

Transcriptome analysis of human ageing in male skin shows mid-life period of variability and central role of NF- κ B

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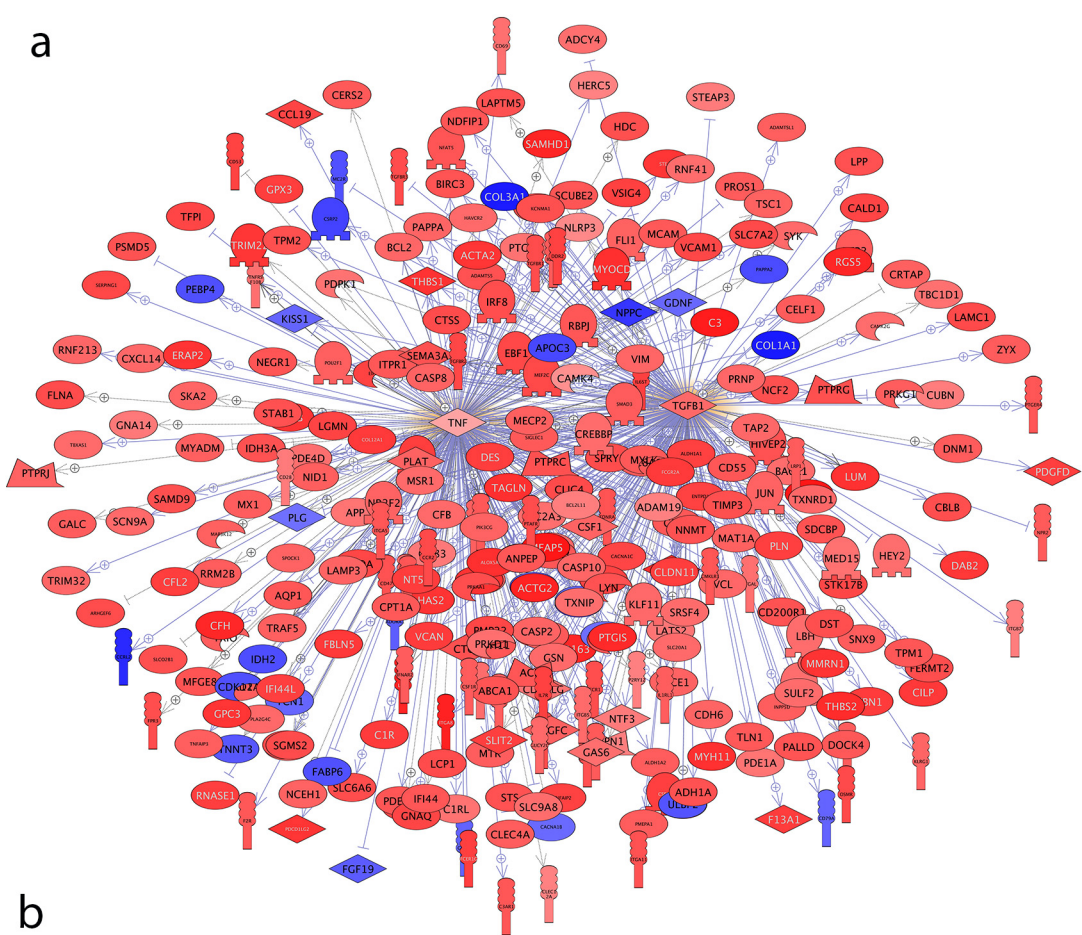
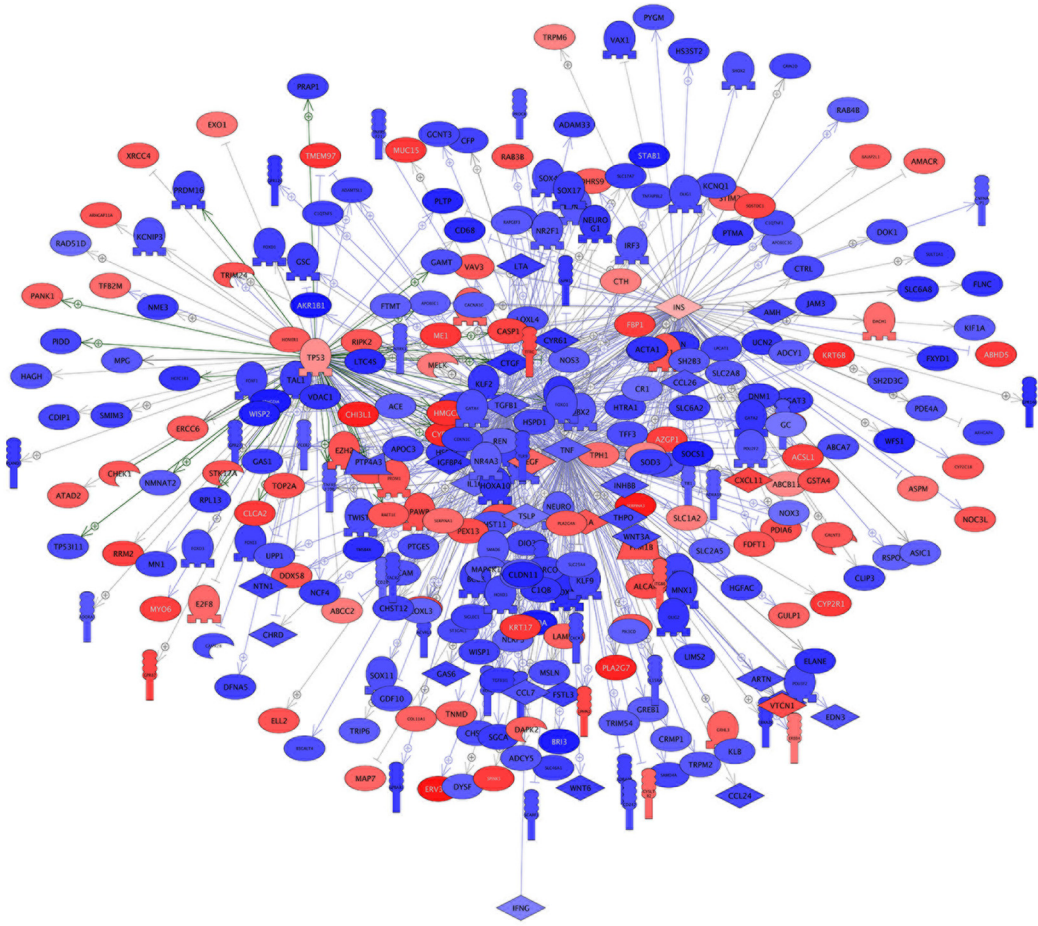
a**b**

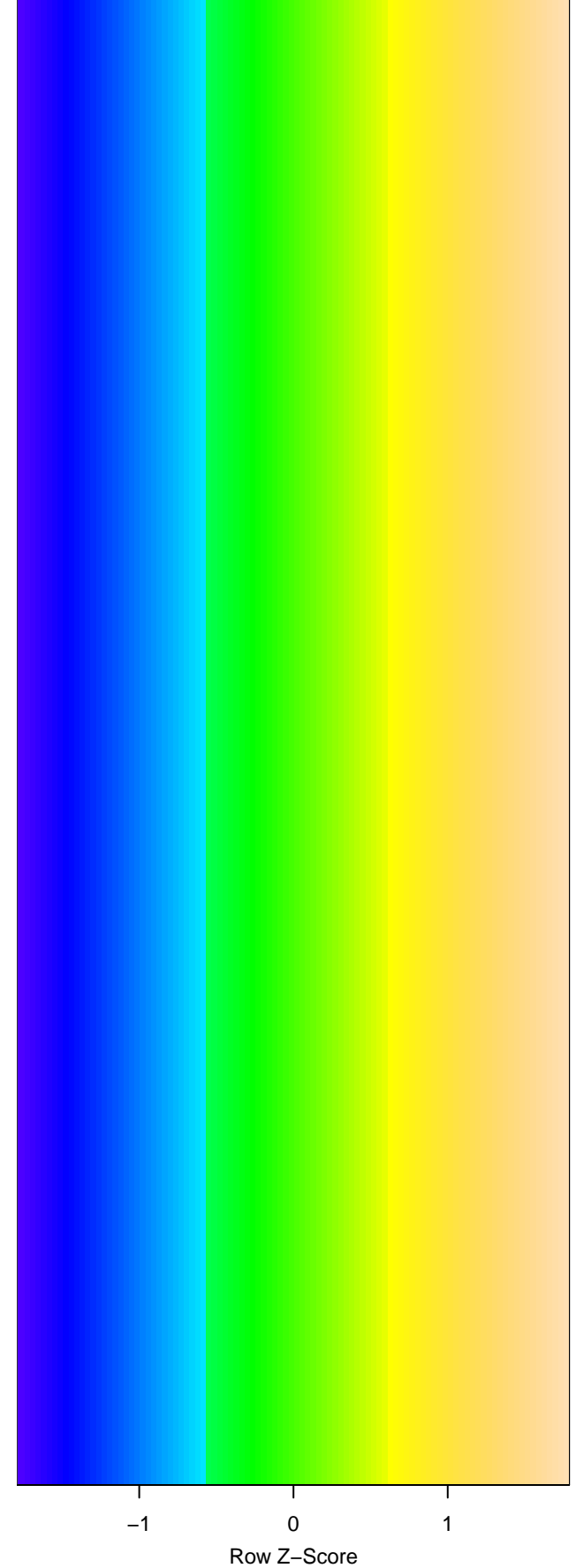
Figure S1

a Pathway showing common regulators with >100 interacting proteins in the pathway list for the eldest versus youngest age groups comparison.

