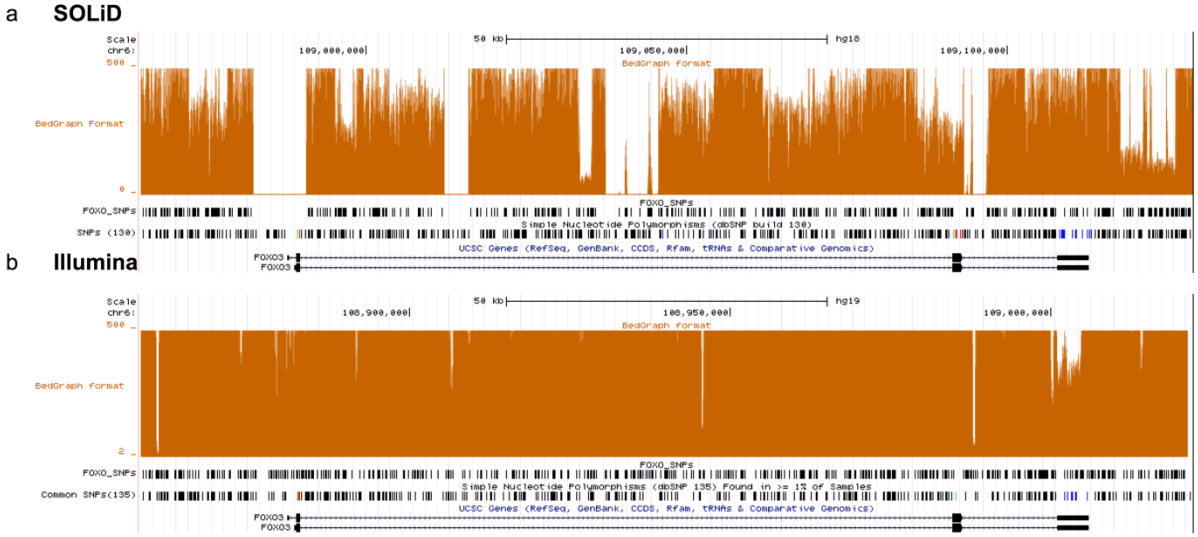
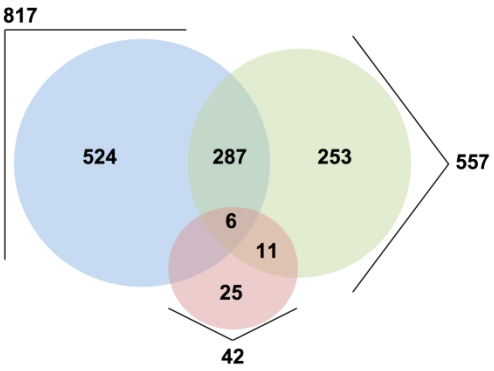
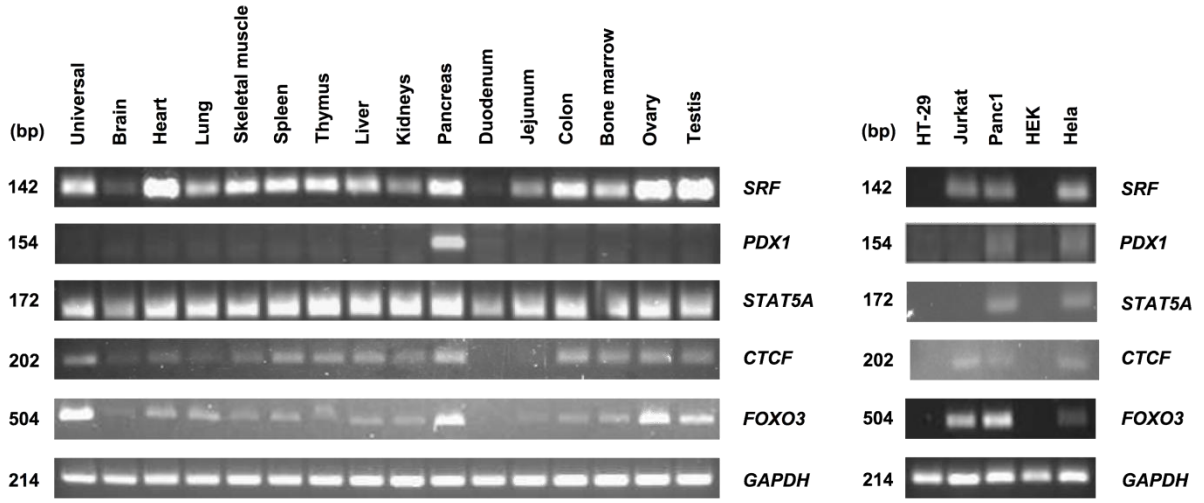



**Supplementary Figure 1.** Sequence coverage of the *FOXO3* gene region using SOLiD sequencing by ligation (SBL) **(a)** and Illumina sequencing by synthesis (SBS) **(b)** technology. SBL resulted in incomplete sequencing reads in some gene regions due to gaps in the long-range PCR products **(a)**. The regions which remained uncovered applying SBL (mainly before and after the 5´UTR and within the last two exons) were closed with SBS technology **(b)**, which resulted in a fully covered *FOXO3* gene region without any gaps. While with SBL 80% of the target sequence was covered with 50-fold coverage, SBS sequencing yielded a 30-fold coverage of 99% of the target region sequenced. This figure was created using UCSC Genome Browser (http://genome.ucsc.edu/[1]).

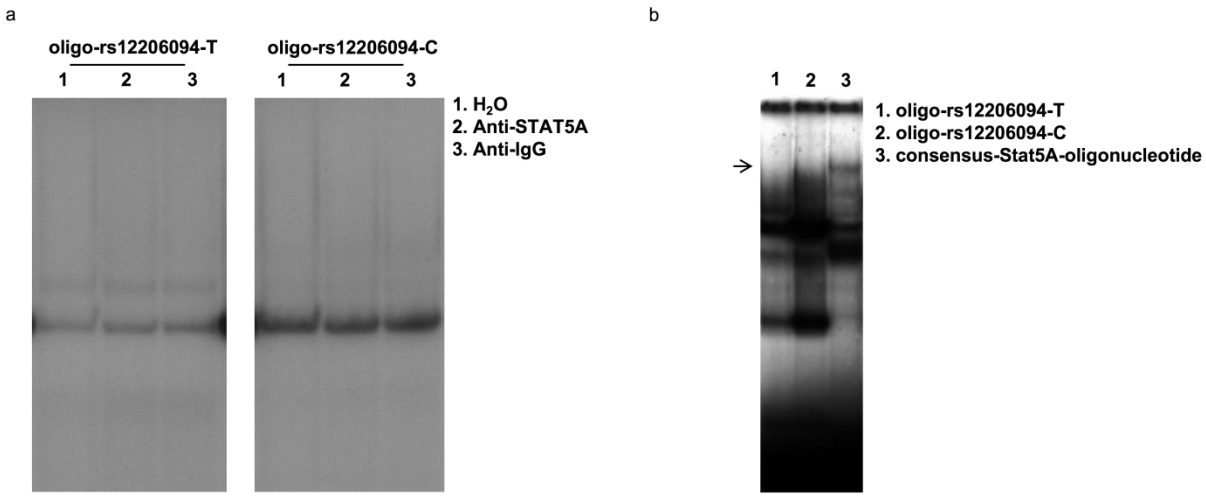
| *FOXO3* resequencing | Sequencing technology | | |
|---|---|---|---|
| | **SOLiD**<br>34 LLI<br>22 C | **Illumina**<br>48 LLI<br>46 C | **Sanger**<br>138 LLI<br>92 C |
| Whole gene region | x | x | - |
| Promoter | x | x | x |
| Exons | x | x | x |
| Number of detected SNVs | 817 | 557 | 42 |



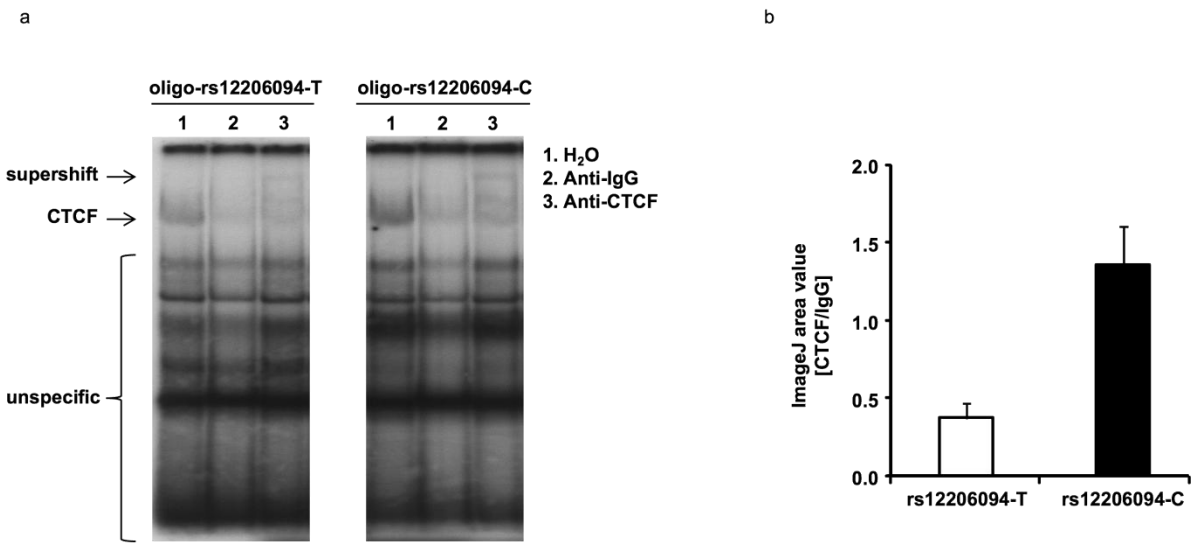

**Supplementary Figure 2.** Number of detected SNVs in the *FOXO3* gene region using SOLiD sequencing by ligation (SBL, blue), Illumina sequencing by synthesis (SBS, green) and Sanger (red) technology and overlap between the three sequencing technologies. SBL and SBS yielded 293 overlapping SNVs; 524 SNVs were only detected with SBL and 264 SNVs only with SBS. Sanger sequencing yielded 42 SNVs in total; of the 42 SNVs, 17 were also detected with SBS and of these, 6 with all three sequencing technologies. C, younger control group; LLI, long-lived individuals; SNV, single nucleotide variant.




