

1 **A joint analysis of longevity and age-related disease variants for gene expression
2 association**

3 Lu Zeng¹, Shouneng Peng¹, Seungsoo Kim, Jun Zhu¹, Bin Zhang¹, Yousin Suh², Zhidong Tu^{1*}

4 ¹Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, NY.

5 ²Department of Obstetrics and Gynecology, Columbia University, NY.

6 *Correspondence:

7 Zhidong Tu. Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai,
8 NY. Address: 1425 Madison Avenue, Box 1498, New York, NY, 10029-6574. Tel: +1 (212) 659-8508.

9 Fax: +1 (212) 659-1388, Email: zhidong.tu@mssm.edu.

10

11 **Abstract**

12 A large number of genetic variants associated with human longevity have been reported but how
13 they play their functions remains elusive. We performed an integrative analysis on 113 genome-
14 wide significant longevity and 14,529 age-related disease variants in the context of putative gene
15 expression regulation. We found that most of the longevity allele types were different from the
16 genotype of disease alleles when they were localized at the same chromosomal positions.
17 Longevity variants were about eight times more likely to be associated with gene expression than
18 randomly selected variants. The directions of the gene expression association were more likely to
19 be opposite between longevity and disease variants when the association occurred to the same
20 gene. Many longevity variants likely function through down-regulating inflammatory response
21 and up-regulating healthy lipid metabolisms. In conclusion, this work helps to elucidate the
22 potential mechanisms of longevity variants for follow-up studies to discover methods to extend
23 human healthspan.

24

25

26

27

28

29

30

31

32

33

34 **Introduction**

35 Longevity is a heritable trait and it was estimated that genetic factors account for approximately
36 20% to 30% of the variation in lifespan from twin studies (Herskind et al., 1996; Mitchell et al.,
37 2001). Although a very limited number of genetic factors have been replicated for association
38 with longevity, e.g., the ones near *APOE* and *FOXO3*, it is widely believed that longevity is
39 influenced by a large number of variants (Pilling et al., 2016) with most of them playing a small
40 effect on lifespan. Currently, hundreds of longevity variants have been reported (Melzer et al.,
41 2020) from association studies that were conducted on increasingly greater population sizes.
42 Validating these variants, elucidating their functions, and eventually translating the key findings
43 into actionable interventions have become an important but challenging task for human aging
44 research.

45

46 In addition to elucidating the determinant mechanisms of human lifespan, research on longevity
47 could also shed light on the genetic regulation of age-related diseases. The relationship between
48 longevity and age-related diseases is complex and remains to be fully elucidated. Although in
49 general, long-lived individuals are healthier than their age-matched peers of average lifespan
50 (Engberg et al., 2009), they are not free of age-related diseases. Actually, half of the centenarians
51 age with at least one chronic disease and about one-fourth with disability (Ailshire et al., 2015).
52 It has been reported that individuals with long lifespan do not have significantly lower
53 frequencies of disease alleles (Beekman et al., 2010). Therefore, further identifying and
54 investigating the longevity variants that can prevent or slow the development of age-related
55 diseases will be of great importance for healthy aging research.

56

57 One strategy to study longevity variants is to experimentally interrogate the function of each
58 variant (Flachsbart et al., 2017); although such approach is critical, it is time consuming and does
59 not scale-up easily. It has been suggested that integrative data-driven approach may help us to
60 gain new insights into the validity and functionality of the longevity variants. For example, Dato
61 et al. performed a pathway-based SNP-SNP interaction analysis to investigate beyond the effect
62 of single SNP (Dato et al., 2018). In this work, we use data from GTEx (Genotype-Tissue
63 Expression) project to portray the landscape of genetic association with gene expression by

64 jointly considering longevity and age-related disease variants. In particular, we ask a few key
65 questions, do longevity variants represent a distinct set of genetic factors from disease variants?
66 What fraction of longevity variants are likely to function through regulating gene expression in
67 human? And finally, when longevity and disease variant are both associated with a gene's
68 expression, will the associations be in the same or different directions? We believe addressing
69 these questions will help us to better understand longevity variants and their relationship with
70 disease variants.

71

72 **Results**

73 **Longevity alleles are mostly different from disease alleles when they are localized at the 74 same chromosomal positions**

75 To obtain a comprehensive list of longevity variants, we relied on three data sources, i.e., the
76 NHGRI-EBI GWAS Catalog (Buniello et al., 2019), LongevityMap (Budovsky et al., 2013) and
77 manually curated published studies, encompassing 90 GWA studies published from 1991 to
78 2019 (Fig. 1). In total, 3,674 genetic loci associated with longevity were collected from these
79 data sources. Among them, 113 longevity variants were genome-wide significant ($p \leq 5 \times 10^{-8}$), and
80 104 of them were genotyped in the GTEx v8 data which contained genotype information for
81 46,569,704 SNPs (Supplemental Table S1).

82

83 We next investigated if the loci for these 113 longevity variants could also be associated with
84 age-related diseases. To do so, we downloaded genetic variants associated with 165 age-related
85 disease categories whose incidence rates increase exponentially with age (Jaul & Barron, 2017)
86 from the NHGRI-EBI GWAS Catalog, covering diseases such as Alzheimer's disease, type 2
87 diabetes, hypertension and cancers. Similar to longevity variants, we only retained disease
88 variants that were genome-wide significant ($p \leq 5 \times 10^{-8}$), we then removed disease variants whose
89 risk alleles were inconsistent within the same disease category (e.g., rs11257238 alleles T and C
90 were both annotated to increase the risk of Alzheimer's disease and were removed due to such
91 inconsistency (Jansen et al., 2019; Jun et al., 2017)), which resulted in a total number of 14,529
92 unique disease variants (Supplemental Table S2). Our results showed that 41% (46/113) of our
93 longevity variants were also associated with these disease traits (Support Table 1). Not
94 surprisingly, we found that for these colocalized longevity alleles, their allele types were mostly

95 different from the disease alleles (42 out of 46), while only four of them shared the same alleles
96 with disease traits, namely, rs429358, rs4420638, rs16991615 and rs3184504. Since in many
97 cases the longevity variants were identified independently from disease GWA studies which
98 relied on different cohorts and/or examined different traits, this indicates that a large proportion
99 of these 113 genome-wide significant longevity variants are likely real and biologically
100 meaningful despite they have been mostly unreproducible so far (otherwise, it will be nearly
101 impossible to observe such a high “reverse” overlap by random chance). For the four longevity
102 variants that shared the same alleles with disease, we found that the alternative alleles of the
103 longevity variants were often associated with some disease traits as well. rs429358, located in the
104 fourth exon of the *APOE* gene, causes amino acid change in *APOE* protein that leads to switch
105 from *APOE ε3/ε2* to *ε4* (Rall et al., 1982). The longevity beneficial allele T (Pilling et al., 2017;
106 Timmers et al., 2019) is somehow associated with an increased risk for type 2 diabetes (Mahajan
107 Taliun, et al., 2018), while the alternative allele C is associated with an increased risk of AD and
108 AD-related measurements (such as amyloid-beta/p-tau/t-tau) (Moreno-Grau et al., 2019).
109 rs4420638, located in the *APOC1* gene and 14kb downstream of the *APOE ε4* allele, has a strong
110 association with AD. It is in a strong linkage equilibrium (LD) with rs429358 ($D'=0.86$) (Nyholt
111 et al., 2009). The longevity allele A (Fortney et al., 2015; McDaid et al., 2017) was found to be
112 associated with increased age-related macular degeneration (AMD) risk (Fritsche et al., 2013);
113 while the alternative allele G was associated with increased risk of LDL, CAD, AD, and higher
114 all-cause mortality (Deelen et al., 2014). rs16991615 is a nonsynonymous SNP on chromosome
115 20. The longevity allele A (Bae et al., 2019) was also associated with increased risk of breast
116 cancer (Michailidou et al., 2017) and heavy menstrual bleeding (Gallagher et al., 2019).
117 rs3184504 is a nonsynonymous SNP in the *SH2B3* gene. The longevity allele C (Pilling et al.,
118 2017) was associated with an increased risk of colorectal cancer while the alternative allele T
119 was associated with an increased risk of CAD (Schunkert et al., 2011) and stroke (Malik et al.,
120 2018).