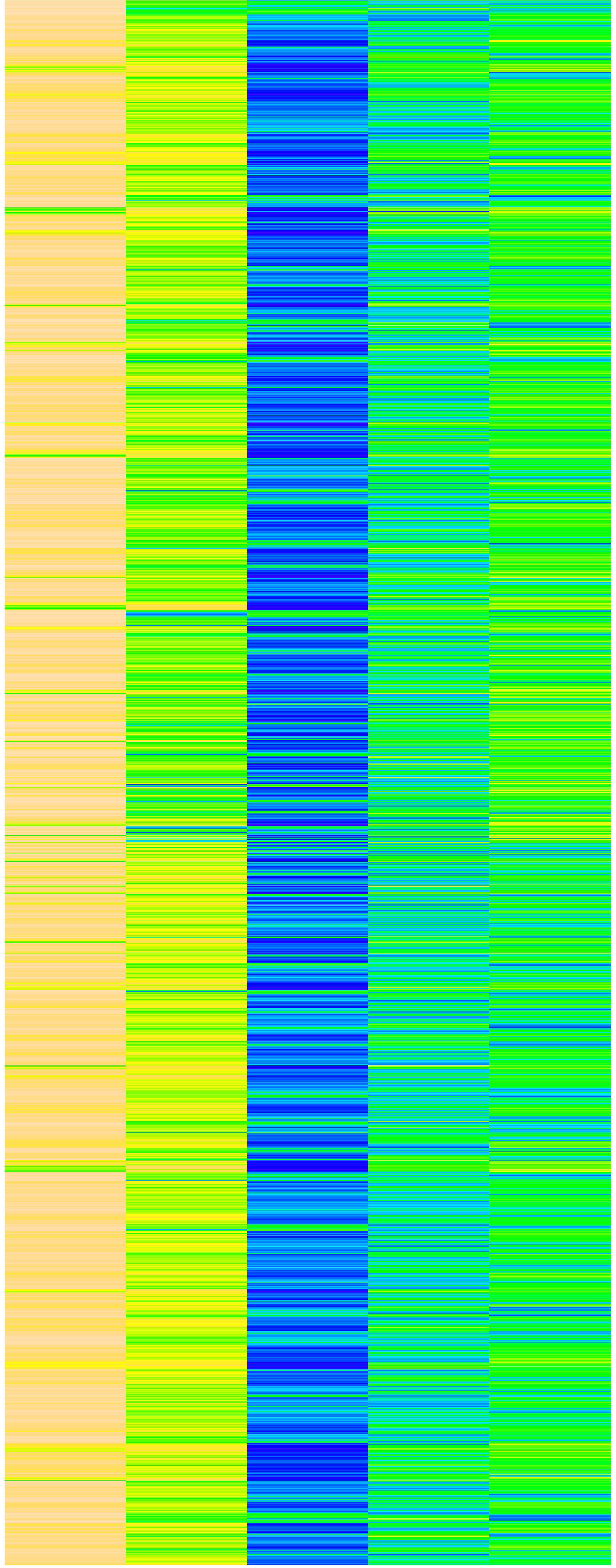
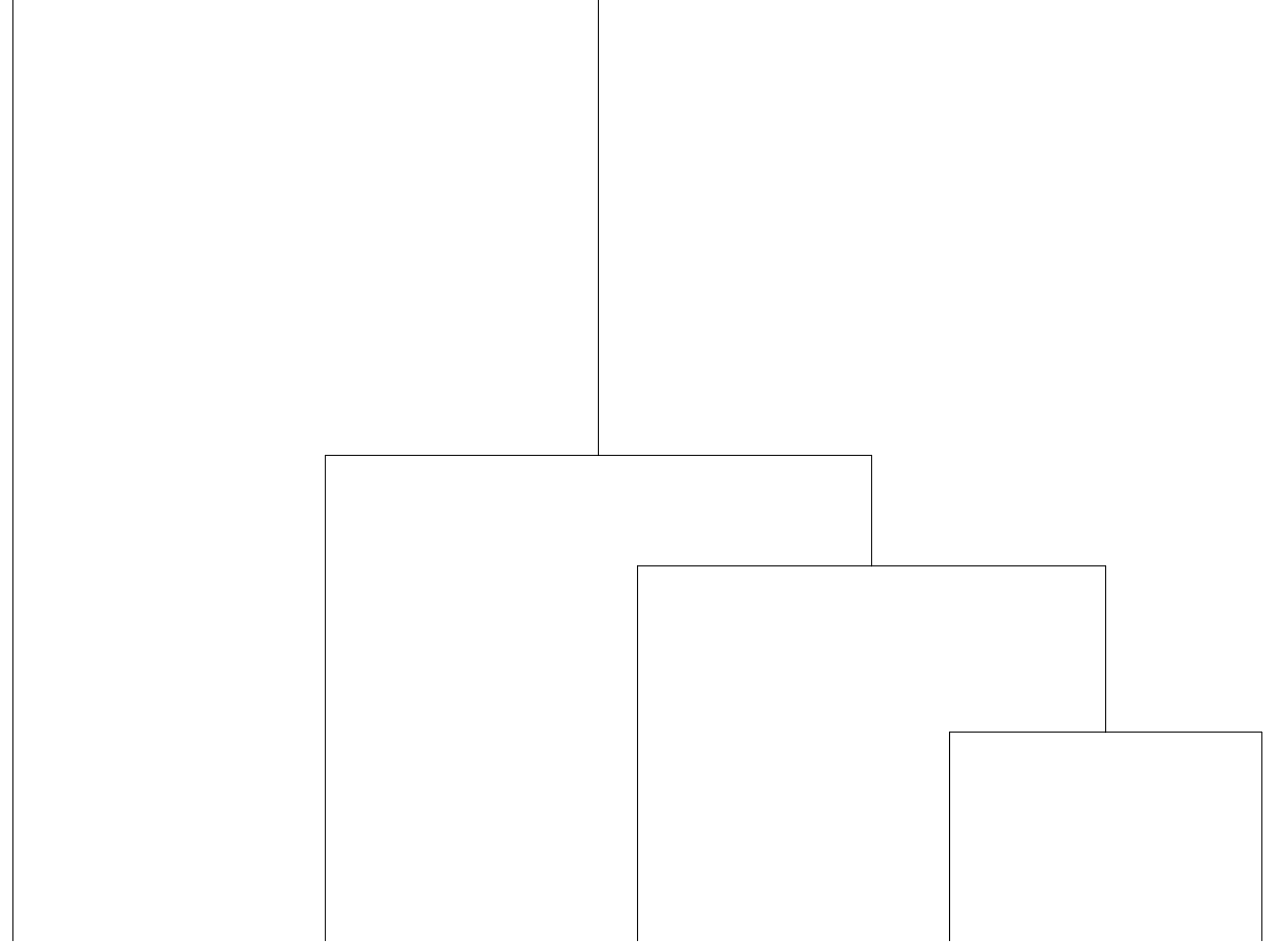
b Pathway showing common regulators with >100 interacting proteins in the pathway list for the 30-45 age group versus all other age groups.

Red indicates increased gene expression, blue indicates decreased gene expression in the eldest (a) and mid-life (b) groups compared to other age groups.

Color Key



-1 0 1
Row Z-Score



92

95

91

93

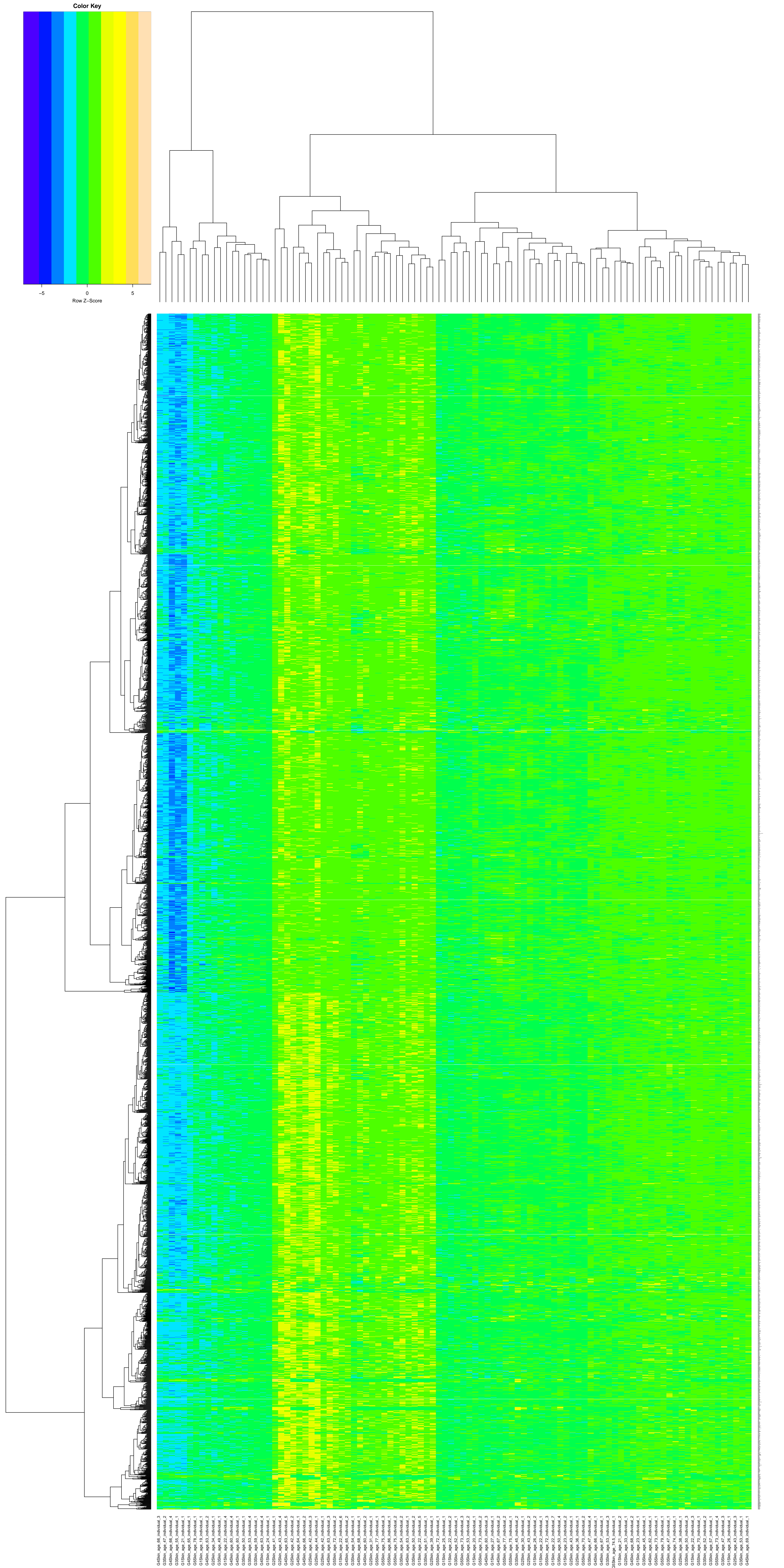
94

Figure S2

a Heatmap of genes upregulated in the 30-45 age group compared to other age groups shown as a group comparison

b Heatmap of genes downregulated in the 30-45 age group compared to other age groups shown as a group comparison

g1 18-29, g2 30-45, g3 46-60, g4 61-75, g5 >75 age groups.