**Supplementary Figure 3.** Gene expression pattern of *SRF*, *PDX1*, *STAT5A*, *CTCF*, and *FOXO3* in various tissues and cell lines. The expression of *GAPDH* served as control. bp, base pairs; *CTCF*, CCCTC-binding factor; *FOXO3*, forkhead box O3; *GAPDH*, glyceraldehyde-3-phosphate dehydrogenase; HEK, human embryonic kidney cell line; Hela, human epithelial carcinoma cell line; HT-29, human colon adenocarcinoma cell line; Jurkat, human acute lymphocytic leukemia cell line; Panc1, human pancreatic epithelial carcinoma cell line; *PDX1*, pancreatic and duodenal homeobox 1; SRF, serum response factor; *STAT5A*, signal transducer and activator of transcription 5A; universal, mix of 20 different human tissues.

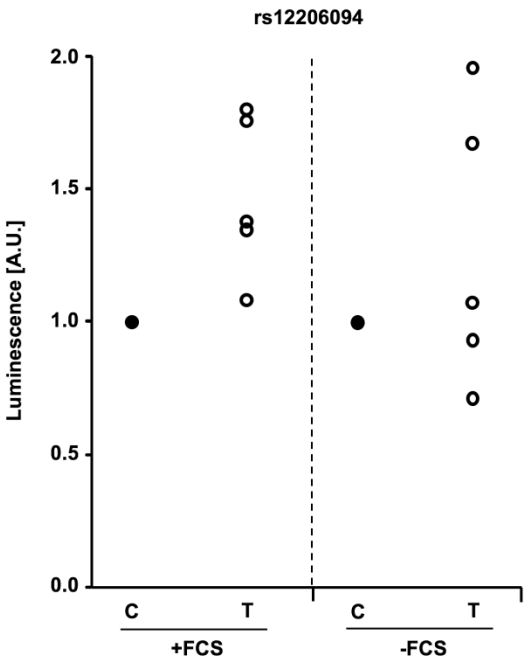



**Supplementary Figure 4.** STAT5A does not bind to the *FOXO3* rs12206094 alleles. **(a)** Nuclear extracts from Panc1 cells were submitted to EMSA with 32-P labeled oligonucleotides containing the longevity allele T (left) or the major allele C (right) of rs12206094. Supershift experiments were performed with the indicated antibodies. One biological replicate of five is shown. **(b)** A consensus-*Stat5A*-oligonucleotide generates, in contrast to rs12206094 oligonucleotides, a specific band in the EMSA (indicated by an arrow). One biological replicate of three is shown. IgG, immunoglobulin G; STAT5A, signal transducer and activator of transcription 5A.




**Supplementary Figure 5.** CTCF shows stronger binding to the rs12206094-C- than to the rs12206094-T-oligonucleotide. **(a)** Nuclear extracts from Jurkat cells were submitted to EMSA with the indicated oligonucleotides. Supershift experiments were performed with the labeled antibodies. The position of the supershifted complex is indicated by an arrow. One biological replicate of four is shown. **(b)** Densitometry of the CTCF-specific band against control + S.D., n=4 independent experiments. CTCF, CCCTC-binding factor; IgG, immunoglobulin G; S.D., standard deviation.

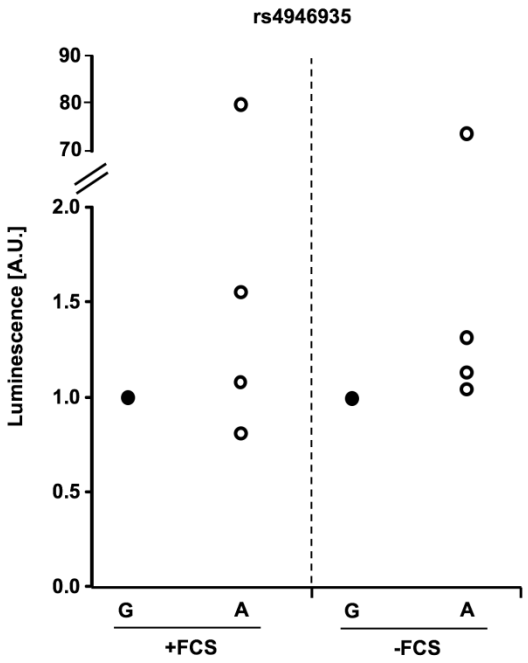
a




| | Luminescence [A.U.] rs12206094-T/rs12206094-C | |
|---|---|---|
| | +FCS | -FCS |
| **Median** | 1.39* | 1.08 |
| **Min** | 1.08 | 0.71 |
| **Max** | 1.81 | 1.97 |

*, $P < 0.05$
(two-sided Wilcoxon signed-rank test for paired data)

b

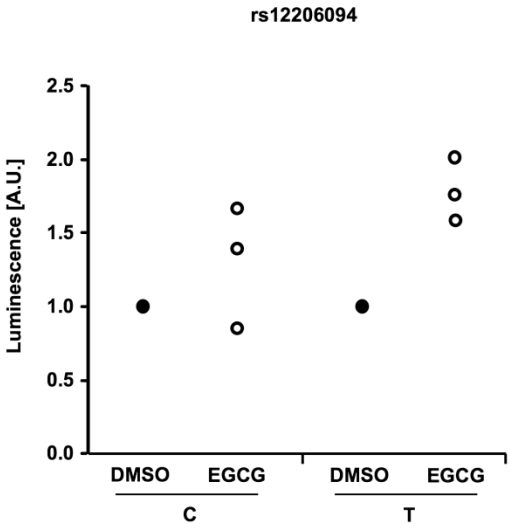



| | Luminescence [A.U.] rs4946935-A/rs4946935-G | |
|---|---|---|
| | +FCS | -FCS |
| **Median** | 1.33 | 1.23$^{n.s.}$ |
| **Min** | 0.81 | 1.05 |
| **Max** | 79.8 | 73.5 |

**n.s.**, $P = 0.068$
(two-sided Wilcoxon signed-rank test for paired data)

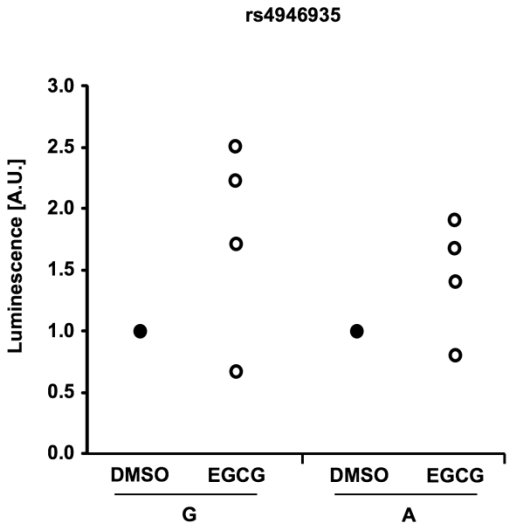
**Supplementary Figure 6.** In Jurkat cells, the *FOXO3* SNVs rs12206094 and rs4946935 influence luciferase promoter activity in an allele-specific manner either in presence (rs12206094, **(a)**) or in absence (rs4946935, **(b)**) of FCS. **(a, b)** For both SNVs, the promoter activity in cells transfected with constructs containing the respective major allele was set = 1 (black dot). Each white dot represents one independent experiment (6a: n = 5, 6b: n = 4). The tables below the figures show the median as well as the minimum and maximum values of the ratio of the longevity allele to the respective alternative allele, taking into account all experiments. For determination of specific luciferase activity, activity of the firefly luciferase was normalized to the activity of the renilla luciferase. A.U., arbitrary luminescence units.

7a



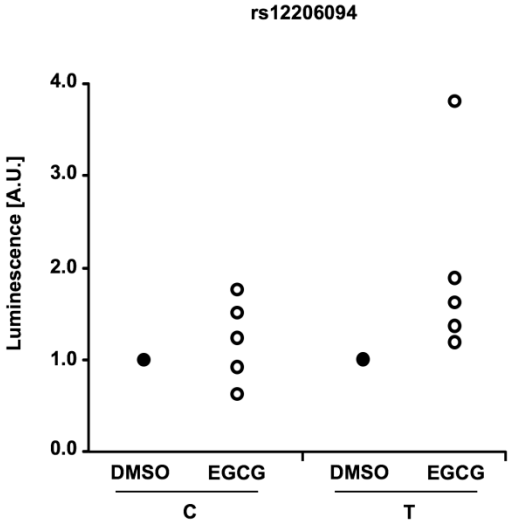

| | Luminescence [A.U.] DMSO/50 µM EGCG | |
|---|---|---|
| | rs12206094-C | rs12206094-T |
| **Median** | 1.40 | 1.77 |
| **Min** | 0.86 | 1.59 |
| **Max** | 1.68 | 2.03 |

7b




| | Luminescence [A.U.] DMSO/50 µM EGCG | |
|---|---|---|
| | rs4946935-G | rs4946935-A |
| **Median** | 1.96 | 1.55 |
| **Min** | 0.69 | 0.82 |
| **Max** | 2.52 | 1.91 |

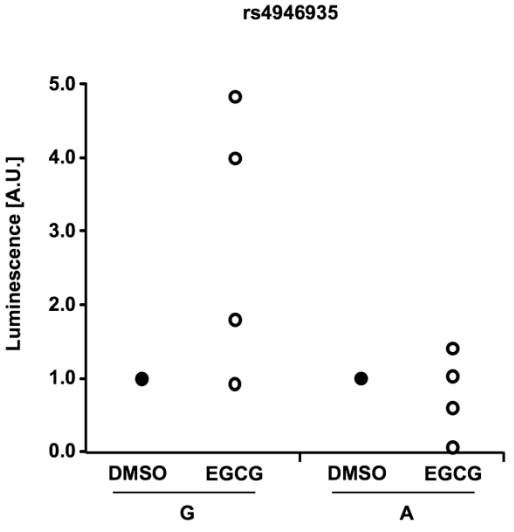
7c




| | Luminescence [A.U.] DMSO/50 µM EGCG | |
|---|---|---|
| | rs12206094-C | rs12206094-T |
| **Median** | 1.25 | 1.63* |
| **Min** | 0.64 | 1.20 |
| **Max** | 1.77 | 3.82 |