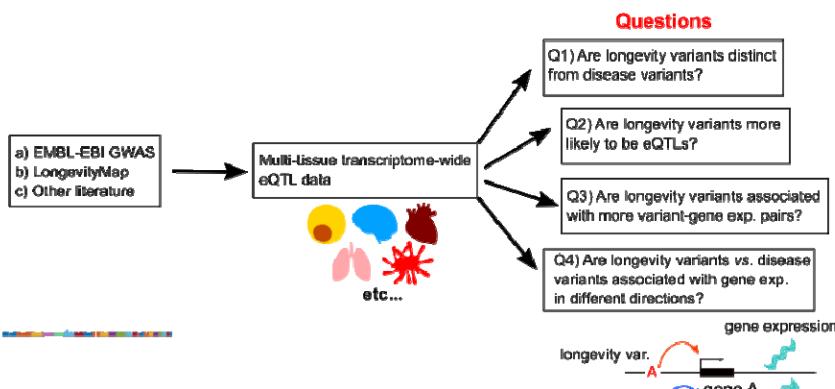
121

122 Among the 46 colocalized variants, 37 (>80%) were eQTLs in the GTEx data, while only 7.8%
123 of randomly selected GTEx SNPs were eQTLs (see details in the next section), indicating
124 longevity variants co-localized with disease traits are highly enriched for loci associated with
125 gene expression.

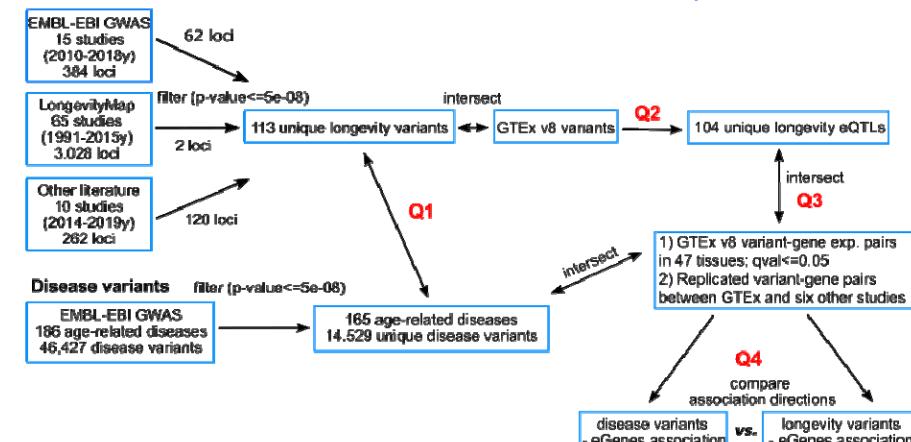
126
127
128
129
130
131
132

Figure 1

A



B Longevity variants



133
134
135
136
137

138 **Longevity variants are significantly more likely to be associated with gene expression**

139 In GTEx data, 67 longevity variants were associated with 183 unique genes' expression (also
140 known as eQTL-eGene pairs) in 47 GTEx tissues (false discovery rate (FDR) ≤ 0.05), which
141 corresponded to a total of 1,793 eQTL-eGene pairs. This reduced to 326 unique variant-gene

142 pairs if we did not consider tissue specificity, i.e., by counting the same eQTL-eGene pair across
143 different tissues as one pair (Support Table 2 & Supplemental Table 3).

144

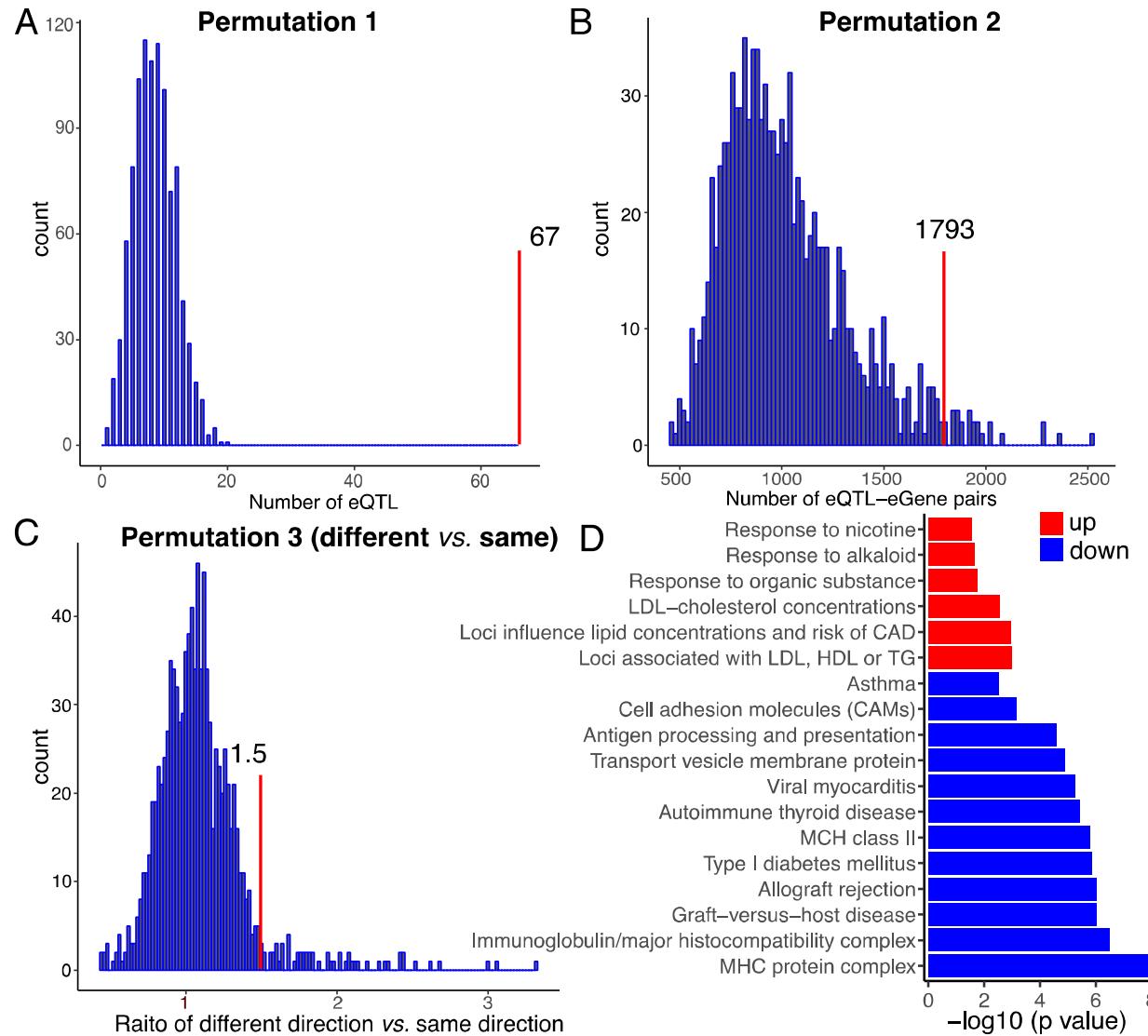
145 Permutation test was used to assess if the observed number of longevity eQTLs would occur by
146 random chance. Since 104 of 113 longevity variants were genotyped in the GTEx v8 data, we
147 randomly selected 104 variants from all the 46,569,704 GTEx SNPs for 1,000 times (without
148 replacement) and counted how many of them were eQTLs. Compared to 67 out of 104 longevity
149 variants that were eQTLs, in the permutation runs, on average, 8.4 randomly selected variants
150 were eQTLs, with a standard deviation (SD) of 3.34. This indicates that longevity variants are
151 significantly more likely to be associated with gene expression compared to random SNPs (Fig.
152 2A, permutation test, mean=8.4, SD=3.34, $p \leq 1.0 \times 10^{-3}$).

153

154 Similarly, to estimate the significance of the observed number of longevity variant-gene
155 expression pairs, we randomly selected 67 GTEx eQTLs for 1,000 times, and calculated the
156 number of variant-gene expression pairs for these eQTLs across 47 GTEx tissues. The
157 permutation analysis revealed that 67 randomly selected eQTLs were involved in an average of
158 1021.4 variant-gene expression pairs (SD=311.90), compared to 1,793 longevity variant-gene
159 pairs (empirical $p=0.025$). When we did not consider the tissue specificity of the eQTLs, the
160 permutation runs identified 198.1 ± 30.68 (mean \pm SD) variant-gene pairs, which is significantly
161 less than the observed 326 longevity variant-gene pairs (empirical $p \leq 1.0 \times 10^{-3}$). This result
162 suggests that longevity eQTLs were significantly associated with more eGenes in GTEx than
163 randomly selected eQTLs (Fig. 2B).