Color Key

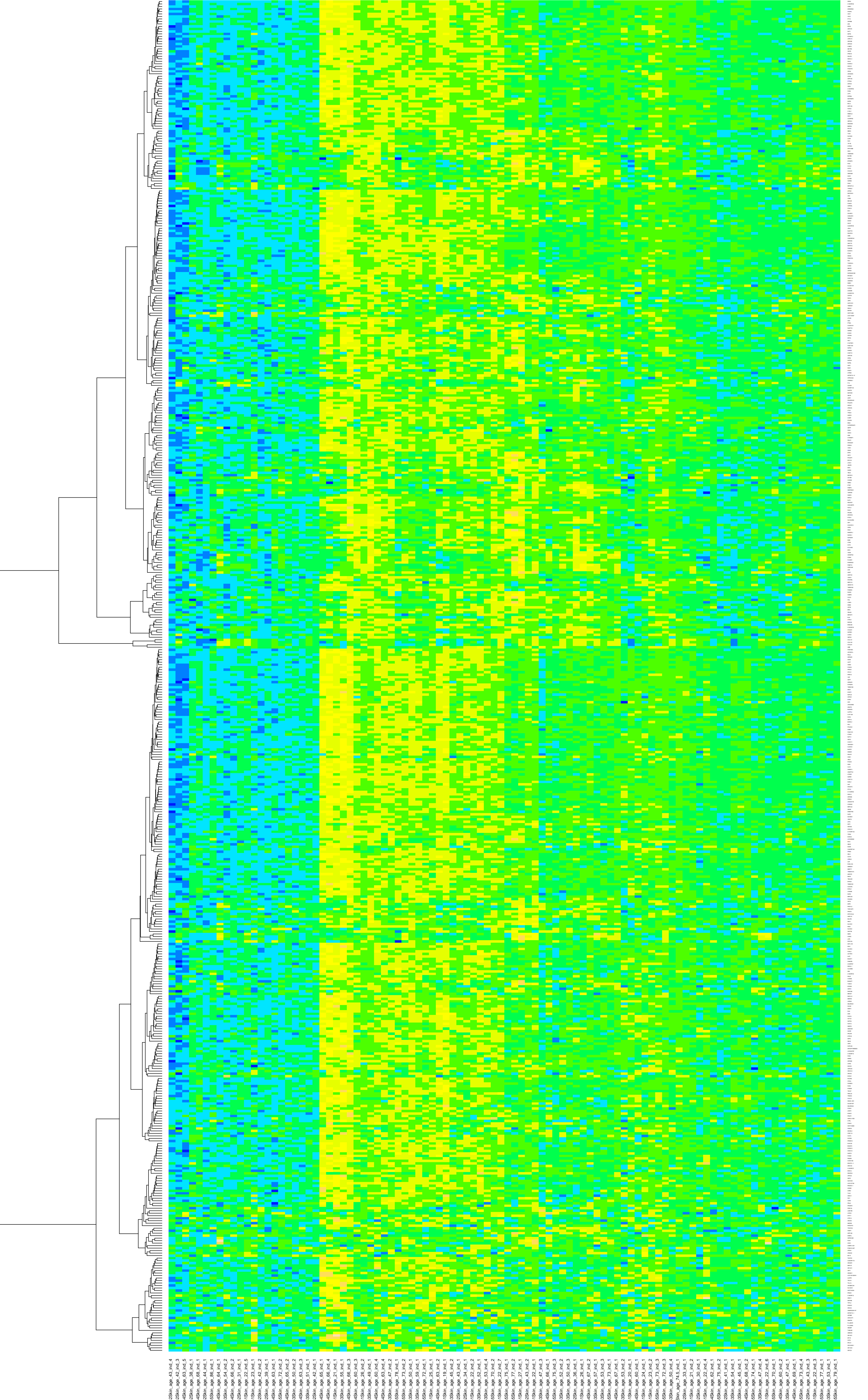
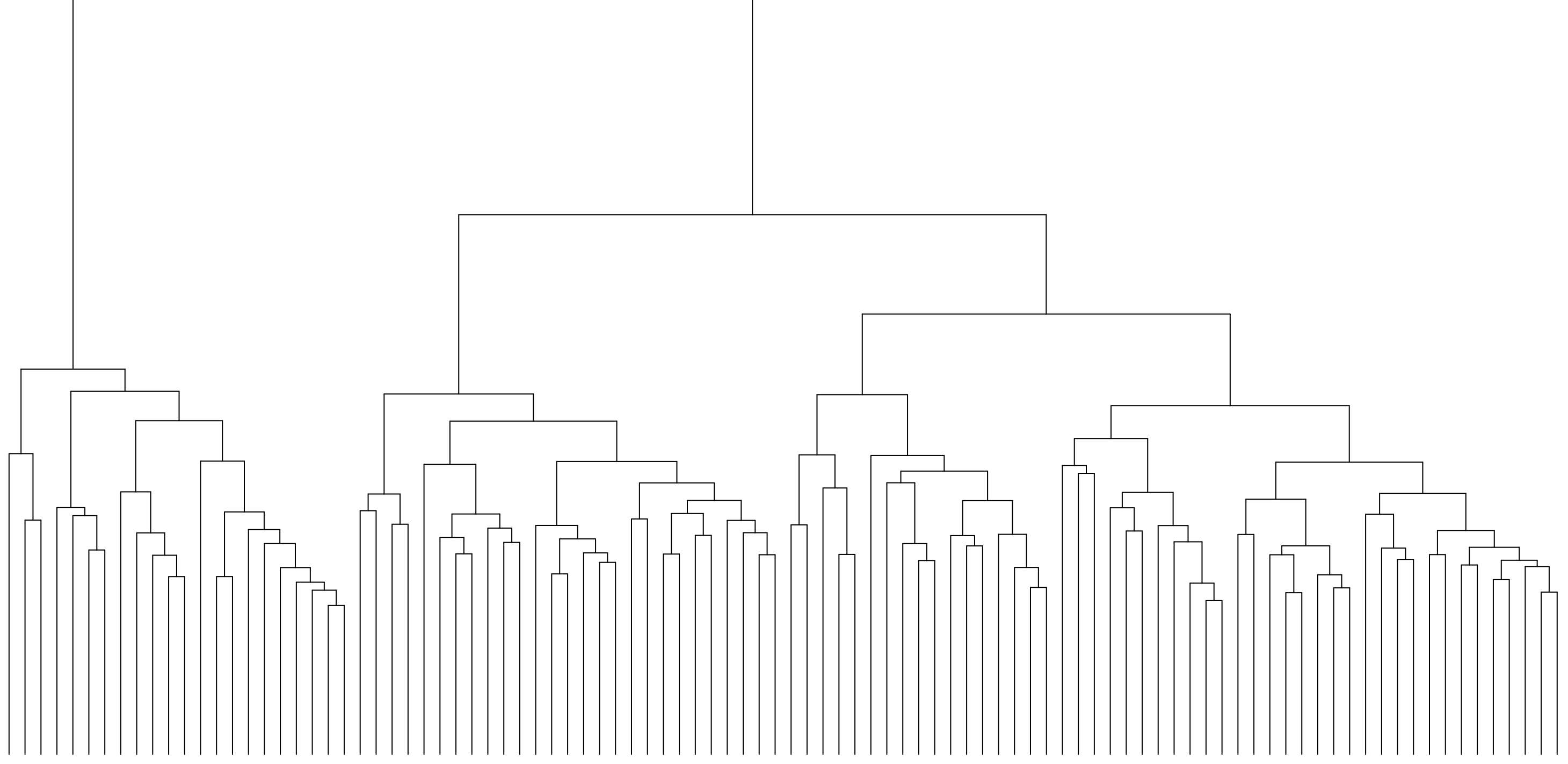
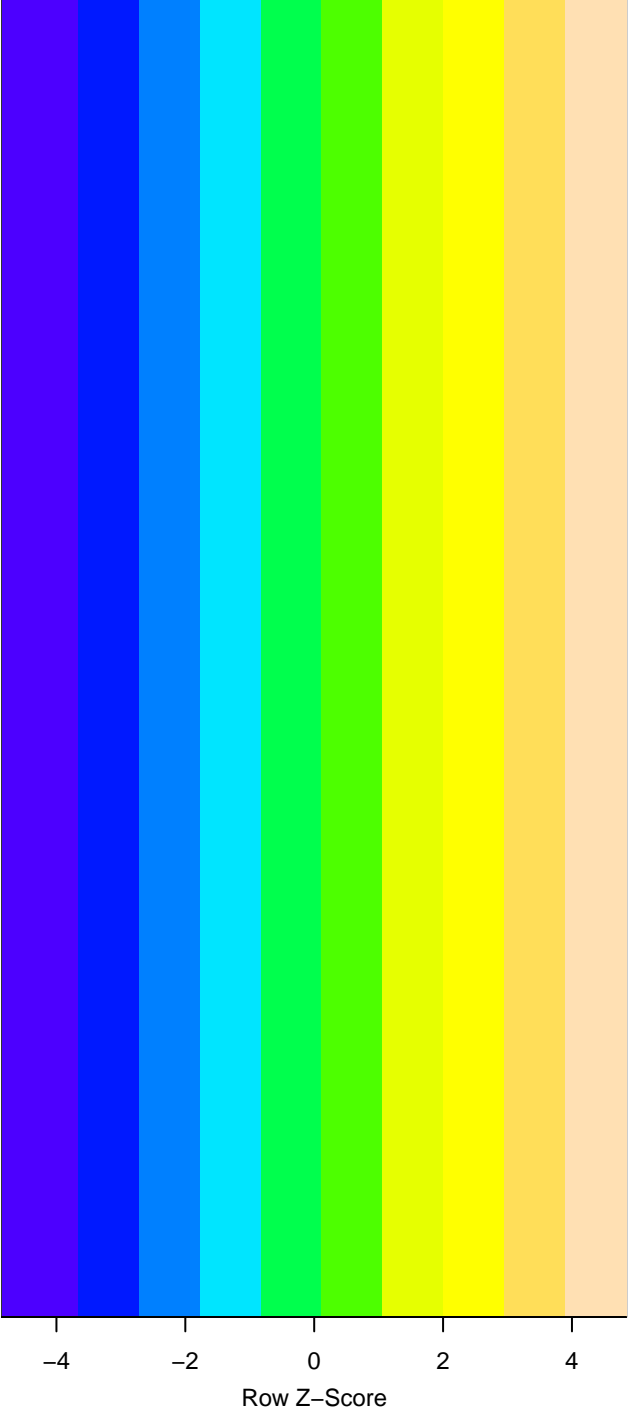


Figure S3

a Heatmap of genes upregulated in the 30-45 age group compared to other age groups showing individual samples.

b Heatmap of genes downregulated in the 30-45 age group compared to other age groups showing individual samples.

