098 |
| EEF2 | 8 | 0.169 | 0.083 | 0.058 |
| FMR1 | 1 | 0.348 | 0.080 | 0.133 |
| MKNK1 | 34 | 0.566 | 0.647 | 0.414 |
| MKNK2 | 7 | 0.013 | 0.645 | 0.169 |
| CYFIP1 | 112 | 0.793 | 0.308 | 0.470 |
| UBE3A | 46 | 0.356 | 0.722 | 0.775 |
| RNF216 | 143 | 0.356 | 0.183 | 0.323 |
| Arc Function | SH3GL1 | 13 | 0.212 | 0.529 | 0.159 |
| SH3GL3 | 150 | 0.039 | 0.061 | 0.017 |
| SH3GL2 | 381 | 0.704 | 0.319 | 0.328 |
| DNM2 | 56 | 0.123 | 0.216 | 0.126 |
| CAMK2B | 39 | 0.897 | 0.614 | 0.707 |
| CFL1 | 4 | 0.549 | 0.959 | 0.835 |
| MAP2 | 215 | 0.674 | 0.245 | 0.495 |
| SPTBN4 | 37 | 0.143 | 0.371 | 0.234 |
| DLG4 | 17 | 0.215 | 0.061 | 0.191 |
| NTRK2 | 378 | 0.356 | 0.031 | 0.091 |
| NOTCH1 | 30 | 0.751 | 0.274 | 0.706 |
| APP | 305 | 0.945 | 0.006 | 0.503 |
| BACE1 | 17 | 0.714 | 0.354 | 0.385 |
| PSEN1 | 47 | 0.034 | 0.372 | 0.050 |
| UBE2I | 27 | 0.617 | 0.391 | 0.694 |
| SUMO1 | 15 | 0.046 | 0.071 | 0.029 |
| PML | 26 | 0.373 | 0.267 | 0.312 |
| KAT5 | 8 | 0.139 | 0.139 | 0.039 |

**Supplementary Table 3. Summary of the top SNPs (point-wise empirical p-value <1.00E-03) observed in the association tests between variants in *ARC* complex and IQ measures in ALSPAC sample at 8.5 years of age.**

“CHR” refers to chromosome, “SNP” refers to single nucleotide polymorphism, “BP” refers to base pair in hg18, “95% CI” refers to 95% confidence interval. Family-wise p-value was calculated based on one million permutations.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Performance IQ (PIQ)** | | | | | | | | |
| CHR | SNP | BP | Effect Allele | | BETA | 95% CI | point-wise p-value | family-wise p-value |
| 21 | rs2830077 | 26424594 | C | | 1.399 | 0.7531-2.045 | 2.22E-05 | 0.01792 |
| 21 | rs432766 | 26429931 | C | | 1.399 | 0.7531-2.045 | 2.22E-05 | 0.01792 |
| 21 | rs375369 | 26436244 | A | | 1.399 | 0.7531-2.045 | 2.22E-05 | 0.01792 |
| 21 | rs467021 | 26438948 | C | | 1.399 | 0.7531-2.045 | 2.22E-05 | 0.01792 |
| 21 | rs12483003 | 26444779 | C | | 1.389 | 0.7432-2.035 | 2.53E-05 | 0.0203 |
| 21 | rs368196 | 26453138 | C | | 1.389 | 0.7432-2.035 | 2.53E-05 | 0.0203 |
| 21 | rs465235 | 26454893 | G | | 1.389 | 0.7432-2.035 | 2.53E-05 | 0.0203 |
| 21 | rs2830072 | 26422531 | T | | 1.368 | 0.7187-2.017 | 3.69E-05 | 0.02911 |
| 21 | rs2830073 | 26423013 | T | | 1.368 | 0.7187-2.017 | 3.69E-05 | 0.02911 |
| 21 | rs2154481 | 26395746 | C | | 1.361 | 0.7111-2.011 | 4.12E-05 | 0.03235 |
| 21 | rs2830066 | 26416073 | C | | 1.272 | 0.6197-1.924 | 0.0001336 | 0.09638 |
| 21 | rs2830088 | 26436611 | C | | 1.267 | 0.6165-1.917 | 0.0001361 | 0.098 |
| 21 | rs2830089 | 26437110 | G | | 1.267 | 0.6165-1.917 | 0.0001361 | 0.098 |
| 21 | rs2154482 | 26442802 | T | | 1.253 | 0.6033-1.904 | 0.0001594 | 0.1134 |
| 21 | rs2830057 | 26403214 | A | | 1.25 | 0.5962-1.903 | 0.00018 | 0.1262 |
| 21 | rs2234990 | 26418053 | T | | 1.25 | 0.5962-1.903 | 0.00018 | 0.1262 |
| 21 | rs2256331 | 26399885 | G | | 1.234 | 0.58-1.887 | 0.0002185 | 0.15 |
| 21 | rs466448 | 26465979 | G | | 1.148 | 0.5029-1.792 | 0.0004889 | 0.2941 |
| 21 | rs8131895 | 26425398 | C | | 1.174 | 0.4963-1.852 | 0.0006906 | 0.3827 |
| **Verbal IQ (VIQ)** | | | | | | | | |
| CHR | SNP | BP | Effect Allele | | BETA | 95% CI | point-wise p-value | family-wise p-value |
| 15 | rs1491579 | 81969683 | T | | -1.155 | -1.795 - -0.5142 | 0.0004134 | 0.2588 |
| **Total Full Scale IQ (FSIQ)** | | | | | | | | |
| CHR | SNP | BP | Effect Allele | BETA | | 95% CI | point-wise p-value | family-wise p-value |
| 15 | rs1491579 | 81969683 | T | -1.263 | | -1.89 - -0.6361 | 7.98E-05 | 0.06036 |
| 15 | rs12905964 | 81970119 | T | 1.081 | | 0.4516 - 1.71 | 0.0007654 | 0.4135 |
| 15 | rs10152284 | 81948278 | T | -1.311 | | -2.075 - -0.5471 | 0.0007749 | 0.4171 |