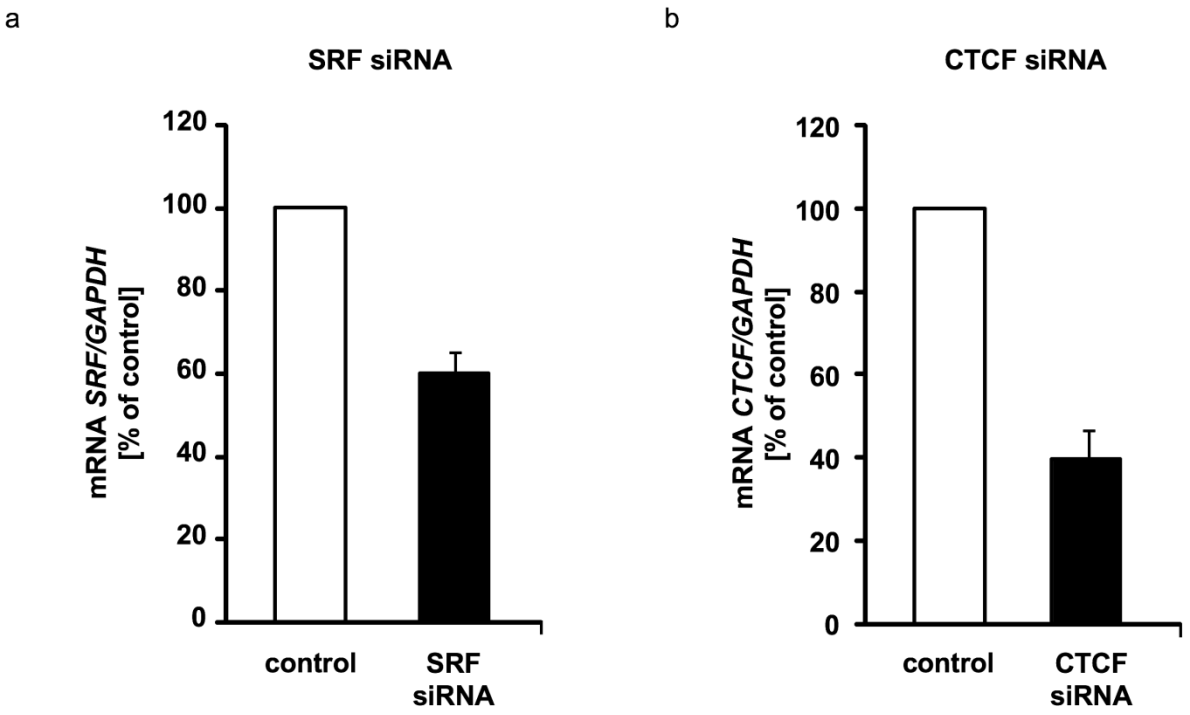
*, $P < 0.05$ *vs.* respective DMSO control (two-sided Wilcoxon signed-rank test for paired data)

7d

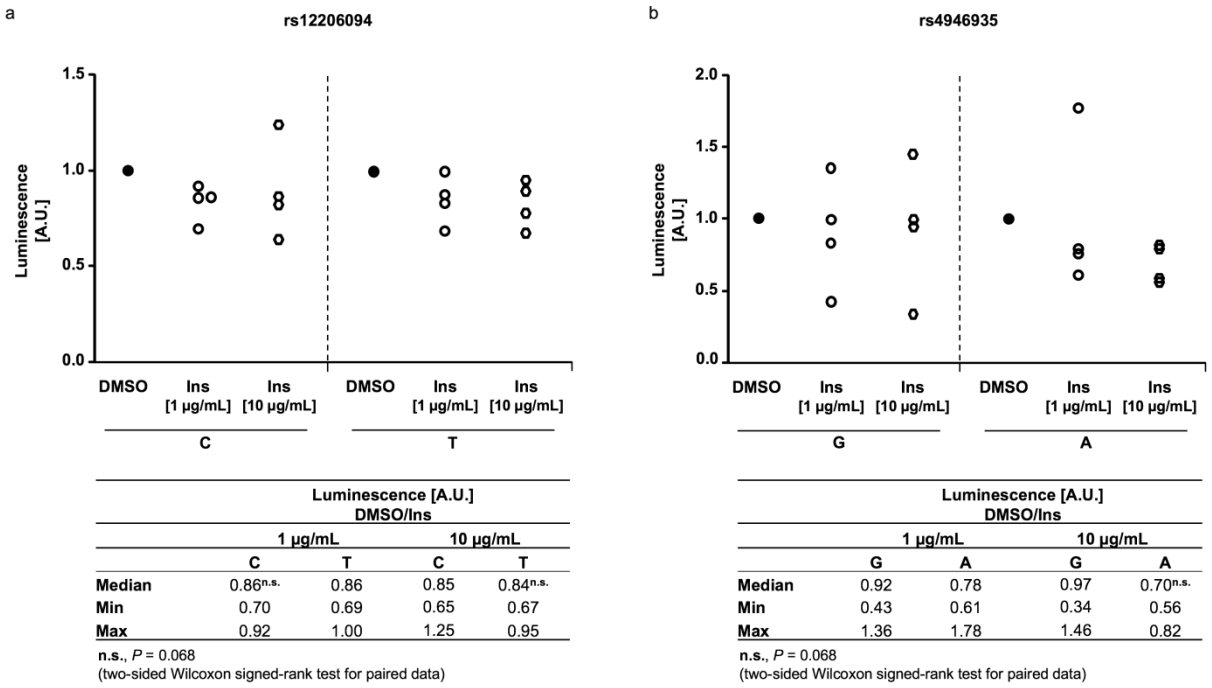



| | Luminescence [A.U.] DMSO/50 µM EGCG | |
|---|---|---|
| | rs4946935-G | rs4946935-A |
| **Median** | 2.91 | 0.83 |
| **Min** | 0.94 | 0.07 |
| **Max** | 4.84 | 1.42 |

**Supplementary Figure 7.** Effect of epigallocatechingallate (EGCG) on luciferase promoter activity in Panc1 **(7a, 7b)** and Jurkat **(7c, 7d)** cells. **(7a-7d)** In both cell lines, the activity of cells treated with DMSO instead of EGCG was set = 1 (black dot) for each allele of each SNV. Each white dot represents one independent experiment (n = 3 **(7a)** and n=4 **(7b)** for Panc1 cells and n = 5 **(7c)** and n = 4 **(7d)** for Jurkat cells). Final DMSO concentrations did not exceed 0.1%. The tables below the figures show the median as well as the minimum and maximum values for the ratios of the activity in presence of DMSO and 50 µM EGCG for each allele, taking into account all experiments. For determination of specific luciferase activity, activity of the firefly luciferase was normalized to the activity of the renilla luciferase. A.U., arbitrary luminescence units; EGCG, epigallocatechingallate.




**Supplementary Figure 8.** Verification of transcription factor knockdown in Panc1 cells at the time of luciferase assay (six days after siRNA transfection). Shown is the mRNA expression of SRF **(a)** and CTCF **(b)** in the cells transfected with the transcription factor-specific siRNA in percent of control siRNA-transfected cells, whose expression was set 100%. Data are means + S.E.M; n=4 independent experiments; CTCF, CCCTC-binding factor; SRF, serum response factor; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.




| Luminescence [A.U.] DMSO/Ins | 1 µg/mL | | 10 µg/mL | |
|---|---|---|---|---|
| | C | T | C | T |
| Median | 0.86$^{n.s.}$ | 0.86 | 0.85 | 0.84$^{n.s.}$ |
| Min | 0.70 | 0.69 | 0.65 | 0.67 |
| Max | 0.92 | 1.00 | 1.25 | 0.95 |

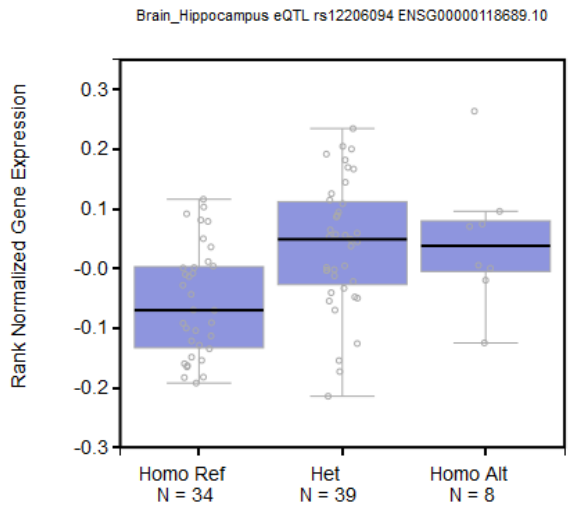
**n.s.**, $P = 0.068$
(two-sided Wilcoxon signed-rank test for paired data)

| Luminescence [A.U.] DMSO/Ins | 1 µg/mL | | 10 µg/mL | |
|---|---|---|---|---|
| | G | A | G | A |
| Median | 0.92 | 0.78 | 0.97 | 0.70$^{n.s.}$ |
| Min | 0.43 | 0.61 | 0.34 | 0.56 |
| Max | 1.36 | 1.78 | 1.46 | 0.82 |

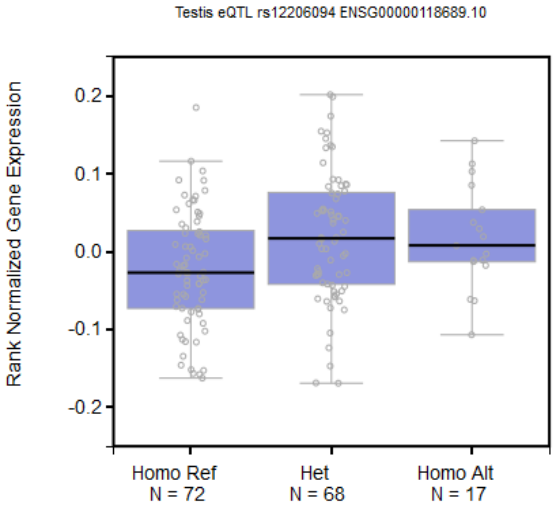
**n.s.**, $P = 0.068$
(two-sided Wilcoxon signed-rank test for paired data)

**Supplementary Figure 9.** Effect of 1 µg/mL and 10 µg/mL, respectively, insulin on luciferase promoter activity in Panc1 cells in presence of either allele of rs12206094 (**a**) and rs4946935 (**b**). (**a, b**) The activity of cells treated with DMSO instead of insulin was set = 1 (black dot) for each allele of each SNV. Each white dot represents one independent experiment (n = 4). Final DMSO concentrations did not exceed 0.1%. The duration of insulin treatment was 48 hours. The tables below the figures show the median as well as the minimum and maximum values for the ratios of the activity in presence of DMSO and 1 µg/mL or 10 µg/mL insulin, respectively, for each allele, taking into account all experiments. For determination of specific luciferase activity, activity of the firefly luciferase was normalized to the activity of the renilla luciferase. A.U., arbitrary luminescence units.