164

165 Figure 2



166

167 Permutation tests were performed to evaluate (a) if longevity variants were more likely to be eQTLs
 168 compared with randomly selected SNPs, (b) if longevity variants were involved in more variant-gene
 169 expression association pairs compared with randomly selected eQTLs, (c) the
 170 ratio = $\frac{\# \text{different association directions}}{\# \text{same association directions}}$ indicates if longevity variants were more likely to associate with gene
 171 expression in the opposite direction from disease alleles when they both were associated with same gene
 172 expression in subcutaneous fat, and (d) functional enrichment of longevity-variants associated eGenes.
 173

174 **Longevity variants associated up- and down- regulated eGenes were involved in distinct**
 175 **functions**

176 We next investigated the function of eGenes that were associated with longevity variants. We
 177 only focused on eQTLs showing relatively consistent association directions with gene expression
 178 across GTEx tissues and we considered up- and down- regulated eGenes separately. In particular,
 179 we kept eQTL-eGene pairs if their directions were consistent across $\geq 60\%$ GTEx tissues, and

180 the expression direction of these eGenes were determined by the majority directions ($\geq 60\%$).
181 For instance, longevity variant rs72738736 allele G (Pilling et al., 2017) showed opposite
182 association with iron responsive element binding protein 2 (*IREB2*) gene expression in two
183 tissues: whole blood (higher gene expression) and testis (lower gene expression) (Support Table
184 2). Since there is no simply way to determine which associations are biologically meaningful, we
185 removed this eQTL-eGene pair for further analysis and only focus on those eQTLs showing an
186 apparent dominant association direction.

187

188 Based on GTEx significant variant-gene expression associations ($FDR \leq 0.05$), a slightly higher
189 proportion of the longevity alleles were associated with increased gene expression. For example,
190 67 longevity eQTLs were found associated with 1,751 variant-gene pairs, and 944 of them were
191 associated with higher gene expression with longevity alleles, corresponding to 94 unique genes,
192 while 807 of them were down-associated with longevity alleles, corresponding to 89 unique
193 genes. When we did not count the tissue specificity, the total number of variant-gene pairs
194 reduced to 317 and among them, 167 were up, and 150 were down for the association with
195 longevity alleles.

196

197 We then inspected the function enrichment for genes associated with longevity variants using
198 DAVID tools (Huang da et al., 2009). GO annotation and pathway analysis demonstrated
199 differential function enrichment between up- and down-associated genes with longevity variants.
200 Among genes down-associated with longevity variants, they were characterized for MHC protein
201 complex (Benjamini-Hochberg (BH)= 9.19×10^{-9}), immunoglobulin (BH= 3.23×10^{-7}) and antigen
202 processing (BH= 2.59×10^{-5}). On the other hand, genes up-associated with longevity variants were
203 enriched for functions such as response to blood low-density lipoprotein cholesterol, high-
204 density lipoprotein or triglycerides in humans (BH= 1.03×10^{-3}), and newly identified loci that
205 influence lipid concentrations and risk of coronary artery disease (BH= 1.07×10^{-3}) (Figure 2D, a
206 full list of functional annotations is provided in Supplemental Table S4). This result suggests that
207 longevity variants could play their beneficial roles through down-regulating the inflammatory
208 response and up-regulating healthy lipid metabolisms.

209

210 **The association directions were more likely to be opposite when longevity and disease
211 variants were associated with same gene's expression**

212 We wanted to obtain a global view of the potential gene expression regulation by longevity
213 variants and compare that with 14,529 unique age-related disease variants as aforementioned.

214

215 To examine the potential influence of longevity and disease variants on gene expression, we
216 focused on eGenes whose expression was simultaneously associated with at least one disease and
217 one longevity variant in GTEx data. Using GTEx subcutaneous fat tissue as an example, 30
218 longevity variants were associated with 60 genes' expression, corresponding to 92 longevity
219 variant-gene expression pairs. 360 unique disease variants from 76 disease traits were also
220 associated with these 60 genes' expression, forming a total of 1,513 unique longevity variant-
221 gene expression-disease variant trios. We then inspected the association directions between the
222 gene expression of these 60 genes with disease *vs.* longevity variants. The comparison showed
223 that the direction of association with gene expression for longevity alleles were different from
224 disease alleles for 931 unique variant-gene-variant trios. For example, the longevity beneficial
225 allele G of rs3130507 (Pilling et al., 2017) was associated with lower expression of transcription
226 factor 19 (*TCF19*), while type 2 diabetes variants rs2073721 (Mahajan Wessel, et al., 2018) was
227 associated with an increased *TCF19* gene expression in GTEx adipose tissue. *TCF19*'s mRNA
228 expression has been reported to increase in nondiabetic obesity (Krautkramer et al., 2013). In
229 contrast, 621 unique variant-gene-variant trios showed same gene expression association
230 direction with longevity *vs.* disease alleles. For example, as we mentioned above, longevity
231 variants rs3130507 was associated with down-regulated gene expression of *TCF19*, while the
232 allele G of rs3094013, a SNP associated with increased body mass index (Graff et al., 2017) was
233 also associated with decreased *TCF19* gene expression in GTEx adipose tissue.

234

235 For nine genes, their gene expression associations with longevity *vs.* disease alleles were
236 consistently in the opposite direction in GTEx subcutaneous fat. These include FES proto-
237 oncogene, tyrosine kinase (*FES*), neutrophil cytosolic factor 1C pseudogene (*NCF1C*),
238 NOP2/sun RNA methyltransferase 5 pseudogene 1 (*NSUN5P1*), PMS1 homolog 2, mismatch
239 repair system component pseudogene 2 (*PMS2P2*), PMS1 homolog 2, mismatch repair system
240 component pseudogene 3 (*PMS2P3*), POM121 transmembrane nucleoporin C (*POM121C*),

241 speedy/RINGO cell cycle regulator family member E5 (*SPDYE5*), and stromal antigen 3-like 1
242 (pseudogene) (*STAG3LI*). Seven of these genes showed decreased gene expression association
243 with longevity alleles, except for *FES* and *PMS2P3* which showed increased gene expression.
244 The *FES* expression was down-regulated in colorectal cancer cell lines (Shaffer & Smithgall,
245 2009).

246
247 Similarly, we performed a permutation test to evaluate the significance of observing more
248 opposite associations with gene expression between longevity and disease variants. Since 30
249 longevity variants were involved in 92 variant-gene pairs in subcutaneous fat, we randomly
250 selected 30 eQTLs for 1,000 times from GTEx subcutaneous adipose tissue while we ensured
251 that these variants were involved in 92 variant-gene pairs in each run (see details in Methods).
252 We then extracted GTEx adipose eGenes associated with these 30 eQTLs to pull out all the
253 variants that were associated with these eGenes; by overlapping these variants with disease
254 variants from the 165 disease categories, we then checked the direction of association between
255 disease alleles and longevity alleles for the corresponding eGenes. From this permutation
256 analysis, we observed a slightly more variant-gene expression-variant trios in the opposite
257 association directions, as the mean value of the ratio between opposite direction of association
258 (506.2 ± 189.82) vs. same direction of association (471.9 ± 177.25) was 1.1 with a SD of 0.23. In
259 the real data, this ratio was 1.5 (931 associations in opposite directions between longevity vs.
260 disease alleles, and 621 associations in the same direction), suggesting longevity and disease
261 variants are significantly more likely to associate with a gene's expression in the opposite
262 directions (empirical $p=0.042$).

263
264 Next, we expanded this analysis to all the other 46 GTEx tissues; we found that 3,148 unique
265 longevity variant-gene expression-disease variant trios showed opposite associations between
266 longevity and disease alleles, while 1,971 unique longevity variant-gene expression-disease
267 variant trios had same association direction, leading to a ratio of 1.6. Twenty eGenes consistently
268 showed opposite gene expression association between longevity and disease alleles (Table 1),
269 including two genes (*NSUN5P1* and *POM121C*) identified from subcutaneous fat and 18 other
270 genes, which are *AP4B1-AS1*, *AREL1*, *CIB4*, *FURIN*, *CASTOR2*, *GULOP*, *KCNK3*, *KLHDC10*,

271 *PBX2*, *PHTF1*, *PMS2*, *PMS2CL*, *RGS12*, *SLC22A1*, *SPDYE12P*, *TOMM40*, *USP28* and
 272 *ZC3HC1* (detailed information can be found in support table 3).