| Age | Yrs in Aus | Past Med Hx | Medications | Cur Smoker | Years post quitting | Amount smoked (pack years) | Fam Hx Skin Ca |
|-----|------------|--------------------|---------------------------|------------|---------------------|----------------------------|-------------------|
| 19 | 13 | No | Nil | No | NA | NA | Nil |
| 20 | 20 | No | Nil | No | NA | NA | Nil |
| 21 | 21 | Hayfever/Allergies | Nil | No | NA | NA | Nil |
| 21 | 21 | No | Nil | No | NA | NA | Nil |
| 22 | 22 | No | Nil | No | NA | NA | Nil |
| 22 | 22 | No | Nil | No | NA | NA | Nil |
| 22 | 20 | No | Nil | No | NA | NA | Nil |
| 22 | 22 | No | Nil | No | NA | NA | Nil |
| 22 | 22 | Migraines | Nil | No | NA | NA | Nil |
| 22 | 22 | migraines | Nil | No | NA | NA | Nil |
| 22 | 20 | No | Nil | No | NA | NA | Nil |
| 23 | 23 | No | Nil | No | NA | NA | Nil |
| 23 | 23 | No | Nil | No | NA | NA | Nil |
| 24 | 24 | No | Nil | No | NA | NA | Nil |
| 25 | 25 | No | Nil | No | 2 years | NA | Nil |
| 26 | 26 | No | Nil | No | NA | NA | Nil |
| 26 | 26 | No | Nil | No | NA | NA | Nil |
| 27 | 27 | No | Nil | No | NA | NA | Nil |
| 30 | 30 | Asthma | Formoterol, Budesonide | No | NA | NA | Nil |
| 31 | 31 | No | Nil | No | NA | NA | Nil |
| 33 | 33 | Deaf in right ear | Nil | No | NA | NA | Nil |
| 34 | 34 | No | Nil | No | NA | NA | Father- benign |
| 36 | 36 | No | Nil | No | NA | NA | Nil |
| 38 | 38 | No | Nil | No | NA | NA | Nil |
| 39 | 39 | Hypertension | Nil | No | 6 years | 1 | Nil |
| 41 | 30 | No | Nil | No | NA | NA | Nil |
| 42 | 21 | No | Nil | No | NA | NA | Nil |
| 42 | 42 | No | Nil | No | 2 years | 3 | Nil |
| 42 | 42 | No | Nil | No | NA | NA | Nil |
| 43 | 43 | No | Nil | No | NA | NA | Nil |
| 43 | 43 | No | Nil | No | NA | NA | Nil |
| 43 | 43 | No | Nil | No | NA | NA | Nil |
| 43 | 43 | No | Nil | No | NA | NA | Nil |
| 44 | 20 | No | Nil | No | NA | NA | Nil |
| 45 | 45 | No | Steroid Creams | No | NA | NA | Nil |
| 45 | 45 | No | Nil | No | NA | NA | Nil |
| 47 | 8 | No | Nil | No | 7 years | NA | Mother- benign |
| 47 | 47 | No | Nil | No | NA | NA | Nil |

| | | | | | | | |
|----|----|---|--------------------------------|----|----------|----|---------------|
| 47 | 34 | No | Multi vitamins | No | NA | NA | Nil |
| 47 | 47 | GORD | Nil | No | NA | NA | Nil |
| 49 | 30 | No | Nil | No | NA | NA | Nil |
| 50 | 50 | No | Fish oils | No | 30 years | 12 | Father-benign |
| 50 | 50 | No | Nil | No | 35 years | NA | Nil |
| 50 | 20 | No | Nil | No | NA | NA | Nil |
| 50 | 18 | No | Nil | No | NA | NA | Nil |
| 51 | 51 | No | Nil | No | 23 years | NA | Nil |
| 52 | 52 | No | Nil | No | NA | NA | Mother |
| 52 | 15 | No | Nil | No | NA | NA | Nil |
| 53 | 53 | No | Nil | No | 20 years | 5 | Father-benign |
| 53 | 53 | No | Multi vitamins | No | NA | NA | Nil |
| 53 | 25 | No | Nil | No | NA | NA | Nil |
| 53 | 53 | No | Nil | No | NA | NA | Nil |
| 54 | 54 | No | Multi vitamins | No | 30 years | NA | Nil |
| 54 | 54 | No | Nil | No | NA | NA | Nil |
| 55 | 55 | No | Nil | No | NA | NA | Nil |
| 57 | 57 | Depression | Citalopram | No | 12 years | 30 | Nil |
| 59 | 59 | No | Nil | No | NA | NA | Nil |
| 60 | 60 | No | Nil | No | NA | NA | Father |
| 60 | 48 | No | Nil | No | 15 years | 5 | Nil |
| 60 | 60 | No | Nil | No | NA | NA | Nil |
| 60 | 60 | No | Nil | No | NA | NA | Nil |
| 62 | 39 | No | Nil | No | NA | NA | Nil |
| 63 | 63 | No | Nil | No | NA | NA | Nil |
| 63 | 63 | No | Nil | No | NA | NA | Nil |
| 63 | 63 | No | Nil | No | 20 years | <1 | Nil |
| 63 | 24 | No | Nil | No | NA | NA | Nil |
| 63 | 63 | Burn to R leg, cholecystitis 1992, pneumonia 1968, appendicitis 1960 | Omeprazole | No | 15 years | NA | Nil |
| 64 | 64 | No | Nil | No | NA | NA | Nil |
| 65 | 65 | No | Nil | No | NA | NA | Nil |
| 65 | 65 | No | Multi vitamins | No | 30 years | <1 | Nil |
| 66 | 40 | Dupuytren's contracture L hand, BPH | Nil | No | NA | NA | Nil |
| 66 | 66 | No | Nil | No | 23 years | NA | Nil |
| 66 | 66 | No | Nil | No | NA | NA | Nil |
| 66 | 66 | No | Atorvastatin, Ramipril 10mg | No | NA | NA | Nil |
| 67 | 67 | Asbestosis | Multi vitamins | No | 45 years | <1 | Nil |

| | | | | | | | |
|----|----|---|--------------------------------------|----|----------|--------|-----|
| 67 | 67 | Cancer- right kidney (previously) | Irbesartan | No | 40 years | 5 | Nil |
| 68 | 13 | No | Multi vitamins | No | 40 years | Jan-04 | Nil |
| 68 | 36 | No | Nil | No | 35 years | 17 | Nil |
| 69 | 40 | No | Nil | No | NA | NA | Nil |
| 70 | 70 | No | Nil | No | NA | NA | Nil |
| 70 | 70 | SVT | Prazosin, Multi vitamins | No | NA | NA | Nil |
| 72 | 72 | Gout, prostate cancer (previously) | Multi vitamins | No | 15 years | 10 | Nil |
| 72 | 10 | No | Nil | No | NA | NA | Nil |
| 72 | 72 | No | Irbesartan, Prazosin, Multi vitamins | No | NA | NA | Nil |
| 73 | 73 | No | Nil | No | NA | NA | Nil |
| 73 | 37 | No | Nil | No | NA | NA | Nil |
| 73 | 73 | No | Irbesartan, Atorvastatin, Amlodipine | No | 25 years | 10 | Nil |
| 73 | 73 | Gout | Allopurinol, Multi vitamins | No | NA | NA | Nil |
| 74 | 27 | No | Nil | No | 30 years | NA | Nil |
| 75 | 75 | No | Nil | No | NA | NA | Nil |
| 75 | 29 | Eczema, diptheria as child | Nil | No | NA | NA | Nil |
| 75 | 44 | No | Nil | No | NA | NA | Nil |
| 75 | 75 | No | Ramipril, Atorvastatin | No | NA | NA | Nil |
| 77 | 55 | BPH | Perindopril, tamsulosin | No | 30 years | 5 | Nil |
| 77 | 77 | No (cataract 07, diptheria 1934, tonsillectomy) | Nil | No | NA | NA | Nil |

Supplementary data table 1. Age, medication, smoking and skin cancer history of volunteers participating in the study

| Symbol | Fold Change | P.Value |
|---------------|--------------------|----------------|
| CACNA1C | 1.44 | 2.27E-06 |
| TMEM176B | 1.55 | 4.06E-06 |
| CASQ2 | 1.94 | 6.90E-06 |
| THBS2 | 1.76 | 7.91E-06 |
| GALNTL2 | 2.21 | 1.13E-05 |
| NOX4 | 1.52 | 1.14E-05 |
| CLDN11 | 1.52 | 1.77E-05 |
| C3 | 2.06 | 2.01E-05 |
| ITGA8 | 1.92 | 3.25E-05 |
| CD163 | 1.85 | 4.67E-05 |
| LMO3 | 1.66 | 5.60E-05 |
| C2 | 1.38 | 5.97E-05 |
| TAGLN | 1.69 | 6.65E-05 |
| CP | 2.14 | 7.66E-05 |
| PTGIS | 1.80 | 7.92E-05 |
| VIT | 1.82 | 9.07E-05 |
| ACTA2 | 1.63 | 9.69E-05 |
| ABCA9 | 2.02 | 1.01E-04 |
| LEPR | 1.87 | 1.24E-04 |
| ITK | 1.36 | 1.35E-04 |
| PRSS12 | 1.41 | 1.37E-04 |
| STMN2 | 1.92 | 1.73E-04 |
| C1S | 1.73 | 1.73E-04 |
| IL10RA | 1.50 | 1.77E-04 |
| TNFAIP2 | 1.48 | 2.01E-04 |
| ALOX5AP | 1.71 | 2.31E-04 |
| LAMA2 | 1.71 | 2.54E-04 |
| PRUNE2 | 1.59 | 2.69E-04 |
| SAMHD1 | 1.85 | 4.48E-04 |
| ACTC1 | 2.52 | 4.50E-04 |
| TLR4 | 1.58 | 4.77E-04 |
| MYOCD | 1.71 | 5.21E-04 |
| MFAP4 | 1.90 | 5.25E-04 |
| GPR133 | 1.41 | 5.29E-04 |
| CD209 | 1.55 | 5.46E-04 |
| TMEM176A | 1.53 | 5.55E-04 |
| SYT11 | 1.41 | 6.26E-04 |
| PCDHB3 | 1.51 | 6.52E-04 |
| RBPMS | 1.41 | 6.87E-04 |
| LMOD1 | 1.45 | 6.92E-04 |
| RGL1 | 1.48 | 7.13E-04 |
| CPE | 1.72 | 7.25E-04 |