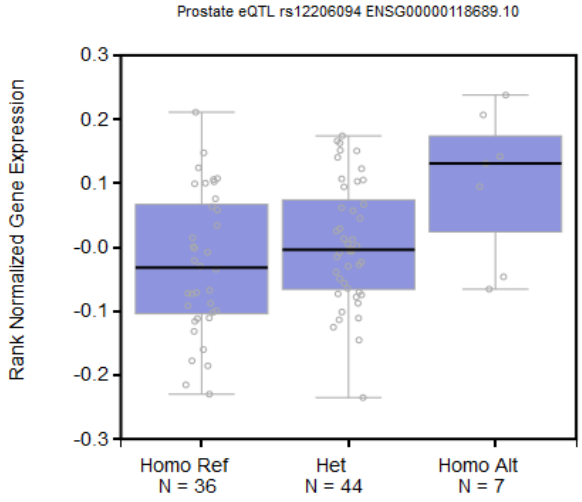
**10a** SNV rs12206094; SNV alleles: C/T; minor allele (= Homo Alt): T



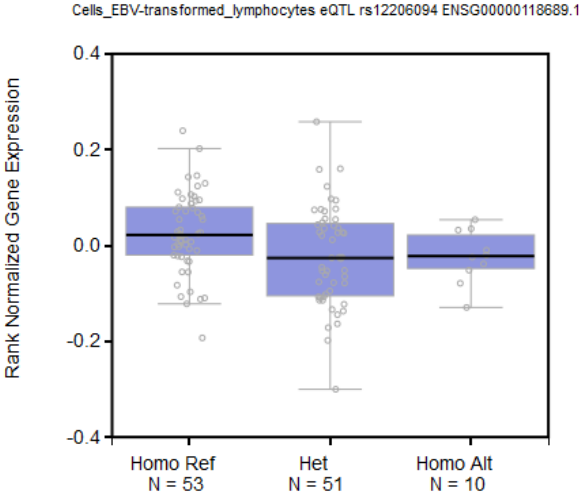

**eQTL *P*-value = 4.1E-4**



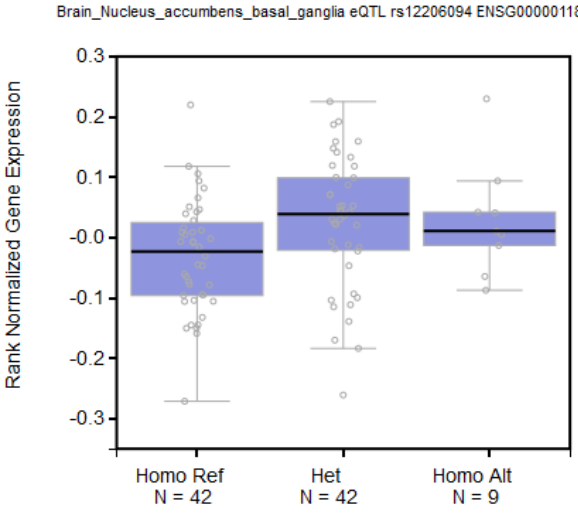

**eQTL *P*-value = 0.0037**



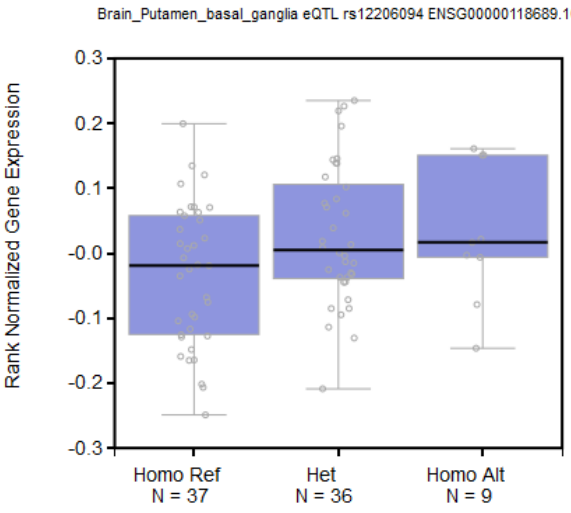

**eQTL *P*-value = 0.007**




**eQTL *P*-value = 0.01**

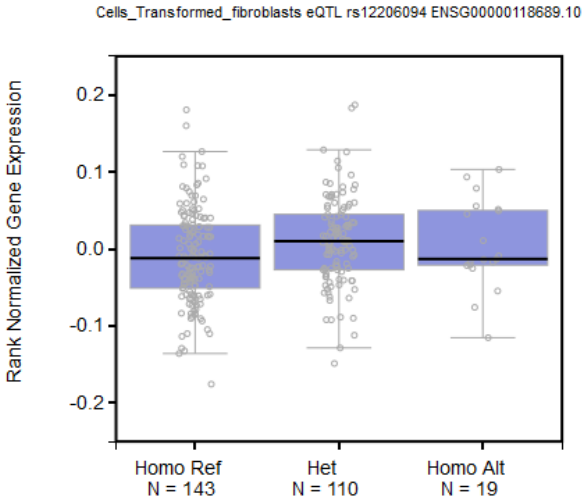



**eQTL *P*-value = 0.013**

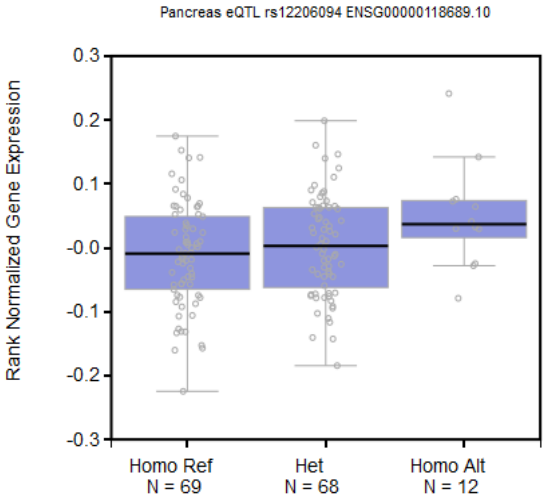



**eQTL *P*-value = 0.023**

**10a** *cont.*

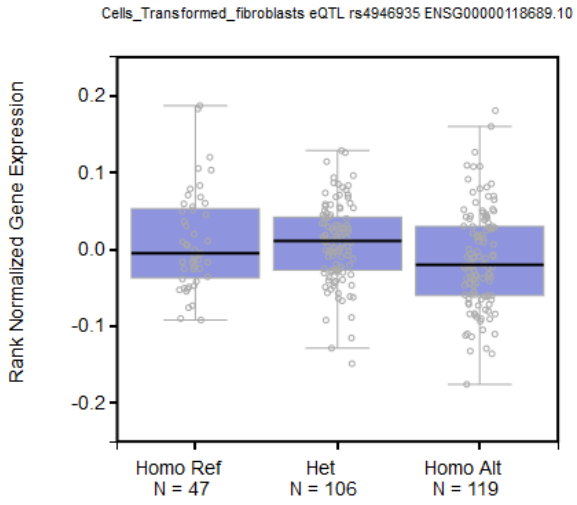



**eQTL *P*-value = 0.024**

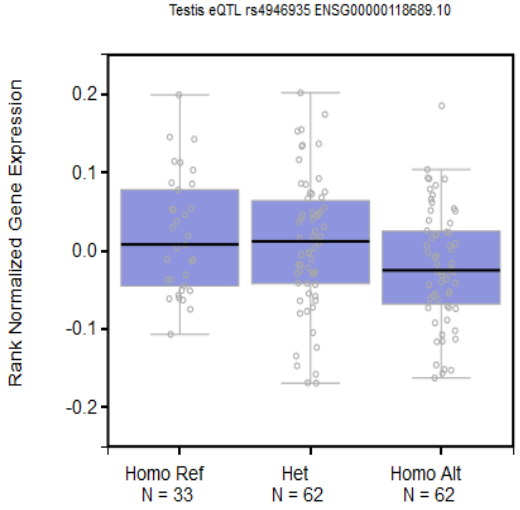



**eQTL *P*-value = 0.026**

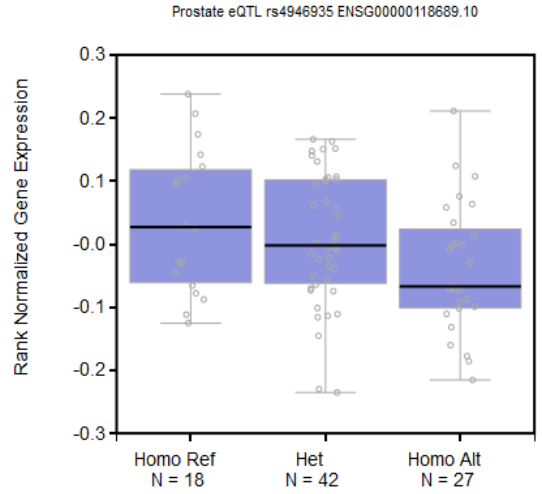
**10b** SNV rs4946935; SNV alleles: A/G; minor allele (= Homo Ref): A