273 **Table 1. List of genes whose expression associated with longevity and disease variants in**
 274 **consistent opposite directions across 47 GTEx tissues.**

275 We identified twenty genes whose association of their gene expression with longevity and disease alleles
 276 were consistently in the opposite directions. The third column shows the longevity eQTL for each gene
 277 and the beneficial allele. The fourth column shows the association direction with the longevity variant. The
 278 fifth column denotes the disease eQTLs and the risk alleles; the sixth column is the association direction
 279 with the disease variant; the last column shows the number of GTEx tissues in which such opposite
 280 associations were observed.

281

Gene symbol	Gene name	Longevity variant and allele type	Exp dir	Disease variant and allele type	Exp dir	No. of GTEx tissues
<i>AP4B1-AS1</i>	Adaptor related protein complex 4 subunit beta 1 antisense RNA 1	rs1230666:G	higher	rs1230666:A rs7513707: A rs11552449:T	lower	2
<i>AREL1</i>	Apoptosis resistant E3 ubiquitin protein ligase 1	rs61978928:C	lower	rs2165197:C	higher	1
<i>CIB4</i>	Calcium and integrin binding family member 4	rs1275922:G	lower	rs1275984:A rs1275982:C rs1731249:T rs1275978:C rs1731243:C rs1275988:C rs11126666:A	higher	1
<i>FURIN</i>	Furin, paired basic amino acid cleaving enzyme	rs6224:G	lower	rs17514846:A rs2071382:T rs2521501:T rs4932371:C rs4932373:C rs8039305:C	higher	3
<i>CASTOR2</i>	Cytosolic arginine sensor for MTORC1 subunit 2	rs113160991:G	higher	rs6944634:G	lower	1
<i>GULOP</i>	Gulonolactone L- oxidase, pseudogene	rs7844965:G	higher	rs2279590:C rs11136000:C rs4236673:G rs1532278:C	lower	1
<i>KCNK3</i>	Potassium two pore domain channel subfamily K member 3	rs1275922:G	higher	rs11126666:A rs1275978:C rs1275982:A rs1275984:A rs1275988:C rs1731243:C rs1731249:T	lower	3
<i>KLHDC10</i>	Kelch domain containing 10	rs56179563:A	higher	rs11556924:C	lower	1
<i>NSUN5P1</i>	NOP2/Sun RNA methyltransferase 5 pseudogene 1	rs113160991:G	lower	rs6963105:G rs6944634:G rs1167821:T rs1167827:G rs1167796:G	higher	36
<i>PBX2</i>	PBX homeobox 2	rs28383322:T	lower	rs2071288:C rs9268856:C	higher	1

				rs41268896:A		
<i>PHTF1</i>	Putative homeodomain transcription factor 1	rs1230666:G	higher	rs1230666:A rs7513707:A rs11552449:T	lower	3
<i>PMS2</i>	PMS1 homolog 2, mismatch repair system component	rs1830074:C	lower	rs1830074:C rs7456039:C	higher	1
<i>PMS2CL</i>	PMS2 C-terminal like pseudogene	rs3764814 :C	higher	rs1830074 :C	lower	2
<i>POM121C</i>	POM121 transmembrane nucleoporin C	rs113160991:G	lower	rs6963105:G rs6944634:G rs1167821:T rs1167827:G rs1167796:G rs34324971:A	higher	24
<i>RGS12</i>	Regulator of G protein signaling 12	rs61348208:T	higher	rs362275:C rs3121419:C rs363066:T	lower	2
<i>SLC22A1</i>	Solute carrier family 22 member 1	rs1510224:T rs111333005:G	higher	rs3798220:C rs9295128:T rs140570886:C rs186696265:T rs2297374:C	lower	7
<i>SPDYE12P</i>	Speedy/RINGO cell cycle regulator family member E12, pseudogene	rs113160991:G	lower	rs35005436:C rs6944634:G	higher	1
<i>TOMM40</i>	Translocase of outer mitochondrial membrane 40	rs71352238:T	lower	rs34342646:A rs71352238:C rs10119:A	higher	1
<i>USP28</i>	Ubiquitin specific peptidase 28	rs61905747:A	higher	rs61904987:T	lower	1
<i>ZC3HC1</i>	Zinc finger C3HC-type containing 1	rs56179563:A	lower	rs11556924:C	higher	2

282

283

284 **Longevity eQTLs from GTEx were replicable in independent studies**

285 To evaluate the robustness of GTEx eQTLs, we collected eQTL-eGene pairs from six
 286 independent eQTL studies which covered five tissues: adipose (MUTHER) (Nica et al., 2011),
 287 brain cortex (ROSMAP) (Ng et al., 2017), heart left ventricle (Koopmann et al., 2014), lung
 288 (Hao et al., 2012) and two blood studies (Võsa et al., 2018; Westra et al., 2013). We compared
 289 eQTLs from these independent studies with the eQTLs identified in the corresponding GTEx
 290 tissues. The comparison showed that eQTLs from these studies were highly enriched in GTEx
 291 data. For example, 37% adipose eQTLs from the MUTHER study were reproducible in GTEx
 292 subcutaneous fat; for two blood eQTL studies, 44% of the eQTLs from Võsa's work and 61% of
 293 the blood eQTLs from Westra's work matched with GTEx whole blood eQTLs. For eQTL-
 294 eGene pairs, a tissue-specific enrichment pattern could be seen for each tissue. For example,
 295 GTEx subcutaneous fat had the most matching eQTL-eGene pairs with the adipose MUTHER
 296 study (>2,000 pairs), while it had much fewer pairs in GTEx brain cortex (893 pairs). Similarly,

297 4,278 eQTL-eGene pairs from the independent lung eQTL study were found replicated in the
298 GTEX lung, but much fewer pairs were found in other tissues (Supplemental Table S5). In
299 addition, we found most of the reproducible variant-gene pairs showed same direction in eQTL-
300 gene expression between independent studies and GTEX (Supplemental Table S5). For instance,
301 in blood tissue, 1,073,253 variant-gene pairs showed the same direction in eQTL-gene
302 expression association between GTEX and independent studies, only 123,723 pairs showed
303 different directions. For the following analysis, we only considered the variant-gene expression
304 pairs that showed the same association direction between GTEX and those independent studies.
305

306 We then repeated part of our analyses with these replicated eQTL-eGene pairs. Our results
307 showed that overall the eQTL-gene expression association directions were different between
308 disease and longevity alleles in all five tissues, resulting 531 unique variant-gene-variant trios
309 showed opposite directions, and 203 unique variant-gene-variant trios showed same directions
310 (Supplemental Tables S6 & 7), a ratio of 2.6 between the two. Since this ratio increased from 1.5
311 in subcutaneous fat, to 1.6 across 47 tissues, to 2.6 in replicated eQTL studies, this indicates that
312 the longevity and disease alleles are more likely to associate with gene expression in the opposite
313 directions when robust eQTLs are considered.

314
315 For these replicated eQTL-eGene pairs, we noticed that longevity alleles showed consistent
316 opposite association compared to disease alleles on eleven genes' expression, five of them were
317 replicated from our previous analysis (*NCF1C*, *NSUN5P1*, *PMS2P3*, *RGS12* and *SLC22A1*), and
318 the rest are *CHRNA5*, *HLA-B*, *MAPKAPK5*, *POU5F1*, *PBX2* and *RNF5*. In several cases,
319 longevity alleles were found to play a putative beneficial role with respect to the associated gene
320 expression (Table 2). For examples, longevity variant rs61348208 (Timmers et al., 2019) was
321 associated with higher *RGS12* gene expression, while its expression level was relatively lower in
322 African American (AA) prostate cancer (Wang et al., 2017). Longevity variants rs3130507,
323 rs1510224 and rs186696265 (Pilling et al., 2017) were found to be associated with higher
324 *SLC22A1* gene expression, while the expression of *SLC22A1* was down-regulated in
325 hepatocellular carcinoma (Okabe et al., 2001). Lower *HLA-B* gene expression was associated
326 with longevity variants rs3131621 and rs3130507 (Pilling et al., 2017), while the down-

327 regulation of *HLA-B/C* expression has been reported to correlate with a lower tumor stage and a
328 longer disease-free survival in colorectal cancer patients (Menon et al., 2002).