| | | |
|----------|------|----------|
| CD84 | 1.42 | 7.57E-04 |
| VSIG4 | 1.49 | 7.85E-04 |
| ALDH1B1 | 1.43 | 8.60E-04 |
| MS4A6A | 1.60 | 8.70E-04 |
| MFAP5 | 2.16 | 9.01E-04 |
| RBMS3 | 1.59 | 9.22E-04 |
| ACTG2 | 1.92 | 9.61E-04 |
| RPL24 | 1.69 | 9.95E-04 |
| PDCD1LG2 | 1.63 | 9.98E-04 |
| NCKAP1L | 1.49 | 1.03E-03 |
| SLIT3 | 1.61 | 1.13E-03 |
| FLNA | 1.38 | 1.15E-03 |
| VCAM1 | 1.42 | 1.17E-03 |
| APOBEC3C | 1.51 | 1.18E-03 |
| TMEM71 | 1.51 | 1.24E-03 |
| GLIPR1 | 1.92 | 1.34E-03 |
| P2RX1 | 1.40 | 1.39E-03 |
| SRPX2 | 1.51 | 1.41E-03 |
| GRK5 | 1.29 | 1.43E-03 |
| PGM5 | 1.41 | 1.48E-03 |
| C7 | 1.63 | 1.54E-03 |
| PLEKHH2 | 1.59 | 1.56E-03 |
| TMOD1 | 1.31 | 1.68E-03 |
| SMOC2 | 1.62 | 1.69E-03 |
| FAT | 1.49 | 1.82E-03 |
| LTBP2 | 1.34 | 1.83E-03 |
| KLF7 | 1.33 | 1.88E-03 |
| PRUNE2 | 1.66 | 1.89E-03 |
| GPC3 | 1.63 | 1.94E-03 |
| REEP3 | 1.64 | 1.96E-03 |
| FAM133B | 1.52 | 2.06E-03 |
| FCGR2A | 1.56 | 2.07E-03 |
| FAM69A | 1.37 | 2.14E-03 |
| ENTPD1 | 1.48 | 2.26E-03 |
| LHFP | 1.41 | 2.33E-03 |
| C1orf162 | 1.54 | 2.36E-03 |
| C10orf64 | 1.29 | 2.43E-03 |
| SLCO2B1 | 1.36 | 2.56E-03 |
| TMEM173 | 1.29 | 2.60E-03 |
| MX2 | 1.44 | 2.62E-03 |
| MYH11 | 1.69 | 2.84E-03 |
| SLC6A6 | 1.38 | 2.86E-03 |
| RNASE1 | 1.52 | 3.02E-03 |
| RGS5 | 1.84 | 3.08E-03 |
| DPYSL3 | 1.39 | 3.28E-03 |
| ISLR | 1.65 | 3.29E-03 |
| KANK2 | 1.35 | 3.35E-03 |

| | | |
|---------|------|----------|
| C1R | 1.54 | 3.43E-03 |
| PCDHB16 | 1.51 | 3.45E-03 |
| CTGF | 1.35 | 3.52E-03 |
| ELK3 | 1.35 | 3.57E-03 |
| ABCA6 | 1.69 | 3.58E-03 |
| CCL13 | 1.75 | 3.72E-03 |
| BHMT2 | 1.33 | 3.72E-03 |
| THBS1 | 1.66 | 3.97E-03 |
| PRRX1 | 1.52 | 4.01E-03 |
| CCR1 | 1.37 | 4.09E-03 |
| CFL2 | 1.52 | 4.23E-03 |
| COLEC12 | 1.33 | 4.29E-03 |
| FBLN5 | 1.58 | 4.38E-03 |
| PLSCR4 | 1.44 | 4.45E-03 |
| DOCK2 | 1.37 | 4.46E-03 |
| CMKLR1 | 1.31 | 4.52E-03 |
| FOLR2 | 1.43 | 4.57E-03 |
| PLEK | 1.40 | 4.58E-03 |
| PLN | 1.50 | 4.60E-03 |
| ST3GAL5 | 1.35 | 4.62E-03 |
| CSRP1 | 1.50 | 4.66E-03 |
| PTPRG | 1.36 | 4.75E-03 |
| STAB1 | 1.35 | 4.83E-03 |
| MS4A4A | 1.68 | 4.84E-03 |
| ALDH1A1 | 1.49 | 4.85E-03 |
| C1QA | 1.43 | 4.94E-03 |
| IL7R | 1.49 | 5.05E-03 |
| MMRN1 | 1.64 | 5.07E-03 |
| IRF8 | 1.37 | 5.11E-03 |
| CFH | 1.82 | 5.22E-03 |
| CYBB | 1.63 | 5.28E-03 |
| FAM70A | 1.24 | 5.38E-03 |
| PRG4 | 2.30 | 5.42E-03 |
| CCBE1 | 1.40 | 5.43E-03 |
| SORBS1 | 1.40 | 5.50E-03 |
| UBLCP1 | 1.58 | 5.59E-03 |
| ITGA5 | 1.31 | 5.68E-03 |
| SPRED2 | 1.33 | 5.89E-03 |
| TNS1 | 1.40 | 5.91E-03 |
| TRIM22 | 1.62 | 6.05E-03 |
| MAOB | 1.34 | 6.23E-03 |
| FHL1 | 1.43 | 6.28E-03 |
| AOX1 | 1.56 | 6.31E-03 |
| SPRY1 | 1.37 | 6.37E-03 |
| TGFBR1 | 1.39 | 6.39E-03 |
| CNN1 | 1.47 | 6.43E-03 |
| FCER1G | 1.50 | 6.46E-03 |

| | | |
|---------|------|----------|
| C1QTNF7 | 1.44 | 6.47E-03 |
| PDGFD | 1.51 | 6.55E-03 |
| TGFBR2 | 1.43 | 6.59E-03 |
| ANK2 | 1.42 | 6.65E-03 |
| TBC1D2B | 1.40 | 6.70E-03 |
| HDC | 1.36 | 6.80E-03 |
| PMP22 | 1.43 | 6.83E-03 |
| CILP | 1.58 | 6.96E-03 |
| FPR3 | 1.37 | 7.11E-03 |
| DPYSL2 | 1.35 | 7.30E-03 |
| CHRD1 | 1.63 | 7.34E-03 |
| LAMC1 | 1.41 | 7.42E-03 |
| TFPI | 1.44 | 7.45E-03 |
| LPP | 1.35 | 7.56E-03 |
| PSD3 | 1.56 | 7.56E-03 |
| IGJ | 2.88 | 7.71E-03 |
| TIMP3 | 1.36 | 7.81E-03 |
| RBPJ | 1.31 | 7.92E-03 |
| ZNFX1 | 1.34 | 7.95E-03 |
| CDH11 | 1.31 | 8.24E-03 |
| NRP1 | 1.39 | 8.24E-03 |
| CD200R1 | 1.33 | 8.25E-03 |
| XPNPEP2 | 1.30 | 8.34E-03 |
| CYBRD1 | 1.43 | 8.54E-03 |
| SIPA1L2 | 1.31 | 8.66E-03 |
| TGFBR3 | 1.38 | 8.69E-03 |
| VCAN | 1.55 | 8.77E-03 |
| MYLK | 1.29 | 8.87E-03 |
| PSCD4 | 1.27 | 8.99E-03 |
| MOXD1 | 1.31 | 9.02E-03 |
| MAP1B | 1.44 | 9.21E-03 |
| PDE3A | 1.31 | 9.37E-03 |
| STEAP4 | 1.62 | 9.42E-03 |
| CTSO | 1.39 | 9.44E-03 |
| EVI2B | 1.53 | 9.54E-03 |
| COL12A1 | 1.57 | 9.59E-03 |
| CBLB | 1.36 | 9.60E-03 |
| C1QC | 1.45 | 9.83E-03 |

Supplementary data table 2 – Genes upregulated in oldest versus youngest age groups (>70 vs 18-29 years)

| Name | GO Term Number | Enrichment(NES) | P.Value |
|--|----------------|-----------------|---------|
| Nuclear Part | 0044428 | 4.11 | 0.00 |
| Intracellular Transport | 0046907 | 4.08 | 0.00 |
| Rna Binding | 0003723 | 3.96 | 0.00 |
| Organelle Membrane | 0031090 | 3.79 | 0.00 |
| Cellular Localization | 0051641 | 3.76 | 0.00 |
| Establishment Of Cellular Localization | 0051234 | 3.72 | 0.00 |
| Mitochondrion | 0005739 | 3.66 | 0.00 |
| Regulation Of Transcription | 0006355 | 3.58 | 0.00 |
| Membrane Enclosed Lumen | 0031974 | 3.58 | 0.00 |
| Organelle Lumen | 0043233 | 3.54 | 0.00 |
| Transcription From Rna Polymerase Ii Promoter | 0006368 | 3.49 | 0.00 |
| Nuclear Lumen | 0031981 | 3.39 | 0.00 |
| Macromolecule Localization | 0033036 | 3.28 | 0.00 |
| Macromolecular Complex Assembly | 0065003 | 3.19 | 0.00 |
| Protein Localization | 0008104 | 3.18 | 0.00 |
| Cytoskeletal Protein Binding | 0008092 | 3.17 | 0.00 |
| Catabolic Process | 0009056 | 3.17 | 0.00 |
| Organelle Envelope | 0031967 | 3.16 | 0.00 |
| Regulation Of Rna Metabolic Process | 0051252 | 3.16 | 0.00 |
| Negative Regulation Of Transcription | 0045892 | 3.15 | 0.00 |
| Endoplasmic Reticulum | 0005783 | 3.14 | 0.00 |
| Cellular Component Assembly | 0022607 | 3.13 | 0.00 |
| Envelope | 0005635 | 3.11 | 0.00 |
| Structural Constituent Of Ribosome | 0003735 | 3.1 | 0.00 |
| Negative Regulation Of Transcription Dna Dependent | 0045892 | 3.08 | 0.00 |
| Cellular Catabolic Process | 0044109 | 3.06 | 0.00 |
| Regulation Of Transcription dna Dependent | 0006355 | 3.06 | 0.00 |
| Rna Processing | 0006396 | 3.05 | 0.00 |
| Negative Regulation Of Rna Metabolic Process | 0051253 | 3.05 | 0.00 |
| Golgi Apparatus | 0005794 | 3.03 | 0.00 |
| Identical Protein Binding | 0042802 | 3.03 | 0.00 |
| Endomembrane System | 0012505 | 3 | 0.00 |
| Protein Transport | 0015031 | 2.98 | 0.00 |
| Establishment Of Protein Localization | 0045184 | 2.94 | 0.00 |
| Vesicle Mediated Transport | 0016192 | 2.93 | 0.00 |
| Organelle Organization And Biogenesis | 0006996 | 2.92 | 0.00 |
| Translation | 0006412 | 2.91 | 0.00 |
| Rna Splicing | 0008380 | 2.86 | 0.00 |
| Protein Kinase Cascade | 0035556 | 2.84 | 0.00 |