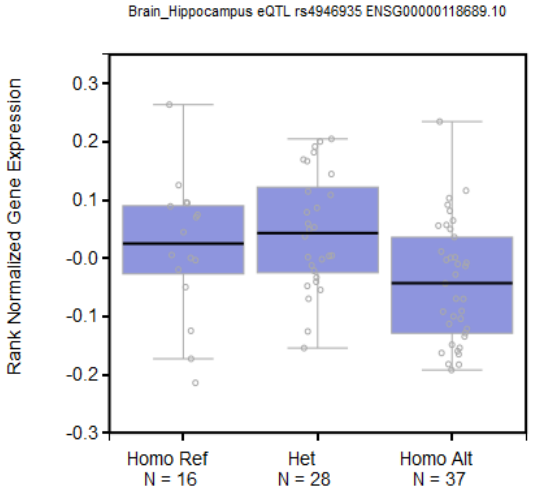

**eQTL *P*-value = 0.002**



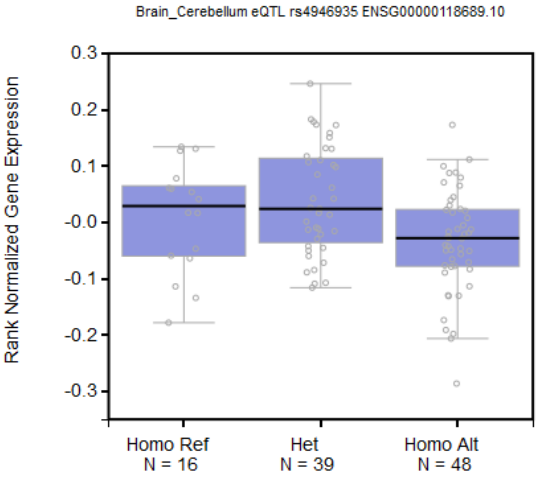

**eQTL *P*-value = 0.0053**




**eQTL *P*-value = 0.0094**

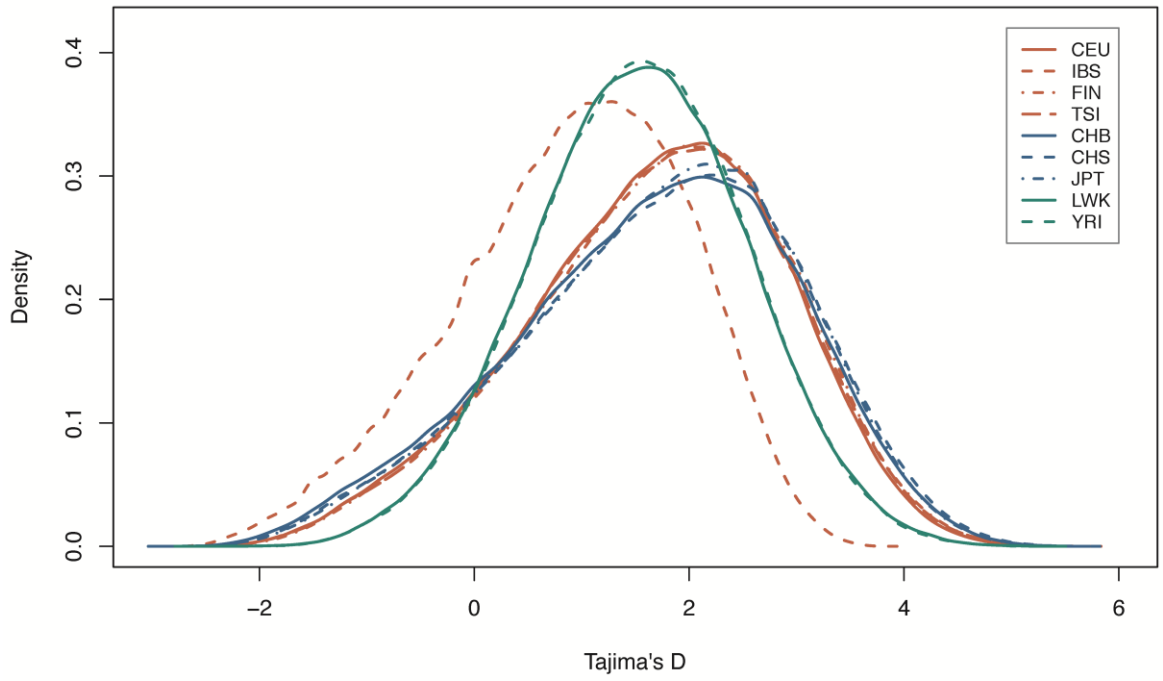



**eQTL *P*-value = 0.0098**




**eQTL *P*-value = 0.012**

**Supplementary Figure 10.** eQTL box plots for the two top-associated SNVs rs12206094 **(a)** or rs4946935 **(b)** and *FOXO3* in different tissues generated with the "Test Your Own SNP-Gene Associations" section (http://www.gtexportal.org/home/testyourown) from the GTEx database. Listed are plots which represent significant eQTL *P*-values. Homo, homozygous; Het, heterozygous; REF, reference allele as determined by the hg19/GRCh37 human genome reference; ALT, alleles that are alternate in comparison to the reference; eQTL, expression quantitative trait loci; eQTL *P*-value, nominal *P*-values were generated for each variant-gene pair by testing the alternative hypothesis that the slope of a linear regression model between genotype and expression deviates from 0.




**Supplementary Figure 11.** Autosome-wide distribution of Tajima's D values in selected populations from the 1000 Genomes Pilot 1 data. Kernel density estimates (Gaussian kernel) for the distribution of Tajima's D values based on 255,393 autosomal regions in selected populations. CEU, Utah residents with ancestry from Northern and Western European, USA; IBS, Iberian Populations in Spain; FIN, Finnish in Finland; TSI, Toscani in Italia; CHB, Han Chinese in Beijing, China; CHS, Han Chinese South, China; JPT, Japanese in Tokyo, Japan; LWK, Luhya in Webuye, Kenya; YRI, Yoruba in Ibadan, Nigeria. Source: dbPSHP, http://jjwanglab.org/dbpshp[2].

**Supplementary Table 1.** Descriptions of the samples used in the three sequencing approaches, separately for each method, and number of cases and controls when all three sequencing methods are combined.

| **Sample descriptives** | **Sequencing technology** | | | |
|---|---|---|---|---|
| | Sanger sequencing | SBS sequencing (Illumina) | SBL sequencing (SOLiD) | **combined** |
| **No. cases** | **138** | **48** | **34** | **118*** |
| No. females | 109 | 33 | 25 | |
| No. males | 29 | 15 | 9 | |
| age range (years) | 99-109 | 100-110 | 100-105 | |
| **No. controls** | **92** | **46** | **22** (incl. 6 HapMap) | **158*** |
| No. females | 69 | 31 | 9 | |
| No. males | 23 | 15 | 7 | |
| age range (years) | 60-75 | 61-75 | 64-75 | |
| **No. HapMap controls** | | | 6 | |
| females | | | 3 | |
| males | | | 3 | |
| age range (years) | | | NA | |

*For quality control, there was an overlap of samples: one control sample overlapped between Sanger and SBS sequencing, one control sample overlapped between SBS and SBL sequencing, one case sample overlapped between Sanger and SBS sequencing, and one case sample overlapped between SBS and SBL sequencing. No., number; SBS, sequencing by synthesis; SBL, sequencing by ligation; NA, data not available.

**Supplementary Table 2.** Association between rs12206094 and rs4946935 and age-related phenotypes in all Danish LLI and controls.

| | rs12206094 | | | | | | rs4946935 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LLI | | | Controls | | | LLI | | | Controls | | |
| **Age-related phenotype** | **N** | **OR** | ***P*** | **N** | **OR** | ***P*** | **N** | **OR** | ***P*** | **N** | **OR** | ***P*** |
| Chair stand | 622 | 1.24 | 0.088 | NA | NA | NA | 623 | 1.16 | 0.221 | NA | NA | NA |
| MMSE | 626 | 0.99 | 0.935 | NA | NA | NA | 627 | 1.00 | 0.976 | NA | NA | NA |
| **Age-related phenotype** | **N** | **β** | ***P*** | **N** | **β** | ***P*** | **N** | **β** | ***P*** | **N** | **β** | ***P*** |
| Age at first child | 478 | 0.08 | 0.809 | NA | NA | NA | 478 | 0.21 | 0.536 | NA | NA | NA |
| Age at last child | 450 | -1.01 | **0.018** | NA | NA | NA | 450 | -0.76 | 0.074 | NA | NA | NA |
| Age at menopause | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Chair stand, timed | NA | NA | NA | 720 | 0.40 | **0.034** | NA | NA | NA | 717 | 0.16 | 0.388 |
| Cognitive composite score | 562 | -0.31 | 0.593 | 731 | -0.95 | 0.117 | 563 | -0.49 | 0.400 | 728 | -0.62 | 0.290 |
| Grip strength | 559 | 0.19 | 0.566 | 728 | -0.002 | 0.096 | 560 | 0.09 | 0.783 | 725 | -0.14 | 0.698 |
| Number of biological children | 640 | -0.17 | 0.122 | 709 | 0.01 | 0.843 | 641 | -0.14 | 0.172 | 706 | 0.02 | 0.783 |

N, number; OR, odds ratio; *P*, *P*-value obtained from linear or ordinal logistic regression adjusted for age at assessment and gender. The *P*-values are not adjusted for multiple testing. *P*-values ≤ 0.05 are shown in bold. MMSE, Mini-Mental-State-Examination; NA, phenotype not available.

**Supplementary Table 3.** Association between rs12206094 and rs4946935 and age-related phenotypes in male Danish LLI and controls.

| | rs12206094 | | | | | | rs4946935 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LLI | | | Controls | | | LLI | | | Controls | | |
| **Age-related phenotype** | **N** | **OR** | ***P*** | **N** | **OR** | ***P*** | **N** | **OR** | ***P*** | **N** | **OR** | ***P*** |
| Chair stand | 145 | 1.01 | 0.984 | NA | NA | NA | 146 | 1.04 | 0.886 | NA | NA | NA |
| MMSE | 146 | 0.67 | 0.106 | NA | NA | NA | 147 | 0.70 | 0.145 | NA | NA | NA |
| **Age-related phenotype** | **N** | **β** | ***P*** | **N** | **β** | ***P*** | **N** | **β** | ***P*** | **N** | **β** | ***P*** |
| Age at first child | 73 | 0.23 | 0.799 | NA | NA | NA | 73 | 0.10 | 0.906 | NA | NA | NA |
| Age at last child | 72 | -1.07 | 0.260 | NA | NA | NA | 72 | -1.04 | 0.271 | NA | NA | NA |
| Age at menopause | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Chair stand, timed | NA | NA | NA | 283 | 0.47 | 0.072 | NA | NA | NA | 282 | 0.01 | 0.979 |
| Cognitive composite score | 134 | -0.94 | 0.470 | 285 | -0.39 | 0.690 | 135 | -0.82 | 0.499 | 284 | 1.22 | 0.195 |
| Grip strength | 132 | 0.34 | 0.712 | 285 | -0.13 | 0.860 | 133 | 0.86 | 0.323 | 284 | -0.09 | 0.904 |
| Number of biological children | 149 | 0.02 | 0.934 | 273 | 0.02 | 0.887 | 150 | 0.27 | 0.238 | 272 | 0.03 | 0.748 |

N, number; OR, odds ratio; *P*, *P*-value obtained from linear or ordinal logistic regression adjusted for age at assessment and gender. The *P*-values are not adjusted for multiple testing. *P*-values ≤ 0.05 are shown in bold. MMSE, Mini-Mental-State-Examination; NA, phenotype not available.

**Supplementary Table 4.** Association between rs12206094 and rs4946935 and age-related phenotypes in female Danish LLI and controls.

| | rs12206094 | | | | | | rs4946935 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LLI | | | Controls | | | LLI | | | Controls | | |
| **Age-related phenotype** | **N** | **OR** | ***P*** | **N** | **OR** | ***P*** | **N** | **OR** | ***P*** | **N** | **OR** | ***P*** |
| Chair stand | 477 | 1.33 | **0.047** | NA | NA | NA | 477 | 1.21 | 0.172 | NA | NA | NA |
| MMSE | 480 | 1.10 | 0.457 | NA | NA | NA | 480 | 1.11 | 0.421 | NA | NA | NA |
| **Age-related phenotype** | **N** | **β** | ***P*** | **N** | **β** | ***P*** | **N** | **β** | ***P*** | **N** | **β** | ***P*** |
| Age at first child | 405 | 0.07 | 0.850 | NA | NA | NA | 405 | 0.24 | 0.529 | NA | NA | NA |
| Age at last child | 378 | -1.01 | **0.033** | NA | NA | NA | 378 | -0.72 | 0.132 | NA | NA | NA |
| Age at menopause | 346 | -0.11 | 0.771 | 433 | -0.78 | 0.087 | 346 | 0.39 | 0.300 | 431 | -0.87 | **0.047** |
| Chair stand, timed | NA | NA | NA | 437 | 0.36 | 0.174 | NA | NA | NA | 435 | 0.24 | 0.347 |
| Cognitive composite score | 428 | -0.13 | 0.846 | 446 | -1.24 | 0.111 | 428 | -0.37 | 0.574 | 444 | -1.62 | **0.031** |
| Grip strength | 427 | 0.14 | 0.673 | 443 | 0.06 | 0.878 | 427 | -0.15 | 0.636 | 441 | -0.17 | 0.647 |
| Number of biological children | 491 | -0.22 | 0.072 | 436 | 0.01 | 0.908 | 491 | -0.26 | **0.027** | 434 | 0.01 | 0.928 |

OR, odds ratio; *P*, *P*-value obtained from linear or ordinal logistic regression adjusted for age at assessment and gender. The *P*-values are not adjusted for multiple testing. *P*-values ≤ 0.05 are shown in bold. MMSE, Mini-Mental-State-Examination; NA, phenotype not available.