329

330 **Table 2. Genes whose expression was associated with longevity vs. disease variants in**
331 **opposite directions in multiple eQTL studies.**

332 We identified eleven genes whose association of their gene expression with longevity and disease alleles
333 were consistently in the opposite directions (gene symbols in bold-fonts are those replicated in GTEx
334 data). The fourth column “Exp dir” shows the association direction of longevity alleles with each gene’s
335 expression; the last column is the putative beneficial expression direction of the corresponding genes
336 based on previous studies, “unknown” indicates that no related expression studies were found for the
337 corresponding gene.

338

Gene symbol	Gene name	Longevity variant and beneficial allele	Exp dir	Disease variant and risk allele	Expr dir	Possible beneficial exp. dir
<i>CHRNA5</i>	Cholinergic receptor nicotinic alpha 5 subunit	rs1317286:A	higher	rs9788721:C rs8034191:C rs17486278:C rs17487223:T rs1317286:G rs8031948:T rs10519203:G rs1051730:A rs931794:G rs2036527:A rs16969968:A rs7180002:T rs951266:A rs17483548:A rs17405217:T	lower	Low (Lung cancer studies demonstrated up-regulation of <i>CHRNA5</i> mRNA expression in lung adenocarcinomas, compared to normal lung tissue (Falvella et al., 2010))
<i>HLA-B</i>	Major histocompatibility complex, class I, B	rs3131621:A rs3130507:G	lower	rs9378249:T rs9378248:A	higher	low (Down-regulation of <i>HLA-B/C</i> expression correlated with a lower tumor stage and a longer disease-free survival in colorectal cancer patients (Menon et al., 2002))
<i>MAPKAPK5</i>	MAPK activated protein kinase 5	rs11066309:G	lower	rs7305242:T rs2301712:T rs4766898:C	higher	low (downregulating MK5 expression inhibited the survival of YAP-activated cancer cell lines and mouse xenograft model (Seo et al., 2019))
<i>NCF1C</i>	Neutrophil cytosolic Factor 1C pseudogene	rs113160991:G	lower	rs6944634 :G	higher	low (negligible <i>NCF1</i> expression was identified in chronic granulomatous disease (Kuhns et al., 2019))
<i>NSUN5P1</i>	NSUN5 pseudogene 1	rs113160991:G	lower	rs6963105:G rs6944634:G rs1167821:T rs1167827:G rs1167796:G	higher	Unknown
<i>PBX2</i>	PBX homeobox 2	rs28383322:T	lower	rs2071288:C	higher	high (reduction or absence)

				rs9268856:C rs41268896:A		of <i>PBX2</i> results in persistent truncus arteriosus (Stankunas et al., 2008))
<i>PMS2P3</i>	Putative postmeiotic segregation increased 2 pseudogene 3	rs113160991:G	higher	rs6963105:G rs6944634:G rs1167821:T rs1167827:G rs1167796:G	lower	Unknown
<i>POU5F1</i>	POU class 5 homeobox 1	rs3130507:G	lower	rs9378249:T	higher	low (high <i>POU5F1</i> expression were significantly more likely to have a poor prognosis than those with a low expression in colorectal cancer patients (Miyoshi et al., 2018))
<i>RGS12</i>	Regulator of G protein signaling 12	rs61348208:T	higher	rs362275:C rs3121419:C rs363066:T	lower	high (down-regulated in AA prostate cancer (Wang et al., 2017))
<i>RNF5</i>	Ring finger protein 5	rs3130507:G	higher	rs3131378:G rs501942:T rs3131379:A rs1150757:A	lower	high (down-regulated in body myositis (Delaunay et al., 2008))
<i>SLC22A1</i>	Solute carrier family 22 member 1	rs3130507:G rs1510224:T rs186696265:C	higher	rs9295128:T rs3798220:C rs140570886:C rs186696265:T	lower	high (down-regulated in hepatocellular carcinoma (Okabe et al., 2001))

339

340 Discussion

341 Thousands of genetic variants have been reported to be associated with human longevity
 342 (Budovsky et al., 2013). Validation and follow-up studies on such a large number of longevity
 343 variants remain to be challenging. For example, many of the variants are located in the non-
 344 coding or intergenic regions and do not pin-point to a protein coding gene, how they may play
 345 beneficial functions (if any) to human lifespan is elusive.

346

347 In this study, we collected 113 genome-wide significant longevity variants, and investigated their
 348 relationship with age-related disease variants in the context of gene expression regulation. It is of
 349 note that heterogeneous study designs were taken to identify the genetic determinants of human
 350 longevity, e.g., population-based case and control cohorts (Fortney et al., 2015; Zeng et al.,
 351 2016), family-based cohorts to study parental survival trait (Joshi et al., 2017; Pilling et al., 2017)
 352 and prospective studies (Broer et al., 2015; McDaid et al., 2017). Therefore, the longevity
 353 variants compiled from these studies may point to different biology of aging and lifespan, even
 354 though we collectively call them longevity variants. The heterogeneity in the derivation of
 355 longevity variants could potentially complicate the interpretation of our results.

356

357 We made several interesting observations in this work: first, from longevity GWA studies, not
358 every hit may be beneficial for longevity, particularly if we are looking for variants responsible
359 for healthspan. This is because some age-related diseases could be enriched in very long-lived
360 individuals, such as the AMD. Therefore, it is possible that some of the GWAS derived longevity
361 variants are causally associated with these diseases and represent increased disease risks
362 although they are also associated with longer lifespan. Second, a large proportion of the genome-
363 wide significant longevity variants may represent true biological signals even though they have
364 been hardly replicated. This is supported by the fact that over 80% of the longevity variants
365 when colocalized with disease variants had different allele types from the disease risk alleles.
366 Since disease and longevity variants were often identified from independent studies and derived
367 based on very different traits, this suggests that many of the genome-wide significant longevity
368 variants are not random hits but convey biological signals. This is expected as long-lived people
369 are less likely to develop age-related chronic conditions than their same-age peers, and they
370 remain healthier longer into the old ages (Sebastiani et al., 2017; Wei et al., 2017). Third, we
371 think that many longevity variants could play their functions through modulating underlying
372 gene expression. This is supported by the observation that longevity variants were about eight
373 times more likely to be eQTLs in the GTEx data compared with randomly selected SNPs. In
374 particular, we observed that when a gene expression is associated with both longevity and
375 disease variants, the association directions are more likely to be different than being the same.
376 This trend is more apparent when we narrowed down to those reproducible eQTL-eGene pairs
377 from independent studies. As a key goal of human aging and geroscience research is to identify
378 methods to promote human healthspan, this joint analysis provides a data-driven approach to
379 prioritize the longevity variants that may function through counteracting the effect of disease
380 variants through gene regulation.

381

382 Although we observed that longevity and disease variants were often associated with a gene
383 expression in opposite directions, many of them also showed same direction in association with
384 gene expression. This could receive multiple explanations. First, reported genetic variants for
385 longevity and diseases may not always be accurate; in fact, some of the reported findings on
386 these variants were inconsistent. For example, allele T of rs660240 was associated with

387 increased heel bone mineral density based on the NHGRI-EBI GWAS Catalog, while it was also
388 reported to associate with increased risk of osteoporosis in certain studies (Morris et al., 2019),
389 while low bone mineral density (BMD) is the major determinant for osteopenia and osteoporosis
390 (Cauley et al., 2007). Currently we largely relied on the GWAS catalog annotation since
391 manually curating 14,529 SNPs will require an extraordinary amount of effort and in some cases
392 impossible without full access to the original genotype/phenotype data; Second, some eQTL
393 calls may not be robust; although we show they are largely consistent across different studies,
394 there were some apparent variations in eQTL calling across studies; Third, eQTLs only indicate
395 association between genetic variants and gene expression, it remains unknown if the eQTLs are
396 actually involved in regulating the gene expression; this becomes even more complicated due to
397 the fact that multiple mapping among variants-gene expression exists. For instance, rs602633
398 (Pilling et al., 2017) was associated with the *PSRC1*, *SYPL2*, *CELSR2*, *SORT1* expression
399 changes across 25 GTEx tissues, it is unclear which variant-gene expression association is
400 biologically functional; last but not least, since it is not known for certain in which tissue(s) a
401 variant plays its function, we may consider eQTLs that are actually not functional in the tissues
402 under consideration. Recently, multiple statistical methods have been developed to facilitate the
403 casual inference between genetic variant, gene expression and phenotypic outcome. For example,
404 the COLOC is a Bayesian test to assess if two traits shared a causal variant (Giambartolomei et
405 al., 2014), S-PrediXcan was developed to perform transcriptome-wide genome association to
406 identify possible gene expression associated with the phenotypic traits (Jasinska, 2020), and
407 transcriptome-wide summary statistics-based Mendelian randomization method TWMR was
408 developed to use multiple SNPs as instruments and multiple gene expression traits as exposures
409 to infer if the causal link between instruments and outcome was mediated by exposures (Porcu et
410 al., 2019). Although these methods are helpful to test the potential involvement of gene
411 expression in causing phenotypic trait, they all require GWAS summary statistics and therefore
412 limited their use in this study.