| | | | |
|--|---------|------|------|
| Transferase Activity Transferring Phosphorus Containing Groups | 0016772 | 2.83 | 0.00 |
| Outer Membrane | 0019867 | 2.82 | 0.00 |
| Biosynthetic Process | 0009058 | 2.81 | 0.00 |
| Negative Regulation Of Nucleobase nucleoside nucleotide And Nucleic Acid Metabolic Process | 0045934 | 2.8 | 0.00 |
| Nucleoplasm | 0005654 | 2.79 | 0.00 |
| Regulation Of Developmental Process | 0050793 | 2.78 | 0.00 |
| Programmed Cell Death | 0012501 | 2.77 | 0.00 |
| Regulation Of Apoptosis | 0042981 | 2.77 | 0.00 |
| Regulation Of Transcription From Rna Polymerase II Promoter | 0006357 | 2.77 | 0.00 |
| Apoptosis Go | 0006915 | 2.72 | 0.00 |
| Organelle Outer Membrane | 0031968 | 2.72 | 0.00 |
| Post Translational Protein Modification | 0043687 | 2.72 | 0.00 |
| Intracellular Protein Transport | 0006886 | 2.71 | 0.00 |
| Cellular Biosynthetic Process | 0044249 | 2.69 | 0.00 |
| Cytosol | 0005829 | 2.68 | 0.00 |
| Regulation Of Programmed Cell Death | 0043067 | 2.67 | 0.00 |
| Transcription Activator Activity | 0016563 | 2.67 | 0.00 |
| Negative Regulation Of Cellular Metabolic Process | 0031324 | 2.67 | 0.00 |
| Transcription Cofactor Activity | 0003712 | 2.67 | 0.00 |
| Negative Regulation Of Metabolic Process | 0009892 | 2.66 | 0.00 |
| I-kappaB kinase/NF-kappaB signaling | 0007249 | 2.64 | 0.00 |
| Transcription Factor Binding | 0000989 | 2.63 | 0.00 |
| Organic Acid Metabolic Process | 0006082 | 2.6 | 0.00 |
| Phosphotransferase Activity Alcohol Group As Acceptor | 0016773 | 2.6 | 0.00 |
| Kinase Activity | 0016301 | 2.59 | 0.00 |
| Protein N Terminus Binding | 0047485 | 2.59 | 0.00 |
| Carboxylic Acid Metabolic Process | 0019752 | 2.58 | 0.00 |
| Hydrolase Activity Acting On Acid Anhydrides | 0016817 | 2.58 | 0.00 |
| Pyrophosphatase Activity | 0016462 | 2.55 | 0.00 |
| Basement Membrane | 0005604 | 2.54 | 0.00 |
| Phosphorylation | 0016310 | 2.53 | 0.00 |
| Nucleoside Triphosphatase Activity | 0017111 | 2.52 | 0.00 |
| Cell Fraction | 0000267 | 2.51 | 0.00 |
| Golgi Apparatus Part | 0044431 | 2.5 | 0.00 |
| Regulation Of I Kappab Kinase Nf Kappab Cascade | 0043122 | 2.5 | 0.00 |
| Protein Targeting | 0006605 | 2.5 | 0.00 |
| Cytoskeleton | 0005856 | 2.5 | 0.00 |

NES- normalised enrichment score (NES of 0 is no enrichment) **Supplementary data table 3 GSEA of positively enriched gene sets in oldest versus youngest age groups**

| Term | GO Term Number | P.value |
|---|----------------|----------|
| intracellular | 0005622 | 3.50E-38 |
| cell | 0007049 | 4.80E-27 |
| biopolymer metabolic process | 0043170 | 4.50E-25 |
| cellular macromolecule metabolic process | 0044260 | 8.50E-22 |
| ribonucleotide binding | 0032553 | 2.80E-21 |
| ATP binding | 0005524 | 9.00E-21 |
| macromolecule metabolic process | 0043170 | 9.10E-21 |
| adenyl ribonucleotide binding | 0032559 | 3.80E-20 |
| nucleus | 0005634 | 5.30E-20 |
| purine nucleotide binding | 0017076 | 1.80E-19 |
| nucleotide binding | 0000166 | 1.30E-18 |
| adenyl nucleotide binding | 0030554 | 2.50E-18 |
| organelle | 0031090 | 4.20E-17 |
| nucleobase, nucleoside, nucleotide and nucleic acid metabolic process | 0055134 | 1.90E-15 |
| intracellular membrane-bounded organelle | 0043231 | 6.00E-14 |
| transferase activity, transferring phosphorus-containing groups | 0016772 | 2.70E-13 |
| primary metabolic process | 0044238 | 2.30E-12 |
| protein serine/threonine kinase activity | 0004674 | 2.30E-12 |
| nuclear part | 0044428 | 4.10E-12 |
| nucleic acid binding | 0003676 | 4.10E-12 |
| ubiquitin-dependent protein catabolic process | 0006511 | 1.00E-11 |
| modification-dependent protein catabolic process | 0019941 | 1.00E-11 |
| cellular biopolymer catabolic process | 0044265 | 1.00E-11 |
| modification-dependent macromolecule catabolic process | 0043632 | 1.00E-11 |
| cellular protein catabolic process | 0044257 | 1.00E-11 |
| proteolysis involved in cellular protein catabolic process | 0051603 | 1.00E-11 |
| protein catabolic process | 0030163 | 1.90E-11 |
| nucleoplasm | 0005654 | 2.20E-11 |
| biopolymer catabolic process | 0043285 | 3.70E-11 |
| zinc ion binding | 0008270 | 1.90E-10 |
| nuclear lumen | 0031981 | 2.70E-10 |
| protein modification process | 0036211 | 3.20E-10 |
| ligase activity | 0016874 | 3.60E-10 |
| cellular metabolic process | 0044237 | 4.40E-10 |
| RNA metabolic process | 0016070 | 5.70E-10 |
| biopolymer modification | 0043412 | 9.70E-10 |
| phosphotransferase activity, alcohol group as acceptor | 0016773 | 1.20E-09 |

| | | |
|--|---------|----------|
| kinase activity | 0016301 | 3.40E-09 |
| gene expression | 0010467 | 4.30E-09 |
| protein kinase activity | 0004672 | 4.50E-09 |
| intracellular organelle lumen | 0070013 | 5.10E-09 |
| post-translational protein modification | 0043687 | 8.10E-09 |
| protein metabolic process | 0019538 | 8.30E-09 |
| cellular protein metabolic process | 0044267 | 8.40E-09 |
| response to DNA damage stimulus | 0006974 | 1.10E-08 |
| helicase activity | 0004386 | 2.30E-08 |
| catalytic activity | 0003824 | 2.50E-08 |
| organelle lumen | 0043233 | 2.60E-08 |
| DNA repair | 0006281 | 3.20E-08 |
| membrane-enclosed lumen | 0031974 | 3.40E-08 |
| cellular response to DNA damage stimulus | 0006974 | 4.70E-08 |
| macromolecule biosynthetic process | 0009059 | 5.40E-08 |
| biopolymer biosynthetic process | 0009059 | 5.70E-08 |
| cellular response to stress | 0033554 | 6.60E-08 |
| cellular macromolecule biosynthetic process | 0034645 | 6.60E-08 |
| cellular macromolecule catabolic process | 0044265 | 7.10E-08 |
| protein amino acid phosphorylation | 0006468 | 7.80E-08 |
| ligase activity, forming carbon-nitrogen bonds | 0016879 | 8.50E-08 |
| macromolecule localization | 0033036 | 8.70E-08 |
| transition metal ion binding | 0046914 | 9.40E-08 |
| nucleoside-triphosphatase activity | 0017111 | 1.10E-07 |
| acid-amino acid ligase activity | 0016881 | 1.20E-07 |
| binding | 0005488 | 1.30E-07 |
| protein complex | 0043234 | 1.90E-07 |
| hydrolase activity, acting on acid anhydrides | 0016817 | 2.10E-07 |
| metabolic process | 0008152 | 2.40E-07 |
| pyrophosphatase activity | 0016462 | 2.80E-07 |
| organelle part | 0044422 | 2.90E-07 |
| ubiquitin thiolesterase activity | 0004221 | 2.90E-07 |
| macromolecule catabolic process | 0009057 | 3.10E-07 |
| ubiquitin-protein ligase activity | 0061630 | 3.20E-07 |
| protein localization | 0008104 | 9.00E-07 |
| protein transport | 0015031 | 1.40E-06 |
| establishment of protein localization | 0045184 | 1.50E-06 |
| ATP-dependent helicase activity | 0008026 | 1.50E-06 |
| GTPase activator activity | 0005096 | 2.00E-06 |
| cell cycle | 0007049 | 2.30E-06 |
| nucleoplasm part | 0044451 | 2.90E-06 |

| | | |
|---|---------|----------|
| GTPase regulator activity | 0030695 | 2.90E-06 |
| cellular response to stimulus | 0051716 | 3.00E-06 |
| RNA binding | 0003723 | 3.30E-06 |
| ATPase activity | 0016887 | 3.30E-06 |
| Ubiquitin mediated proteolysis | 0043161 | 4.10E-06 |
| nucleobase, nucleoside, nucleotide and nucleic acid transport | 0015931 | 5.40E-06 |
| DNA metabolic process | 0006259 | 6.10E-06 |
| nucleic acid transport | 0050657 | 6.40E-06 |
| transcription | 0003700 | 6.90E-06 |
| phosphate metabolic process | 0006796 | 7.10E-06 |
| hydrolase activity, acting on ester bonds | 0016788 | 8.10E-06 |
| macromolecular complex | 0032991 | 9.90E-06 |
| hydrolase activity | 0016787 | 1.20E-05 |
| transferase activity | 0016740 | 1.20E-05 |
| DNA binding | 0003677 | 1.40E-05 |
| regulation of gene expression | 0010468 | 1.50E-05 |
| intracellular transport | 0046907 | 1.90E-05 |
| cellular process | 0009987 | 2.00E-05 |
| chromosome organization | 0051276 | 2.10E-05 |
| DNA replication | 0006260 | 2.60E-05 |
| cellular protein localization | 0034613 | 2.60E-05 |
| ATPase activity, coupled | 0042623 | 2.80E-05 |
| small conjugating protein ligase activity | 0061659 | 2.90E-05 |
| intracellular protein transport | 0006886 | 3.00E-05 |
| microtubule organizing center | 0005815 | 3.30E-05 |
| thiolester hydrolase activity | 0016790 | 3.40E-05 |
| non-membrane-bounded organelle | 0043228 | 3.50E-05 |
| mRNA transport | 0051028 | 3.60E-05 |
| nuclear pore | 0005643 | 4.00E-05 |
| centrosome | 0005813 | 4.40E-05 |
| cell division | 0051301 | 4.50E-05 |
| regulation of macromolecule biosynthetic process | 0010556 | 5.30E-05 |
| RNA Degredation | 0000292 | 6.00E-05 |
| regulation of small GTPase mediated signal transduction | 0051056 | 6.70E-05 |
| RNA biosynthetic process | 0032774 | 6.70E-05 |
| RNA processing | 0006396 | 7.30E-05 |
| phosphorylation | 0016310 | 7.40E-05 |
| regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process | 0019219 | 7.60E-05 |
| cellular localization | 0051641 | 7.80E-05 |
| protein modification by small protein conjugation | 0032446 | 8.60E-05 |

| | | |
|--|---------|----------|
| cysteine-type peptidase activity | 0008234 | 8.80E-05 |
| organelle organization | 0006996 | 9.10E-05 |
| microtubule cytoskeleton | 0015630 | 9.90E-05 |
| mitotic cell cycle checkpoint | 0007093 | 1.00E-04 |
| cell cycle checkpoint | 0000075 | 1.00E-04 |
| transcription initiation from RNA polymerase II promoter | 0006367 | 1.00E-04 |
| regulation of cellular biosynthetic process | 0031326 | 1.00E-04 |
| regulation of biosynthetic process | 0009889 | 1.00E-04 |
| DNA-dependent DNA replication | 0006261 | 1.00E-04 |
| pore complex | 0046930 | 1.00E-04 |
| metal ion binding | 0046872 | 1.00E-04 |
| nucleotidyltransferase activity | 0016779 | 1.00E-04 |
| small GTPase regulator activity | 0030695 | 1.00E-04 |
| protein transporter activity | 0008565 | 1.00E-04 |
| DNA-directed DNA polymerase activity | 0003887 | 1.00E-04 |
| Cell cycle | 0007049 | 1.60E-04 |
| T cell receptor signalling pathway | 0050852 | 1.10E-03 |
| MAPKinase Signaling Pathway | 0008349 | 3.60E-03 |