**Supplementary Table 5.** Descriptives of age-related phenotypes investigated in the Danish LLI and controls.

| | LLI | | Controls | |
|---|---|---|---|---|
| **Age-related phenotype** | **N** | **No. individuals (%)** | **N** | **No. individuals (%)** |
| *Chair stand* | | | | |
| Cannot | 623 | 52 (8.3%) | NA | NA |
| Can, with use of arms | | 256 (41.1%) | | NA |
| Can, without use of arms | | 315 (50.6%) | | NA |
| *MMSE* | | | | |
| Severe impairment (0-17) | | 110 (17.6%) | | NA |
| Mild impairment (18-22) | 627 | 153 (24.4%) | NA | NA |
| Normal (23-27) | | 246 (39.2%) | | NA |
| Maximum (28-30) | | 118 (18.8%) | | NA |
| **Age-related phenotype** | **N** | **Mean (SE)** | **N** | **Mean (SE)** |
| Age at first child | 478 | 26.99 (0.23) | NA | NA |
| Age at last child | 450 | 34.35 (0.28) | NA | NA |
| Age at menopause | 346 | 49.22 (0.25) | 433 | 48.96 (0.28) |
| Chair stand, timed | NA | NA | 721 | 9.71 (0.12) |
| Cognitive composite score | 563 | 27.63 (0.38) | 732 | 46.99 (0.37) |
| Grip strength | 560 | 15.96 (0.27) | 729 | 36.49 (0.43) |
| Number of biological children | 641 | 2.40 (0.07) | 709 | 2.07 (0.04) |

MMSE, Mini-Mental-State-Examination; N, total number of individuals; NA, phenotype not available; SE, standard error.

Data on age-related phenotypes was collected as part of a comprehensive home-based interview focusing on health and lifestyle issues as well as objective assessments of cognitive and physical abilities. Cognitive function was assessed by the MMSE and a cognitive composite score, which evaluates verbal fluency, forward and backward digit span, and immediate and delayed recall[3]. The MMSE score ranges from 0 to 30 and was here divided into four groups: severe impairment (MMSE 0-17), mild impairment (MMSE 18-22), normal impairment (MMSE 23-27), and maximum impairment (28-30). The cognitive composite score was standardized using the mean and standard deviation of cognitive composite scores measured in 46-50-year olds born from 1949-1952. Physical function was assessed by chair stand and grip strength. In the younger controls, chair stand was measured as the time used (in seconds) to stand up from a chair five times in a row as quickly as possible, whereas in the LLI chair stand assessed the ability to stand up from a chair with the outcome categories 'cannot', 'can, with use of arms', and 'can, without use of arms'. Grip strength was measured using a handheld dynamometer (SMEDLEY's dynamometer, Scandidact, Kvistgaard, Denmark) and the maximum of three measurements with the strongest hand was used. Information about age at first child, age at last child, age at menopause and number of biological children was obtained by asking the questions: 'How old were you when you had your first/last child?', 'At what age did you reach menopause?', and 'How many biological children do you have?'.

**Supplementary Table 6.** Prediction of CCCTC-binding factor (CTCF) binding sites in *FOXO3* sequences containing either rs12206094-C or rs12206094-T.

| Motif PWM | Motif sequence | Motif start location | Motif length | Motif orientation | PWM score |
|---|---|---|---|---|---|
| *Input sequence: GRCh38:6:108584752:108585151:1, rs12206094-C* | | | | | |
| EMBL_M1 | CACCCTGTGCAGGC | 165 | 14 | - | 7.20 |
| EMBL_M2 | AGAATTGCT | 250 | 9 | + | 7.84 |
| REN_20 | GTAGCCTGCACAGGGTGGTA | 162 | 20 | + | 9.59 |
| MIT_LM2 | CCTGCACAGGGTGGTAGAG | 166 | 19 | + | 3.99 |
| MIT_LM7 | TAGCCTGCACAGGGTGGTAG | 163 | 20 | + | 6.38 |
| **MIT_LM23** | **TTGCCACCAAGAATTGCTAT** | **241** | 20 | **+** | **5.29** |
| *Input sequence: GRCh38:6:108584752:108585151:1, rs12206094-T* | | | | | |
| EMBL_M1 | CACCCTGTGCAGGC | 165 | 14 | - | 7.28 |
| EMBL_M2 | AGAATTGCT | 250 | 9 | + | 7.83 |
| REN_20 | GTAGCCTGCACAGGGTGGTA | 162 | 20 | + | 9.61 |
| MIT_LM2 | CCTGCACAGGGTGGTAGAG | 166 | 19 | + | 4.03 |
| MIT_LM7 | TAGCCTGCACAGGGTGGTAG | 163 | 20 | + | 6.41 |
| **MIT_LM23** | **TAGCCTGCACAGGGTGGTAG** | **163** | 20 | **+** | **2.23** |

The CCCTC-binding factor (CTCF) binding site database (CTCFBSDB 2.0; http://insulatordb.uthsc.edu/home_new.php)[4,5] for CTCF binding site identification uses a position weight matrix (PWM) of six core motifs of CTCF binding sites. These core motifs include the EMBL_M1 and EMBL_M2 motifs[6], the Ren_20 motif[7], and the LM2, LM7 and LM23 motifs[8]. STORM[9] program is used in the CTCFBSDB to scan for each PWM in the query sequences and a score is calculated based on the log-odds of the observed sequence being generated by the motif versus being generated by the background. Usually, a PWM score >3.0 is a suggestive match[5]. For more information, please refer to the CTCFBSDB 2.0 webpage (http://insulatordb.uthsc.edu/home_new.php). The *FOXO3* sequence containing rs12206094-C was predicted to comprise a LM23-similar CTCFBS motif with a score of 5.29; on the contrary, in the presence of rs12206094-T, a much lower score of only 2.23 was detected. In the table, the lines referring to the LM23 motif are highlighted in bold.

**Supplementary Table 7.** Results of significant eQTL associations for rs12206094 and rs4946935 (and SNVs in LD with these two).

| SNV | SNV position (hg18) | eQTL *P*-value | Tissue | Chr. | SNV alleles | minA | Effect direction of minA | eQTL gene | eQTL gene position (hg18) | Browser |
|---|---|---|---|---|---|---|---|---|---|---|
| rs12206094 | 109012893 | 4.1E-4 | brain - hippocampus | 6 | C/T | T | + | FOXO3 | chr6:108988762-109112664 | GTEx (Test Your Own)* |
| | | 0.0037 | testis | | | | + | | | |
| | | 0.0070 | prostate | | | | + | | | |
| | | 0.010 | cells - EBV-transformed lymphocytes | | | | - | | | |
| | | 0.013 | brain - nucleus accumbens (basal ganglia) | | | | + | | | |
| | | 0.023 | brain - putamen (basal ganglia) | | | | + | | | |
| | | 0.024 | cells - transformed fibroblasts | | | | + | | | |
| | | 0.026 | pancreas | | | | + | | | |
| rs4946935 | 109107435 | 0.0020 | cells - transformed fibroblasts | 6 | A/G | A | + | FOXO3 | chr6:108988762-109112664 | GTEx (Test Your Own)* |
| | | 0.0053 | testis | | | | + | | | |
| | | 0.0094 | prostate | | | | + | | | |
| | | 0.0098 | brain - hippocampus | | | | + | | | |
| | | 0.012 | brain - cerebellum | | | | + | | | |
| rs1536057** | 108992316 | 6.9E-5 | nerve - tibial | 6 | C/T | T | - | LINC00222 | chr6:109179550-109197838 | GTEx |
| | | 4.3E-4 | lung | | | | - | | | |
| | | 4.5E-4 | thyroid | | | | - | | | |
| | | 0.009 | brain-cerebellum | | | | - | | | |
| rs2022464*** | 109052063 | 3.7E-5 | nerve - tibial | 6 | A/C | A | - | LINC00222 | chr6:109179550-109197838 | GTEx |
| | | 5.2E-5 | thyroid | | | | - | | | |
| | | 10.0E-3 | lung | | | | - | | | |
| | | 4.4E-3 | brain-cerebellum | | | | - | | | |
| | | 0.006 | adrenal gland | | | | - | | | |
| | | 0.007 | artery tibial | | | | - | | | |

**Supplementary Table 7** *cont.*

| SNV | SNV position (hg18) | eQTL *P*-value | Tissue | Chr. | SNV alleles | minA | Effect direction of minA | eQTL gene | eQTL gene position (hg18) | Browser |
|---|---|---|---|---|---|---|---|---|---|---|
| rs2153960**** | 109094877 | 7.6E-5 | thyroid | 6 | C/T | C | - | LINC00222 | chr6:109179550-109197838 | GTEx |
| | | 7.3E-4 | nerve - tibial | | | | - | | | |
| | | 3.4E-3 | adipose-visceral | | | | - | | | |
| | | 0.007 | muscle-skeletal | | | | - | | | |
| rs4946935 | 109107435 | 2.3E-6 | whole blood | 6 | A/G | A | - | HS.133419 | chr6:109128786-109129470 | Blood eQTL browser |
| rs12206094 | 109012893 | 3.1E-4 | whole blood | 6 | C/T | T | - | HS.133419 | chr6:109128786-109129470 | Blood eQTL browser |

*the corresponding eQTL box plots are listed in Supplementary Fig. 10

**in LD with rs12206094; $r^2 = 1.00$ based on HapMap-CEU individuals, 1000 Genomes

***in LD with rs4946935; $r^2 = 0.96$ based on HapMap-CEU individuals, 1000 Genomes

****in LD with rs4946935; $r^2 = 0.96$ based on HapMap-CEU individuals, 1000 Genomes

SNV, single nucleotide variant; Chr, chromosome; minA, minor allele; eQTL, expression quantitative trait loci

eQTL *P*-value, GTEx information: nominal *P*-values were generated for each variant-gene pair by testing the alternative hypothesis that the slope of a linear regression model between genotype and expression deviates from 0

GTEx (Test Your Own SNP-Gene Associations): http://www.gtexportal.org/home/testyourown

GTEx: http://www.gtexportal.org/home/

Blood eQTL browser: http://genenetwork.nl/bloodeqtlbrowser/[10]