413

414 We noticed that two well-known longevity genes *APOE* and *FOXO3* were not included in our
415 gene list as shown in Tables 1 and 2. Two common *APOE* alleles were found either significantly
416 depleted ($\epsilon 4$ allele) or enriched ($\epsilon 2$ allele) in long-lived individuals as compared to controls (Ryu
417 et al., 2016). The variants for both alleles are located in protein-coding regions and may not

418 affect regulatory regions to impact gene expression. In fact, we found three of our longevity
419 variants (rs283811 (Sebastiani et al., 2017), rs7412 (Deelen et al., 2019) and rs4420638 (McDaid
420 et al., 2017)) were associated with *APOE*'s gene expression only in GTEx skin tissues but not in
421 other tissues. Although *FOXO3* has been identified to associate with longevity in human, none of
422 the reported SNPs reached genome-wide significant ($p \leq 5 \times 10^{-8}$) in our initial longevity variants
423 collection, therefore the longevity variants associated with *FOXO3* were filtered out (Flachsbart
424 et al., 2009; Li et al., 2009; Willcox et al., 2008). In addition, none of our longevity variants were
425 significantly associated with *FOXO3*'s gene expression in GTEx data.

426

427 Longevity is believed to be a highly polygenic phenotype and we have only examined a small
428 fraction of all possible longevity variants as we focused on genome-wide significant variants in
429 this study. We expect to see more longevity variants to emerge and to be replicated as genetic
430 information will be increasingly available from larger populations. This work therefore
431 establishes a new direction for further exploration to prioritize the longevity variants that could
432 be truly beneficial to extending human health span.

433

434 **Methods**

435 **Longevity and disease variants collection**

436 In order to get a comprehensive list of longevity variants, we went through three sources: 1)
437 LongevityMap: a database of human genetic variants associated with longevity, including 65
438 GWA studies carried out from 1991 to 2015, with 3,028 loci collected; 2) The NHGRI-EBI
439 GWAS Catalog: a curated collection of human genome-wide association studies, including 15
440 longevity GWAS studies with 384 loci; 3) last but not least, by going through recent longevity
441 studies that were not covered by either LongevityMap or the NHGRI-EBI GWAS Catalog. We
442 manually curated 262 longevity variants (Fig. 1). We only considered longevity variants with a
443 genome-wide significant p-value ($\leq 5 \times 10^{-8}$), which resulted to 113 longevity variants with
444 reported beneficial alleles (Supplemental Table S1). 104 of these 113 longevity variants were
445 covered in GTEx genotype data. The 104 longevity variants were then intersected with
446 68,129,832 significant variant-gene expression associations (FDR ≤ 0.05) identified in GTEx v8.
447 67 longevity variants were found associated with 183 unique genes' expression, corresponding to
448 1,793 variant-gene pairs across 47 tissues in a tissue-specific manner.

449

450 Genetic variant information for 186 age-related diseases were downloaded from the NHGRI-EBI
451 Catalog (accessed on July 10, 2019), only variants reaching genome-wide significance ($p \leq 5 \times 10^{-8}$)
452 with known risk alleles were kept. We removed disease variants whose risk alleles were
453 inconsistent within the same disease category. After filtering, a total of 14,529 unique variants
454 with respect to 165 disease traits were compiled for further analysis.

455

456 **Permutation test**

457 Permutation analyses were carried out to: 1) test if longevity variant is more likely to be an
458 eQTL; we randomly selected 104 variants from all SNPs genotyped in GTEx for 1,000 times,
459 and we checked for each run how many SNPs were associated with gene expression. Empirical
460 p-value was then calculated to estimate the significance of the observed number of eQTLs for
461 longevity variants; 2) test if longevity variants were involved in more variant-gene pairs than
462 randomly selected variants; we randomly selected 67 variants that were eQTLs in GTEx for
463 1,000 times, and counted how many variant-gene expression pairs were linked to these eQTLs in
464 GTEx, similarly, empirical p-value was then calculated to test the significance of observed
465 eQTL-eGene pairs for longevity variants; 3) finally, we tested the significance of the difference
466 between longevity *vs.* disease alleles on gene expression association direction. We used
467 subcutaneous fat as an example, 30 unique longevity variants were found to be associated with
468 60 genes' expression, corresponding to 92 variant-gene pairs. To perform the permutation test,
469 we first randomly selected 30 GTEx eQTLs for 1,000 times that had same structures as longevity
470 eQTLs in subcutaneous fat. For example, 15 longevity variants were found to be associated with
471 only one gene's expression, while 6 longevity variants were associated with two genes'
472 expression in the adipose tissue and so on. GTEx eQTLs were thus randomly selected
473 accordingly based on the same structure in subcutaneous fat, i.e., to randomly select 15 eQTLs
474 that were associated with only one gene's expression, and 6 eQTLs that were associated with two
475 genes' expression, etc. In addition, 20 out of 30 longevity beneficial alleles were major alleles
476 for GTEx adipose, and 10 were minor alleles. We then randomly selected 20 major alleles and 10
477 minor alleles as longevity beneficial alleles in each random eQTL set.

478

479 **Cross-studies eQTL comparison**

480 Six independent eQTL studies were downloaded to evaluate the robustness of GTEx eQTLs,
481 covering five tissues: adipose (Nica et al., 2011), brain cortex (Ng et al., 2017), left ventricle
482 (Koopmann et al., 2014), lung (Hao et al., 2012) and two blood studies (Võsa et al., 2018;
483 Westra et al., 2013). The reproducible variant-gene pairs between these studies and the
484 corresponding GTEx tissues were then counted based on three criteria: 1) eQTLs from other
485 studies were replicated in GTEx v8; 2) these replicated eQTLs associated with same eGene as in
486 GTEx; 3) variant-gene pairs showed same association direction in eQTL-gene expression
487 between independent studies and GTEx.

488

489 **Acknowledgements**

490 This work was funded by NIH grant R01AG055501 to Z.T. and Y.S. The content is solely the
491 responsibility of the authors and does not necessarily represent the official views of the National
492 Institutes of Health. This work was also supported in part through the computational resources
493 and staff expertise provided by Scientific Computing at the Icahn School of Medicine at Mount
494 Sinai.

495

496 **Competing interests**

497 No competing interests declared.

498

499 **Reference**

- 500 Ailshire, J. A., Beltran-Sanchez, H., & Crimmins, E. M. (2015, Feb). Becoming centenarians:
501 disease and functioning trajectories of older US Adults as they survive to 100. *J Gerontol*
502 *A Biol Sci Med Sci*, 70(2), 193-201. <https://doi.org/10.1093/gerona/glu124>
503
- 504 Bae, H., Lunetta, K. L., Murabito, J. M., Andersen, S. L., Schupf, N., Perls, T., Sebastiani, P., &
505 Long Life Family, S. (2019, Oct). Genetic associations with age of menopause in familial
506 longevity. *Menopause*, 26(10), 1204-1212.
507 <https://doi.org/10.1097/GME.0000000000001367>
508
- 509 Beekman, M., Nederstigt, C., Suchiman, H. E., Kremer, D., van der Breggen, R., Lakenberg, N.,
510 Alemayehu, W. G., de Craen, A. J., Westendorp, R. G., Boomsma, D. I., de Geus, E. J.,
511 Houwing-Duistermaat, J. J., Heijmans, B. T., & Slagboom, P. E. (2010, Oct 19).
512 Genome-wide association study (GWAS)-identified disease risk alleles do not
513 compromise human longevity. *Proc Natl Acad Sci U S A*, 107(42), 18046-18049.
514 <https://doi.org/10.1073/pnas.1003540107>