Supplementary data table 4a GO of gene sets positively enriched in the 30-45 age group

| Term | GO Term number | P.Value |
|---|-----------------------|----------------|
| multicellular organismal process | 0032501 | 3.00E-15 |
| sequence-specific DNA binding | 0043565 | 2.10E-13 |
| extracellular region | 0005576 | 6.10E-12 |
| transcription factor activity | 0000989 | 3.10E-11 |
| anatomical structure morphogenesis | 0009653 | 2.70E-09 |
| system process | 0003008 | 3.10E-09 |
| anatomical structure development | 0048856 | 3.80E-09 |
| developmental process | 0032502 | 7.30E-09 |
| organ morphogenesis | 0009887 | 1.20E-08 |
| system development | 0048731 | 1.30E-08 |
| transcription regulator activity | 0030528 | 2.10E-08 |
| neuron differentiation | 0030182 | 2.50E-08 |
| multicellular organismal development | 0007275 | 2.80E-08 |
| neurogenesis | 0022008 | 3.40E-08 |
| organ development | 0048799 | 5.80E-08 |
| generation of neurons | 0048699 | 7.00E-08 |
| G-protein coupled receptor protein signaling pathway | 0007186 | 1.10E-07 |
| cell surface receptor linked signal transduction | 0007166 | 1.40E-07 |
| cell development | 0048468 | 2.50E-07 |
| cell fate commitment | 0045165 | 4.40E-07 |
| voltage-gated ion channel activity | 0005244 | 6.90E-07 |
| voltage-gated channel activity | 0022832 | 6.90E-07 |
| embryonic development ending in birth or egg hatching | 0009792 | 7.50E-07 |
| neurological system process | 0050877 | 9.10E-07 |
| cellular developmental process | 0048869 | 1.00E-06 |
| hormone activity | 0005179 | 1.00E-06 |
| cell differentiation | 0030154 | 1.10E-06 |
| substrate specific channel activity | 0022838 | 1.60E-06 |
| ion channel activity | 0005216 | 2.30E-06 |
| regulation of developmental process | 0050793 | 2.50E-06 |
| sensory organ development | 0007423 | 2.60E-06 |
| extracellular region part | 0044421 | 2.70E-06 |
| chordate embryonic development | 0043009 | 2.90E-06 |
| regulation of biological process | 0050789 | 3.20E-06 |
| embryonic skeletal system development | 0048706 | 3.40E-06 |
| regulation of growth | 0001558 | 3.40E-06 |
| axonogenesis | 0007409 | 3.60E-06 |
| gated channel activity | 0005244 | 4.10E-06 |

| | | |
|---|---------|----------|
| positive regulation of biological process | 0048518 | 4.60E-06 |
| nervous system development | 0007399 | 5.50E-06 |
| neurite morphogenesis | 0048812 | 6.60E-06 |
| G-protein coupled receptor activity | 0004930 | 8.60E-06 |
| cell morphogenesis involved in neuron differentiation | 0048667 | 8.70E-06 |
| embryonic skeletal system morphogenesis | 0048704 | 1.20E-05 |
| neuron development | 0048666 | 1.20E-05 |
| embryonic development | 0009790 | 1.20E-05 |
| potassium ion binding | 0030955 | 1.20E-05 |
| cell projection morphogenesis | 0048858 | 1.50E-05 |
| neuropeptide signaling pathway | 0007218 | 1.60E-05 |
| regulation of nervous system development | 0051960 | 1.60E-05 |
| biological regulation | 0051960 | 1.70E-05 |
| growth | 0040007 | 1.90E-05 |
| cell morphogenesis involved in differentiation | 0000904 | 2.00E-05 |
| regulation of transcription from RNA polymerase II promoter | 0006357 | 2.00E-05 |
| neuron fate commitment | 0048663 | 2.40E-05 |
| potassium channel activity | 0005267 | 2.70E-05 |
| neurite development | 0031175 | 2.90E-05 |
| positive regulation of cellular process | 0048522 | 3.00E-05 |
| regulation of cellular process | 0050794 | 3.00E-05 |
| regulation of cellular biosynthetic process | 0031326 | 3.20E-05 |
| cell-cell signaling | 0007267 | 4.40E-05 |
| positive regulation of developmental process | 0051094 | 6.70E-05 |
| regulation of cell development | 0060284 | 7.30E-05 |
| regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolic process | 0019219 | 7.60E-05 |
| alkali metal ion binding | 0031420 | 7.60E-05 |
| embryonic morphogenesis | 0048598 | 8.50E-05 |
| regulation of neuron differentiation | 0045664 | 9.00E-05 |
| skeletal system morphogenesis | 0048705 | 1.00E-04 |
| cation channel activity | 0005261 | 1.00E-04 |
| neuropeptide receptor activity | 0008188 | 1.00E-04 |
| Chondroitin sulfate biosynthesis | 0030206 | 3.10E-03 |

Supplementary data table 4b GO of gene sets negatively enriched in the 30-45 age group

| NAME | NES | NOM p-val |
|---|-------|-----------|
| KEGG_MTOR_SIGNALING_PATHWAY | 3.98 | 0.00 |
| BIOPOLYMER_METABOLIC_PROCESS | 3.98 | 0.00 |
| ORGANELLE_PART | 3.48 | 0.00 |
| INTRACELLULAR_ORGANELLE_PART | 3.43 | 0.00 |
| REACTOME_CELL_CYCLE_MITOTIC | 3.26 | 0.00 |
| NUCLEUS | 3.09 | 0.00 |
| MICROTUBULE_CYTOSKELETON | 2.96 | 0.00 |
| PROTEIN_SERINE_THREONINE_KINASE_ACTIVITY | 2.94 | 0.00 |
| TRANSFERASE_ACTIVITY_TRANSFERRING_PHOSPHORUS_CONTAINING_GROUPS | 2.81 | 0.00 |
| CHR4Q31 | 2.79 | 0.00 |
| NUCLEOPLASM | 2.72 | 0.00 |
| NUCLEAR_PART | 2.72 | 0.00 |
| PROTEIN_MODIFICATION_PROCESS | 2.60 | 0.00 |
| BIOPOLYMER_MODIFICATION | 2.59 | 0.00 |
| NUCLEOBASENUCLEOSIDENUCLEOTIDE_AND_NUCLEIC_ACID_METABOLIC_PROCESS | 2.58 | 0.00 |
| MICROTUBULE_ORGANIZING_CENTER | 2.56 | 0.00 |
| CHR1P22 | 2.56 | 0.00 |
| REACTOME_LATE_PHASE_OF_HIV_LIFE_CYCLE | 2.56 | 0.00 |
| DNA_METABOLIC_PROCESS | 2.51 | 0.00 |
| RECEPTOR_ACTIVITY | -2.51 | 0.000 |
| OXIDOREDUCTASE_ACTIVITY_ACTING_ON_CH_OH_GROUP_OF_DONORS | -2.53 | 0.000 |
| INTEGRAL_TO_PLASMA_MEMBRANE | -2.63 | 0.000 |
| CHR11Q12 | -2.64 | 0.000 |
| G_PROTEIN_COUPLED_RECEPTOR_ACTIVITY | -2.69 | 0.000 |
| TGFBETA EARLY UP | -2.70 | 0.000 |
| INTRINSIC_TO_PLASMA_MEMBRANE | -2.72 | 0.000 |
| MULTICELLULAR_ORGANISMAL_DEVELOPMENT | -2.78 | 0.000 |
| REACTOME_RNA_POLYMERASE_I_PROMOTER_OPENING | -2.80 | 0.000 |
| SYSTEM_PROCESS | -2.81 | 0.000 |
| SYSTEM_DEVELOPMENT | -2.82 | 0.000 |
| REACTOME_PACKAGING_OF_TELOMERE_ENDS | -2.83 | 0.000 |
| ANATOMICAL_STRUCTURE_DEVELOPMENT | -2.85 | 0.000 |
| CELL_CELL_SIGNALING | -2.86 | 0.000 |
| PLASMA_MEMBRANE_PART | -2.89 | 0.000 |
| KEGG_NEUROACTIVE_LIGAND_RECEPTOR_INTERACTION | -2.97 | 0.000 |
| CHR17Q25 | -3.01 | 0.000 |
| REACTOME_PEPTIDE_LIGAND_BINDING_RECEPTORS | -3.02 | 0.000 |
| REACTOME_G_ALPHA_I_SIGNALLING_EVENTS | -3.02 | 0.000 |
| REACTOME_DOWNSTREAM_EVENTS_IN_GPCR_SIGNALING | -3.03 | 0.000 |
| CHR16P11 | -3.04 | 0.000 |
| CHR1P36 | -3.05 | 0.000 |

| | | |
|--|-------|-------|
| KEGG_SYSTEMIC_LUPUS_ERYTHEMATOSUS | -3.06 | 0.000 |
| CHR16P13 | -3.08 | 0.000 |
| RHODOPSIN_LIKE_RECEPTOR_ACTIVITY | -3.10 | 0.000 |
| EXTRACELLULAR_SPACE | -3.12 | 0.000 |
| G_PROTEIN_COUPLED_RECEPTOR_PROTEIN_SIGNALING_PATHWAY | -3.12 | 0.000 |
| PLASMA_MEMBRANE | -3.20 | 0.000 |
| CHR17P13 | -3.49 | 0.000 |
| CHR11Q13 | -3.76 | 0.000 |
| EXTRACELLULAR_REGION_PART | -3.79 | 0.000 |
| REACTOME_CLASS_A1_RHODOPSIN_LIKE_RECEPTORS | -3.85 | 0.000 |
| OXIDOREDUCTASE_ACTIVITY | -3.88 | 0.000 |
| EXTRACELLULAR_REGION | -4.04 | 0.000 |
| CHR19Q13 | -4.16 | 0.000 |
| REACTOME_GPCR_LIGAND_BINDING | -4.60 | 0.000 |
| CHR19P13 | -4.83 | 0.000 |
| KEGG_OLFACTORY_TRANSDUCTION | -5.67 | 0.000 |
| REACTOME_OLFACTORY_SIGNALING_PATHWAY | -5.81 | 0.000 |