**Supplementary Table 8.** Allele frequencies for the two *FOXO3* SNVs rs4946935 and rs12206094 across diverse populations according to NCBI dbSNV (accessed September 07, 2016) and in the control group of the present study (in italics).

| Ancestry | Population | Individual group (Origin, residency) | rs4946935 | | | rs12206094 | | |
|---|---|---|---|---|---|---|---|---|
| | | | Sample size | Allele frequencies | | Sample size | Allele frequencies | |
| | | | | A[*, #] | G | | C[#] | T[*] |
| **European** | HapMap-CEU | Europeans, US | 118 | 0.297 | 0.703 | 226 | 0.726 | 0.274 |
| | | | 226 | 0.265 | 0.735 | | | |
| | HapMap-TSI | Tuscans, Italy | 176 | 0.341 | 0.659 | 176 | 0.648 | 0.352 |
| | *Controls in our study* | *Germans, Germany* | *918* | *0.304* | *0.696* | *918* | *0.713* | *0.287* |
| **Asian** | HapMap-HCB | Han Chinese, China | 90 | 0.178 | 0.822 | 86 | 0.860 | 0.140 |
| | | | 86 | 0.174 | 0.826 | | | |
| | HapMap-CHB | Han Chinese, China | 82 | 0.171 | 0.829 | 82 | 0.854 | 0.146 |
| | HapMap-JPT | Asians, Japan | 90 | 0.189 | 0.811 | 172 | 0.843 | 0.157 |
| | | | 172 | 0.192 | 0.808 | | | |
| **African** | HapMap-YRI | Yorubas, Nigeria | 120 | 0.983 | 0.017 | 226 | 0.558 | 0.442 |
| | | | 226 | 0.951 | 0.049 | | | |
| | HapMap-LWK | Luhyas, Kenya | 180 | 0.822 | 0.178 | 180 | 0.672 | 0.328 |
| | HapMap-MKK | Maasai, Kenya | 286 | 0.636 | 0.364 | 284 | 0.676 | 0.323 |
| **Ancient DNA**[b] | | Hunter-gatherers | 9 | 0.620[a] | 0.380[a] | 9 | 0.463 | 0.537 |
| | | Early farmers | 79 | 0.453[a] | 0.547[a] | 79 | 0.525 | 0.475 |

[*], longevity allele,

[#], ancestral allele,

[a], LD-SNP (rs1935949) of rs4946935, $r^2$ (CEU) = 0.96 (1000 genomes pilot 1; SNAP Proxy Search; https://archive.broadinstitute.org/mpg/snap/ldsearch.php).

[b]Data from Mathieson et al. (2015)[11]

**Supplementary Table 9.** Allele frequencies and Tajima's D values in selected populations from the 1000 Genomes Pilot 1 data.

| | EUR | | | | EAS | | | AFR | |
|---|---|---|---|---|---|---|---|---|---|
| | **CEU** | **IBS** | **FIN** | **TSI** | **CHB** | **CHS** | **JPT** | **LWK** | **YRI** |
| **rs12206094** | | | | | | | | | |
| **DAF** | 0.26 | 0.32 | 0.26 | 0.35 | 0.14 | 0.22 | 0.16 | 0.31 | 0.45 |
| **Tajima's D** | 1.94 (0.57) | 0.96 (0.50) | 1.98 (0.57) | 2.09 (0.61) | -0.20 (0.09) | 0.37 (0.19) | 0.10 (0.15) | 1.39 (0.44) | 1.29 (0.40) |
| **rs4946935** | | | | | | | | | |
| **DAF** | 0.75 | 0.71 | 0.65 | 0.66 | 0.82 | 0.74 | 0.81 | 0.19 | 0.05 |
| **Tajima's D** | 2.52 (0.75) | 1.61 (0.73) | 2.50 (0.73) | 3.57 (0.95) | 0.42 (0.20) | 1.58 (0.45) | 0.95 (0.29) | 1.56 (0.51) | 0.91 (0.27) |

Given are absolute values and, in parentheses, the corresponding quantile with regard to the autosome-wide distribution of those values in selected populations. Quantiles are within the main body of the population-specific distributions, except for Tuscans, where the observed value was within the top 5% of all autosomal values. DAF, derived allele frequency; EUR, European meta-population; EAS, East Asian meta-population; AFR, African meta-population; CEU, Utah residents with ancestry from Northern and Western European, USA; IBS, Iberian populations in Spain; FIN, Finnish in Finland; TSI, Toscani in Italy; CHB, Han Chinese in Beijing, China; CHS, Han Chinese South, China; JPT, Japanese in Tokyo, Japan; LWK, Luhya in Webuye, Kenya; YRI, Yoruba in Ibadan, Nigeria. Source: dbPSHP, http://jjwanglab.org/dbpshp[2].

**Supplementary Table 10.** Sequences of primers used for *FOXO3* sequencing with the SOLiD sequencing by ligation technology.

| Primer name | Sequence 5'-3' | Amplicon |
|---|---|---|
| SFOXO3A_1E_F | TTGAGAGATACATGAAGCACAGTAAGT | 7467 bp |
| SFOXO3A_1E_R | GGAATTCTACCCTAATAGAGAATGGAC | |
| FX3A_2.f | GGTCTCATCCCTGAGGTGAA | 6976 bp |
| FX3A_2.r | ATGACCCTGGTTGATGGTGT | |
| FX3A_3_A1_F1 | GGAAGGGAGGTAAGCCTTTCTA | 3960 bp |
| FX3A_3_A1_R1 | CACTTCCCCAACCTGTCTAAAG | |
| **gap in long-range PCR production** | | |
| FX3A_4_A2_F5 | TGTAATGACTTCCTGCAGTTGG | 4411 bp |
| FX3A_4_A2_R3 | CCCAGCAACTTCTTAGCAGAGT | |
| FX3A_5_A1_F3 | ATTTCACAAGTGTGGGGGATAC | 6033 bp |
| FX3A_5_A1_R2 | ATCCTTGGTGTTCTTTGGCTTA | |
| FX3A_5_A2_F1 | CAACCAGCCTTCCTTGTATTTC | 4930 bp |
| FX3A_5_A2_R5 | ATCGCAACGCTTTTAAATTAGG | |
| FX3A_6_F2 | AAAGGGACAACTCTGGGTACAA | 9228 bp |
| FX3A_6_R1 | TCAGCAAGACTTCCCTTCTTTC | |
| **gap in long-range PCR production** | | |
| FX3A_7_A2_F6 | AAAGGAACGTGCTTCCTAAGTG | 5121 bp |
| FX3A_7_A2_R6 | CAAGTCCAGCTAACATGATCCA | |
| FX3A_8.f | GTTGGTGCACGTGGTAATTG | 7278 bp |
| FX3A_8.r | GTCAGCCACAGAAGCTTTCC | |
| FX3A_9_F1 | CACCTGCATCTGTGTTGGTC | 9428 bp |
| FX3A_9_R2 | AGCAGACAATGCCCTCAGTC | |
| **gap in long-range PCR production** | | |
| FX3A_11.f | CAGGATGAGCATGCCACTAA | 9043 bp |
| FX3A_11.r | CATGGCCAACTAGGGAACAT | |
| FX3A_12.f | TTTCCTAGCAAGTGGACGCT | 7545 bp |
| FX3A_12.r | CTGAAGGTTGCCTGTGGATT | |
| FX3A_13.f | AGCCAAGCTTTGATGCATTT | 8455 bp |
| FX3A_13.r | TTTGTGCTTCAAGTCTCATGC | |
| FX3A_14.f | CAAGCCTGTGGTGTATGTGG | 9145 bp |
| FX3A_14.r | CGACACTCCTGGGTGCTAAT | |
| FX3A_15_F1 | TCCAGAAAGTTTGGGGAGATAA | 7869 bp |
| FX3A_15_R1 | GAATGCTGTGTTTGGTTGAAAA | |
| FX3A_16.f | CCTTAAGGAAGGCACATCCC | 7790 bp |
| FX3A_16.r | AAGTACGACCCAAGCTTCCC | |
| **gap in long-range PCR production** | | |
| FX3A_17_A2_F1 | TGTGAAATGGACCTGGTGAA | 5591 bp |
| FX3A_17_A2_R1 | CCATGCTTTAAGGCCCACTA | |
| FX3A_18_F5 | CCCAGTAAATGCAGTGAAGAGTC | 9378 bp |
| FX3A_18_R5 | CTCCCATTAACAGGAGTGACAAG | |
| FX3A_19.f | CAGGGCTCCAGAACCTGATA | 6725 bp |
| FX3A_19.r | AGCTCTGCTCTGAAAGCTGG | |
| FX3A_20_A1_F1 | GGTGATTTCCACACACAGAAGA | 4509 bp |
| FX3A_20_A1_R1 | TACGGTTCTTTCCTTTTCCTCA | |
| FX3A_20_A2n_F1 | ATTCATGCACTGGATGTGGA | 5807 bp |
| FX3A_20_A2n_R1 | TCATCAAAACTGCTGCGAAC | |
| FX3A_21.f | TTTCCACATTGTGCCTACCA | 2637 bp |
| FX3A_21.r | AGGCAGCCTCAGGAGTGTTA | |