- 515
516 Broer, L., Buchman, A. S., Deelen, J., Evans, D. S., Faul, J. D., Lunetta, K. L., Sebastiani, P.,
517 Smith, J. A., Smith, A. V., Tanaka, T., Yu, L., Arnold, A. M., Aspelund, T., Benjamin, E.
518 J., De Jager, P. L., Eirkisdottir, G., Evans, D. A., Garcia, M. E., Hofman, A., Kaplan, R.
519 C., Kardia, S. L., Kiel, D. P., Oostra, B. A., Orwoll, E. S., Parimi, N., Psaty, B. M.,
520 Rivadeneira, F., Rotter, J. I., Seshadri, S., Singleton, A., Tiemeier, H., Uitterlinden, A. G.,
521 Zhao, W., Bandinelli, S., Bennett, D. A., Ferrucci, L., Gudnason, V., Harris, T. B.,
522 Karasik, D., Launer, L. J., Perls, T. T., Slagboom, P. E., Tranah, G. J., Weir, D. R.,
523 Newman, A. B., van Duijn, C. M., & Murabito, J. M. (2015, Jan). GWAS of longevity in
524 CHARGE consortium confirms APOE and FOXO3 candidacy. *J Gerontol A Biol Sci
525 Med Sci*, 70(1), 110-118. <https://doi.org/10.1093/gerona/glu166>
526
- 527 Budovsky, A., Craig, T., Wang, J., Tacutu, R., Csordas, A., Lourenco, J., Fraifeld, V. E., & de
528 Magalhaes, J. P. (2013, Oct). LongevityMap: a database of human genetic variants
529 associated with longevity. *Trends Genet*, 29(10), 559-560.
530 <https://doi.org/10.1016/j.tig.2013.08.003>
531
- 532 Buniello, A., MacArthur, J. A. L., Cerezo, M., Harris, L. W., Hayhurst, J., Malangone, C.,
533 McMahon, A., Morales, J., Mountjoy, E., Sollis, E., Suveges, D., Vrousgou, O., Whetzel,
534 P. L., Amode, R., Guillen, J. A., Riat, H. S., Trevanion, S. J., Hall, P., Junkins, H., Flliceck,
535 P., Burdett, T., Hindorff, L. A., Cunningham, F., & Parkinson, H. (2019, Jan 8). The
536 NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted
537 arrays and summary statistics 2019. *Nucleic Acids Res*, 47(D1), D1005-D1012.
538 <https://doi.org/10.1093/nar/gky1120>
539
- 540 Cauley, J. A., Hochberg, M. C., Lui, L. Y., Palermo, L., Ensrud, K. E., Hillier, T. A., Nevitt, M.
541 C., & Cummings, S. R. (2007, Dec 19). Long-term risk of incident vertebral fractures.
542 *JAMA*, 298(23), 2761-2767. <https://doi.org/10.1001/jama.298.23.2761>
543
- 544 Dato, S., Soerensen, M., De Rango, F., Rose, G., Christensen, K., Christiansen, L., & Passarino,
545 G. (2018, Jun). The genetic component of human longevity: New insights from the
546 analysis of pathway-based SNP-SNP interactions. *Aging Cell*, 17(3), e12755.
547 <https://doi.org/10.1111/ace.12755>
548
- 549 Deelen, J., Beekman, M., Uh, H. W., Broer, L., Ayers, K. L., Tan, Q., Kamatani, Y., Bennet, A.
550 M., Tamm, R., Trompet, S., Guethbjartsson, D. F., Flachsbart, F., Rose, G., Viktorin, A.,
551 Fischer, K., Nygaard, M., Cordell, H. J., Crocco, P., van den Akker, E. B., Bohringer, S.,
552 Helmer, Q., Nelson, C. P., Saunders, G. I., Alver, M., Andersen-Ranberg, K., Breen, M.
553 E., van der Breggen, R., Caliebe, A., Capri, M., Cevenini, E., Collerton, J. C., Dato, S.,
554 Davies, K., Ford, I., Gampe, J., Garagnani, P., de Geus, E. J., Harrow, J., van Heemst, D.,
555 Heijmans, B. T., Heinsen, F. A., Hottenga, J. J., Hofman, A., Jeune, B., Jonsson, P. V.,
556 Lathrop, M., Lechner, D., Martin-Ruiz, C., McNerlan, S. E., Mihailov, E., Montesanto,
557 A., Mooijaart, S. P., Murphy, A., Nohr, E. A., Paternoster, L., Postmus, I., Rivadeneira,
558 F., Ross, O. A., Salvioli, S., Sattar, N., Schreiber, S., Stefansson, H., Stott, D. J., Tiemeier,
559 H., Uitterlinden, A. G., Westendorp, R. G., Willemse, G., Samani, N. J., Galan, P.,
560 Sorensen, T. I., Boomsma, D. I., Jukema, J. W., Rea, I. M., Passarino, G., de Craen, A. J.,

- 561 Christensen, K., Nebel, A., Stefansson, K., Metspalu, A., Magnusson, P., Blanche, H.,
562 Christiansen, L., Kirkwood, T. B., van Duijn, C. M., Franceschi, C., Houwing-
563 Duistermaat, J. J., & Slagboom, P. E. (2014, Aug 15). Genome-wide association meta-
564 analysis of human longevity identifies a novel locus conferring survival beyond 90 years
565 of age. *Hum Mol Genet*, 23(16), 4420-4432. <https://doi.org/10.1093/hmg/ddu139>
566
- 567 Deelen, J., Evans, D. S., Arking, D. E., Tesi, N., Nygaard, M., Liu, X., Wojczynski, M. K., Biggs,
568 M. L., van der Spek, A., Atzmon, G., Ware, E. B., Sarnowski, C., Smith, A. V., Seppala,
569 I., Cordell, H. J., Dose, J., Amin, N., Arnold, A. M., Ayers, K. L., Barzilai, N., Becker, E.
570 J., Beekman, M., Blanche, H., Christensen, K., Christiansen, L., Collerton, J. C.,
571 Cubaynes, S., Cummings, S. R., Davies, K., Debrabant, B., Deleuze, J. F., Duncan, R.,
572 Faul, J. D., Franceschi, C., Galan, P., Gudnason, V., Harris, T. B., Huisman, M., Hurme,
573 M. A., Jagger, C., Jansen, I., Jylha, M., Kahonen, M., Karasik, D., Kardia, S. L. R.,
574 Kingston, A., Kirkwood, T. B. L., Launer, L. J., Lehtimaki, T., Lieb, W., Lyytikainen, L.
575 P., Martin-Ruiz, C., Min, J., Nebel, A., Newman, A. B., Nie, C., Nohr, E. A., Orwoll, E.
576 S., Perls, T. T., Province, M. A., Psaty, B. M., Raitakari, O. T., Reinders, M. J. T., Robine,
577 J. M., Rotter, J. I., Sebastiani, P., Smith, J., Sorensen, T. I. A., Taylor, K. D., Uitterlinden,
578 A. G., van der Flier, W., van der Lee, S. J., van Duijn, C. M., van Heemst, D., Vaupel, J.
579 W., Weir, D., Ye, K., Zeng, Y., Zheng, W., Holstege, H., Kiel, D. P., Lunetta, K. L.,
580 Slagboom, P. E., & Murabito, J. M. (2019, Aug 14). A meta-analysis of genome-wide
581 association studies identifies multiple longevity genes. *Nat Commun*, 10(1), 3669.
582 <https://doi.org/10.1038/s41467-019-11558-2>
583
- 584 Delaunay, A., Bromberg, K. D., Hayashi, Y., Mirabella, M., Burch, D., Kirkwood, B., Serra, C.,
585 Malicdan, M. C., Mizisin, A. P., Morosetti, R., Broccolini, A., Guo, L. T., Jones, S. N.,
586 Lira, S. A., Puri, P. L., Shelton, G. D., & Ronai, Z. (2008, Feb 13). The ER-bound RING
587 finger protein 5 (RNF5/RMA1) causes degenerative myopathy in transgenic mice and is
588 deregulated in inclusion body myositis. *PLoS One*, 3(2), e1609.
589 <https://doi.org/10.1371/journal.pone.0001609>
590
- 591 Engberg, H., Oksuzyan, A., Jeune, B., Vaupel, J. W., & Christensen, K. (2009, Jun).
592 Centenarians--a useful model for healthy aging? A 29-year follow-up of hospitalizations
593 among 40,000 Danes born in 1905. *Aging Cell*, 8(3), 270-276.
594 <https://doi.org/10.1111/j.1474-9726.2009.00474.x>
595
- 596 Falvella, F. S., Galvan, A., Colombo, F., Frullanti, E., Pastorino, U., & Dragani, T. A. (2010, Sep
597 8). Promoter polymorphisms and transcript levels of nicotinic receptor CHRNA5. *J Natl
598 Cancer Inst*, 102(17), 1366-1370. <https://doi.org/10.1093/jnci/djq264>
599
- 600 Flachsbart, F., Caliebe, A., Kleindorp, R., Blanche, H., von Eller-Eberstein, H., Nikolaus, S.,
601 Schreiber, S., & Nebel, A. (2009, Feb 24). Association of FOXO3A variation with human
602 longevity confirmed in German centenarians. *Proc Natl Acad Sci U S A*, 106(8), 2700-
603 2705. <https://doi.org/10.1073/pnas.0809594106>
604
- 605 Flachsbart, F., Dose, J., Gentschew, L., Geismann, C., Caliebe, A., Knecht, C., Nygaard, M.,
606 Badarinarayan, N., ElSharawy, A., May, S., Luzius, A., Torres, G. G., Jentzsch, M.,