Supplementary data Table 4c GSEA of gene sets positively and negatively enriched in the 30-45 age group

| | | |
|---|----------|-----|
| Cadmium Ion Binding | 9.40E-11 | 200 |
| Antigen Processing And Presentation Of Peptide Via Mhc Class Ii | 1.40E-05 | 36 |
| Immune System Process | 3.20E-05 | 2.8 |
| Copper Ion Binding | 3.60E-05 | 11 |
| Basal Part Of Cell | 5.90E-05 | 23 |
| IgG Binding | 6.00E-05 | 58 |
| Endopeptidase Inhibitor Activity | 6.30E-05 | 6.5 |
| B Cell Mediated Immunity | 6.70E-05 | 9.8 |
| Peptidase Inhibitor Activity | 9.20E-05 | 6.2 |
| Response To Muscle Activity | 1.30E-04 | Inf |
| Mhc Class Ii Protein Complex | 1.30E-04 | 42 |
| Myeloid Cell Differentiation | 1.50E-04 | 5.7 |
| Inflammatory Response | 2.10E-04 | 3.7 |
| Response To Wounding | 2.20E-04 | 3.2 |
| Enzyme Inhibitor Activity | 2.40E-04 | 4.3 |
| Acute Inflammatory Response | 2.80E-04 | 7.4 |
| Antigen Processing And Presentation | 3.10E-04 | 9.5 |
| Immune Response | 3.20E-04 | 2.7 |
| Hemidesmosome | 3.20E-04 | 190 |
| Immunoglobulin Receptor Activity | 3.20E-04 | 190 |
| Cell Differentiation | 3.70E-04 | 2.2 |
| Pattern Recognition Receptor Activity | 3.70E-04 | 26 |
| Cellular Developmental Process | 4.00E-04 | 2.2 |
| Regulation Of Cell Differentiation | 4.30E-04 | 3.4 |
| T Cell Selection | 4.60E-04 | 24 |
| Immunoglobulin Binding | 4.60E-04 | 24 |
| Lymphocyte Mediated Immunity | 5.20E-04 | 6.5 |
| Hematopoiesis | 5.50E-04 | 3.8 |
| Immunoglobulin Mediated Immune Response | 5.60E-04 | 8.2 |
| Regulation Of Immune System Process | 5.60E-04 | 3.6 |
| Response To Biotic Stimulus | 7.10E-04 | 3.4 |
| Regulation Of Developmental Process | 8.00E-04 | 2.3 |
| Basal Plasma Membrane | 8.00E-04 | 19 |
| Mhc Protein Binding | 8.00E-04 | 19 |
| Adaptive Immune Response | 8.20E-04 | 5.9 |
| Response To Other Organism | 8.70E-04 | 3.9 |
| Hemopoietic Or Lymphoid Organ Development | 9.40E-04 | 3.6 |

Supplementary data table 5a GO of transcripts changing across the lifespan using a regression analysis

| NAME | NES | NOM p-val |
|---|------|-----------|
| NUCLEAR_PART | 4.64 | 0.000 |
| PROGRAMMED_CELL_DEATH | 4.56 | 0.000 |
| REGULATION_OF_TRANSCRIPTION | 4.49 | 0.000 |
| APOPTOSIS_GO | 4.48 | 0.000 |
| STRUCTURAL_CONSTITUENT_OF_RIBOSOME | 4.44 | 0.000 |
| TRANSCRIPTION_FROM_RNA_POLYMERASE_II_PROMOTER | 4.43 | 0.000 |
| RNA_BINDING | 4.37 | 0.000 |
| ORGANELLE_MEMBRANE | 4.36 | 0.000 |
| REGULATION_OF_PROGRAMMED_CELL_DEATH | 4.14 | 0.000 |
| OXIDOREDUCTASE_ACTIVITY | 4.10 | 0.000 |
| MITOCHONDRION | 4.09 | 0.000 |
| STRUCTURAL_MOLECULE_ACTIVITY | 4.07 | 0.000 |
| REGULATION_OF_APOPTOSIS | 4.06 | 0.000 |
| EXTRACELLULAR_REGION | 3.97 | 0.000 |
| CELLULAR_LOCALIZATION | 3.92 | 0.000 |
| INTRACELLULAR_TRANSPORT | 3.92 | 0.000 |
| REGULATION_OF_RNA_METABOLIC_PROCESS | 3.90 | 0.000 |
| ORGANELLE_LUMEN | 3.89 | 0.000 |
| MEMBRANE_ENCLOSED_LUMEN | 3.87 | 0.000 |
| ESTABLISHMENT_OF_CELLULAR_LOCALIZATION | 3.86 | 0.000 |
| NEGATIVE_REGULATE_CELLULAR_METABOLIC_PROCESS | 3.84 | 0.000 |
| REGULATION_OF_DEVELOPMENTAL_PROCESS | 3.83 | 0.000 |
| EXTRACELLULAR_REGION_PART | 3.80 | 0.000 |
| NEGATIVE_REGULATION_OF_METABOLIC_PROCESS | 3.79 | 0.000 |
| NUCLEAR_LUMEN | 3.78 | 0.000 |
| BIOSYNTHETIC_PROCESS | 3.78 | 0.000 |
| REGULATION_OF_TRANSCRIPTIONDNA_DEPENDENT | 3.76 | 0.000 |
| CELL_PROLIFERATION_GO_0008283 | 3.74 | 0.000 |
| IDENTICAL_PROTEIN_BINDING | 3.74 | 0.000 |
| ORGANELLE_ORGANIZATION_AND_BIOGENESIS | 3.72 | 0.000 |
| REGULATION_OF_BIOLOGICAL_QUALITY | 3.72 | 0.000 |
| VESICLE_MEDIATED_TRANSPORT | 3.70 | 0.000 |
| ENDOMEMBRANE_SYSTEM | 3.66 | 0.000 |
| CELLULAR_BIOSYNTHETIC_PROCESS | 3.63 | 0.000 |
| REGULATION_OF_TRANSCRIPTION_FROM_RNA_POLYMERASE_II_PROMOTER | 3.63 | 0.000 |
| MACROMOLECULAR_COMPLEX_ASSEMBLY | 3.62 | 0.000 |
| IMMUNE_SYSTEM_PROCESS | 3.62 | 0.000 |
| NEGATIVE_REGULATION_OF_TRANSCRIPTION | 3.62 | 0.000 |
| PROTEIN_KINASE_CASCADE | 3.60 | 0.000 |
| NEGATIVE_REGULATION_OF_APOPTOSIS | 3.56 | 0.000 |
| NEGATIVE_REGULATION_OF_PROGRAMMED_CELL_DEATH | 3.55 | 0.000 |

| | | |
|--|------|-------|
| CELLULAR_COMPONENT_ASSEMBLY | 3.54 | 0.000 |
| CELLULAR_LIPID_METABOLIC_PROCESS | 3.54 | 0.000 |
| REGULATION_OF_SIGNAL_TRANSDUCTION | 3.52 | 0.000 |
| ANTI_APOPTOSIS | 3.48 | 0.000 |
| REGULATION_OF_CELL_PROLIFERATION | 3.45 | 0.000 |
| ENDOPLASMIC_RETICULUM | 3.43 | 0.000 |
| CELL_FRACTION | 3.43 | 0.000 |
| NEGATIVE_REGULATION_OF_NUCLEOBASENUCLEOSIDENUCL EOTIDE_AND_NUCLEIC_ACID_METABOLIC_PROCESS | 3.42 | 0.000 |
| TRANSLATION | 3.40 | 0.000 |
| MACROMOLECULE_LOCALIZATION | 3.38 | 0.000 |
| ENZYME_REGULATOR_ACTIVITY | 3.38 | 0.000 |
| TRANSCRIPTION_FACTOR_BINDING | 3.36 | 0.000 |
| ORGANELLE_ENVELOPE | 3.35 | 0.000 |
| IMMUNE_RESPONSE | 3.34 | 0.000 |
| NUCLEOPLASM | 3.34 | 0.000 |
| PROTEINACEOUS_EXTRACELLULAR_MATRIX | 3.31 | 0.000 |
| EXTRACELLULAR_MATRIX | 3.31 | 0.000 |
| RNA_PROCESSING | 3.30 | 0.000 |
| NEGATIVE_REGULATION_OF_DEVELOPMENTAL_PROCESS | 3.26 | 0.000 |
| MACROMOLECULE_BIOSYNTHETIC_PROCESS | 3.23 | 0.000 |
| LIPID_METABOLIC_PROCESS | 3.22 | 0.000 |
| ENVELOPE | 3.21 | 0.000 |
| ORGANIC_ACID_METABOLIC_PROCESS | 3.20 | 0.000 |
| EXCRETION | 3.19 | 0.000 |
| MEMBRANE_FRACTION | 3.14 | 0.000 |
| RNA_POLYMERASE_II_TRANSCRIPTION_FACTOR_ACTIVITY | 3.14 | 0.000 |
| MULTI_ORGANISM_PROCESS | 3.13 | 0.000 |
| CARBOXYLIC_ACID_METABOLIC_PROCESS | 3.13 | 0.000 |
| I_KAPPAB_KINASE_NF_KAPPAB_CASCADE | 3.12 | 0.000 |
| TRANSCRIPTION_COFACTOR_ACTIVITY | 3.12 | 0.000 |
| CYTOSOL | 3.11 | 0.000 |
| REGULATION_OF_MOLECULAR_FUNCTION | 3.10 | 0.000 |
| CYTOSKELETON | 3.07 | 0.000 |
| PROTEIN_LOCALIZATION | 3.06 | 0.000 |
| RESPONSE_TO_STRESS | 3.06 | 0.000 |
| POST_TRANSLATIONAL_PROTEIN_MODIFICATION | 3.06 | 0.000 |
| PROTEIN_BINDING_BRIDGING | 3.05 | 0.000 |
| POSITIVE_REGULATION_OF_SIGNAL_TRANSDUCTION | 3.04 | 0.000 |
| CYTOSKELETAL_PROTEIN_BINDING | 3.01 | 0.000 |
| GTPASE_REGULATOR_ACTIVITY | 3.01 | 0.000 |
| REGULATION_OF_I_KAPPAB_KINASE_NF_KAPPAB_CASCADE | 3.00 | 0.000 |

Supplementary data table 5b. Gene Set Enrichment Analysis upregulated with increasing age using a regression analysis