**Supplementary Table 11.** Sequences of primers used for *FOXO3* sanger sequencing and long-range PCR.

| Gene region | Primer name | Sequence (5´-3´) | Amplicon |
|---|---|---|---|
| ***Long-range* PCR** | | | |
| Promoter, Exon1, Exon2 | F3_LR_34_MM2_F | GGCAGATTTGGCCAGATAAC | 8407 bp |
| | F3_LR_34_M02_R | CCCAACTGCAGGAAGTCATT | |
| Exon3 | FOX_ex3_LR_2F | AAAGGTAGACGTTGTGCCTCTATACTA | 2704 bp |
| | FOX_ex3_LR_2R | ACATGTAACACTGAAGATTGACAAAAG | |
| Exon4 | FOXO3A_3U_LR1F | CCATTCCCTTTGGGCTTTTC | 5523 bp |
| | FOXO3A_3U_LR1R | GGCCGTCTCTAAGTCCCAAC | |
| ***Nested* PCR** | | | |
| Promoter, NM201559 | ProFOX_201_F1 | CCCTTTTTCCCTCTCCTCTC | 690 bp |
| | ProFOX_201_R1 | TTACCCCCGTCCTACATTCA | |
| | ProFOX_201_F2 | CGCGAAACTCTCAATCAGGT | 722 bp |
| | ProFOX_201_R2 | GCCGCTTACTCGTCAAGG | |
| Promoter, NM001455 | ProFOX_0014_F1 | TGATGAACGTGCTGGTCCGGGT | 766 bp |
| | ProFOX_0014_R1 | CAGGAACAGGAGGACCTGAA | |
| | ProFOX_0014_F2 | GGAGGAGGAATGTGGAAGGT | 526 bp |
| | ProFOX_0014_R2 | GGGTTTTGTGTGGTTTGCAT | |
| | ProFOX_0014_F3 | TCTAACAGGGAACCGGACAC | 729 bp |
| | ProFOX_0014_R3 | CTCGCTTCCTTCCCTTCAG | |
| | ProFOX_0014_F4 | GGGCACGGATCGTAGAATAA | 602 bp |
| | ProFOX_0014_R4M_1R | AGGGAGAAGGGGGAGCGG | |
| Exon1 | FOX_ex1_F | CTAGGTTGAGGCGCCCTG | 386 bp |
| | FOX_ex1_R | TTAAAAACACTAGCGGGCGA | |
| Exon2 | FOX_ex2_a1_F1 | AACATAAACAAACGCACGCA | 633 bp |
| | FOX_ex2_a1_R1 | AGGGGCCACGTACAGGAT | |
| | FOX_ex2_a2_F4 | GATGGCAGAGGCACCGGCT | 702 bp |
| | FOX_ex2_a2_R2 | ACTCCGACGAATCCGAGAC | |
| Exon3 | FOX_ex3_a1_F1 | CTATATCATCTGGGTGCTCGG | 600 bp |
| | FOX_ex3_a1_R1 | TTCAGTCAGCCCATCATTCA | |
| | FOX_ex3_a2_F2 | CCATGCTCTACAGCAGCTCA | 653 bp |
| | FOX_ex3_a2_R2 | GGACTCACTCAAGCCCATGT | |
| | FOX_ex3_a3_F3 | ATCCGATGATGTCCTTTGCT | 636 bp |
| | FOX_ex3_a3_R3 | ACCACTGCTCCATGGTTTTC | |
| Exon4 | FOXO3A_ex4_F001 | GATGGAAGGCCTTGACAGGT | 529 bp |
| | FOXO3A_ex4_R001 | AGGGGAAGGACGGTTAACAT | |
| | FOXO3A_ex4_F01 | CGATGGTTTATGGGACGTTT | 571 bp |
| | FOXO3A_ex4_R01 | CATTTGGCAATGAGTGGAGA | |
| | FOXO3A_ex4_P_F1 | TTGCTTTGCAGAACAAATGAA | 414 bp |
| | FOXO3A_ex4_R1 | CAAAGGTGGTCCCAACTATTCC | |
| | FOXO3A_ex4_F2 | CTTTTTTTTCTGCTTCTATGGATTTC | 606 bp |
| | FOXO3A_ex4_R2 | TTCAGTAAAAGGCAGGGTGAA | |

**Supplementary Table 11**, *cont.*

| Gene region | Primer name | Sequence (5´-3´) | Amplicon |
|---|---|---|---|
| Exon4, *cont.* | FOXO3A_ex4_F3 | TTGTGCGCCTTGGCTTTA | 601 bp |
| | FOXO3A_ex4_R3 | TTTTGTTAGTCACTTTGCATGTTTC | |
| | FOXO3A_ex4_F4 | GGATGCATTGCAGAGGCACTA | 608 bp |
| | FOXO3A_ex4_R4 | CGGGACCCTAGACAGGCTTC | |
| | FOXO3A_ex4_F5 | TGAAGAGGGAATGCTTTGGTT | 603 bp |
| | FOXO3A_ex4_R5R | GGTATCAGGTTCTGGAGCCC | |
| | FOXO3A_ex4_F6 | CAGCTGTAATGTTTGATTTATGATGA | 662 bp |
| | FOXO3A_ex4_R6 | TGGAGGACTTCTTTTTGACTGC | |
| | FOXO3A_ex4_F7 | TGATTTCAGGTGGCTTCCAAA | 669 bp |
| | FOXO3A_ex4_R7 | GCATCCGCTTCAAGACCTCA | |
| | FOXO3A_ex4_F8 | TATTTGGGTGAACATTGTATGATTAGG | 652 bp |
| | FOXO3A_ex4_R8 | AGATTATATGGGATATGAGCAAGGA | |
| | FOXO3A_ex4_F9 | TGAAGGAGGACCAGAAAAATTAGTTAA | 651 bp |
| | FOXO3A_ex4_R9 | AGAGTCTCTCAGCTTTGTGGC | |
| | FOXO3A_ex4_F1La | CAAGTCTACGGGTGCCAGAT | 358 bp |
| | FOXO3A_ex4_R1La | GCAAGGCTGAAAATAATCAAGG | |

**Supplementary Table 12.** *In silico* analysis results for the SNVs detected in the coding exons 2 and 3.

| SNV No. | SNV ID | Localization | AA Subsitiution | PhyloP[12] | Grantham Score[13] | PolyPhen-2[14] | SNPs&GO[15] | MutPred[16] | SIFT[17] | Mutation Taster2[18] | Mutation Assessor[19] | FATHMM[20] | IMHOTEP (RF)[21] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 148 | rs11757217 | Exon 2 | synonym | - | - | - | - | - | - | - | - | - | - |
| 149 | snv_chr6_108989376 | Exon 2 | G91A | consequential | inconsequential | inconsequential | inconsequential | inconsequential | inconsequential | consequential | inconsequential | consequential | consequential |
| 150 | rs111556510 | Exon 2 | A140V | consequential | inconsequential | inconsequential | inconsequential | inconsequential | inconsequential | inconsequential | inconsequential | consequential | inconsequential |
| 151 | rs150320900 | Exon 2 | synonym | - | - | - | - | - | - | - | - | - | - |
| 769 | rs61756661 | Exon 3 | synonym | - | - | - | - | - | - | - | - | - | - |
| 770 | rs145259784 | Exon 3 | A341T | inconsequential | inconsequential | inconsequential | consequential | inconsequential | inconsequential | inconsequential | inconsequential | consequential | consequential |
| 771 | rs374860833 | Exon 3 | synonym | - | - | - | - | - | - | - | - | - | - |
| 772 | rs181686373 | Exon 3 | A521S | consequential | inconsequential | inconsequential | inconsequential | inconsequential | inconsequential | consequential | inconsequential | inconsequential | consequential |
| 773 | snv_chr6_109092246 | Exon 3 | R506H | inconsequential | inconsequential | consequential | consequential | inconsequential | consequential | consequential | consequential | consequential | consequential |
| 774 | snv_chr6_109092372 | Exon 3 | R548H | inconsequential | inconsequential | inconsequential | inconsequential | inconsequential | inconsequential | consequential | inconsequential | consequential | consequential |
| 775 | rs113367269 | Exon 3 | synonym | - | - | - | - | - | - | - | - | - | - |

SNV, single nucleotide variant; AA, amino acid; RF, random forest; -, no prediction (synonymous SNV)

**Supplementary Table 13.** *In silico* analysis results (MutationTaster2) for the associated SNVs detected in non-coding exon 4.

| SNV No. | SNV ID | Prediction | Probability |
|---|---|---|---|
| 946 | rs4945816 | inconsequential | 1.000000 |
| 952 | rs4946936 | inconsequential | 0.999977 |
| 956 | rs9400241 | inconsequential | 0.999999 |
| 975 | rs1062034 | inconsequential | 0.000185 |

SNV, single nucleotide variant

**Supplementary Table 14.** Sequences of primers and oligonucleotides used in the functional experiments.

| | |
|---|---|
| **A. Sequences of primers used in the generation of the plasmids containing the specific *FOXO3* alleles of rs4946935 and rs12206094** | |
| rs4946935-G | Forward:<br>TAAT**G**TGGCTTTCTTTATCTCCCAAAGTGAATGATCCCATTCCCTTTGGGCTTT<br>TCAACTTCAGAGCACGGGCTCGAGATCTGCGA<br>Reverse:<br>GGGGTGTTTTGGTGGGTCCTTTTTAGTTAGATGTTCAAGGTGCAGATAAGATT<br>CTGTTCTAGACTTGGCTAGCACGCGTAAGAG |
| rs4946935-A | Forward:<br>TAAT**A**TGGCTTTCTTTATCTCCCAAAGTGAATGATCCCATTCCCTTTGGGCTTT<br>TCAACTTCAGAGCACGGGCTCGAGATCTGCGA<br>Reverse:<br>GGGGTGTTTTGGTGGGTCCTTTTTAGTTAGATGTTCAAGGTGCAGATAAGATT<br>CTGTTCTAGACTTGGCTAGCACGCGTAAGAG |
| rs12206094-T | Forward:<br>GGCACTTGCTTTGC**T**ACCAAGAATTGCTATCTCCAAAATCCGGGCTCGAGATC<br>TGCGA<br>Reverse:<br>AAAGCCATAGATCAGGAATTCAACTTCTCATTTCAAAACGGGCTAGCACGCG<br>TAAGAG |
| rs12206094-C | Primer used to generate the rs12206094-C plasmid from the rs12206094-T plasmid:<br>TTG GCA CTT GCT TTG C**C**A CCA AGA ATT GCT ATC TCC |
| **B. Oligonucleotides used in gel-shift experiments** | |
| rs4946935-A | 5´- ACACCCCTAATATGGCTTTCTTT-3´ |
| rs4946935-G | 5´- ACACCCCTAATGTGGCTTTCTTT-3´ |
| rs12206094-C | 5´- CAC TTG CTT TGC CAC CAA GAA TTG C-3´ |
| rs12206094-T | 5´- CAC TTG CTT TGC TAC CAA GAA TTG C-3´ |
| **C. Sequences of primers used in endpoint-PCR (analysis of tissue-specific expression patterns)** | |
| *FOXO3A*<br>(NM_001455.3) | Forward: GGCAAAGCAGACCCTCAAAC<br>Reverse: GCTCGAACCCGGAATGGTAA<br>Amplicon: 504 bp |
| *SRF*<br>(NM_003131.2) | Forward: CTCAACTCGCCAGACTCTCC<br>Reverse: CCGGCTTCAGTGTGTCCTTG<br>Amplicon: 142 bp |
| *PDX*<br>(NM_000209.3) | Forward: CAGTGGGCAGGCGGC<br>Reverse: TCAACATGACAGCCAGCTCC<br>Amplicon: 154 bp |
| *STAT5A*<br>(NM_001288718.1) | Forward: GTCCTGAAGACCCAGACCAA<br>Reverse: TCAGGATCTCACCACTGCA<br>Amplicon: 172 |
| *CTCF*<br>(NM_006565.3) | Forward: TCTGACAGTGAAAATGCTGA<br>Reverse: TCTGGTCTTCAACCTGAATG<br>Amplicon: 202 |
| *GAPDH*<br>(NM_001289745.1) | Forward: GGCATGGCCTTCCGTGTCCC<br>Reverse: TGCCAGCCCCAGCGTCAAAG<br>Amplicon: 214 |

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