- 607 Forster, M., Hasler, R., Pallauf, K., Lieb, W., Derbois, C., Galan, P., Drichel, D., Arlt, A.,
608 Till, A., Krause-Kyora, B., Rimbach, G., Blanche, H., Deleuze, J. F., Christiansen, L.,
609 Christensen, K., Nothnagel, M., Rosenstiel, P., Schreiber, S., Franke, A., Sebens, S., &
610 Nebel, A. (2017, Dec 12). Identification and characterization of two functional variants in
611 the human longevity gene FOXO3. *Nat Commun*, 8(1), 2063.
612 <https://doi.org/10.1038/s41467-017-02183-y>
613
- 614 Fortney, K., Dobriban, E., Garagnani, P., Pirazzini, C., Monti, D., Mari, D., Atzman, G., Barzilai,
615 N., Franceschi, C., Owen, A. B., & Kim, S. K. (2015, Dec). Genome-Wide Scan
616 Informed by Age-Related Disease Identifies Loci for Exceptional Human Longevity.
617 *PLoS Genet*, 11(12), e1005728. <https://doi.org/10.1371/journal.pgen.1005728>
618
- 619 Fritzsche, L. G., Chen, W., Schu, M., Yaspan, B. L., Yu, Y., Thorleifsson, G., Zack, D. J.,
620 Arakawa, S., Cipriani, V., Ripke, S., Igo, R. P., Jr., Buitendijk, G. H., Sim, X., Weeks, D.
621 E., Guymer, R. H., Merriam, J. E., Francis, P. J., Hannum, G., Agarwal, A., Armbrecht,
622 A. M., Audo, I., Aung, T., Barile, G. R., Benchaboune, M., Bird, A. C., Bishop, P. N.,
623 Branham, K. E., Brooks, M., Brucker, A. J., Cade, W. H., Cain, M. S., Campochiaro, P.
624 A., Chan, C. C., Cheng, C. Y., Chew, E. Y., Chin, K. A., Chowers, I., Clayton, D. G.,
625 Cojocaru, R., Conley, Y. P., Cornes, B. K., Daly, M. J., Dhillon, B., Edwards, A. O.,
626 Evangelou, E., Fagerness, J., Ferreyra, H. A., Friedman, J. S., Geirsdottir, A., George, R.
627 J., Gieger, C., Gupta, N., Hagstrom, S. A., Harding, S. P., Haritoglou, C., Heckenlively, J.
628 R., Holz, F. G., Hughes, G., Ioannidis, J. P., Ishibashi, T., Joseph, P., Jun, G., Kamatani,
629 Y., Katsanis, N., C. N. K., Khan, J. C., Kim, I. K., Kiyohara, Y., Klein, B. E., Klein, R.,
630 Kovach, J. L., Kozak, I., Lee, C. J., Lee, K. E., Lichtner, P., Lotery, A. J., Meitinger, T.,
631 Mitchell, P., Mohand-Said, S., Moore, A. T., Morgan, D. J., Morrison, M. A., Myers, C.
632 E., Naj, A. C., Nakamura, Y., Okada, Y., Orlin, A., Ortube, M. C., Othman, M. I., Pappas,
633 C., Park, K. H., Pauer, G. J., Peache, N. S., Poch, O., Priya, R. R., Reynolds, R.,
634 Richardson, A. J., Ripp, R., Rudolph, G., Ryu, E., Sahel, J. A., Schaumberg, D. A.,
635 Scholl, H. P., Schwartz, S. G., Scott, W. K., Shahid, H., Sigurdsson, H., Silvestri, G.,
636 Sivakumaran, T. A., Smith, R. T., Sobrin, L., Souied, E. H., Stambolian, D. E.,
637 Stefansson, H., Sturgill-Short, G. M., Takahashi, A., Tosakulwong, N., Truitt, B. J.,
638 Tsironi, E. E., Uitterlinden, A. G., van Duijn, C. M., Vijaya, L., Vingerling, J. R., Vithana,
639 E. N., Webster, A. R., Wichmann, H. E., Winkler, T. W., Wong, T. Y., Wright, A. F.,
640 Zelenika, D., Zhang, M., Zhao, L., Zhang, K., Klein, M. L., Hageman, G. S., Lathrop, G.
641 M., Stefansson, K., Allikmets, R., Baird, P. N., Gorin, M. B., Wang, J. J., Klaver, C. C.,
642 Seddon, J. M., Pericak-Vance, M. A., Iyengar, S. K., Yates, J. R., Swaroop, A., Weber, B.
643 H., Kubo, M., Deangelis, M. M., Leveillard, T., Thorsteinsdottir, U., Haines, J. L., Farrer,
644 L. A., Heid, I. M., Abecasis, G. R., & Consortium, A. M. D. G. (2013, Apr). Seven new
645 loci associated with age-related macular degeneration. *Nat Genet*, 45(4), 433-439,
646 439e431-432. <https://doi.org/10.1038/ng.2578>
647
- 648 Gallagher, C. S., Makinen, N., Harris, H. R., Rahmioglu, N., Uimari, O., Cook, J. P., Shigesi, N.,
649 Ferreira, T., Velez-Edwards, D. R., Edwards, T. L., Mortlock, S., Ruhioglu, Z., Day, F.,
650 Becker, C. M., Karhunen, V., Martikainen, H., Jarvelin, M. R., Cantor, R. M., Ridker, P.
651 M., Terry, K. L., Buring, J. E., Gordon, S. D., Medland, S. E., Montgomery, G. W.,
652 Nyholt, D. R., Hinds, D. A., Tung, J. Y., andMe Research, T., Perry, J. R. B., Lind, P. A.,

- 653 Painter, J. N., Martin, N. G., Morris, A. P., Chasman, D. I., Missmer, S. A., Zondervan, K.
654 T., & Morton, C. C. (2019, Oct 24). Genome-wide association and epidemiological
655 analyses reveal common genetic origins between uterine leiomyomata and endometriosis.
656 *Nat Commun*, 10(1), 4857. <https://doi.org/10.1038/s41467-019-12536-4>
657
- 658 Giambartolomei, C., Vukcevic, D., Schadt, E. E., Franke, L., Hingorani, A. D., Wallace, C., &
659 Plagnol, V. (2014, May). Bayesian test for colocalisation between pairs of genetic
660 association studies using summary statistics. *PLoS Genet*, 10(5), e1004383.
661 <https://doi.org/10.1371/journal.pgen.1004383>
662
- 663 Graff, M., Scott, R. A., Justice, A. E., Young, K. L., Feitosa, M. F., Barata, L., Winkler, T. W.,
664 Chu, A. Y., Mahajan, A., Hadley, D., Xue, L., Workalemahu, T., Heard-Costa, N. L., den
665 Hoed, M., Ahluwalia, T. S., Qi, Q., Ngwa, J. S., Renstrom, F., Quaye, L., Eicher, J. D.,
666 Hayes, J. E., Cornelis, M., Kutalik, Z., Lim, E., Luan, J., Huffman, J. E., Zhang, W.,
667 Zhao, W., Griffin, P. J., Haller, T., Ahmad, S., Marques-Vidal, P. M., Bien, S., Yengo, L.,
668 Teumer, A., Smith, A. V., Kumari, M., Harder, M. N., Justesen, J. M., Kleber, M. E.,
669 Hollensted, M., Lohman, K., Rivera, N. V., Whitfield, J. B., Zhao, J. H., Stringham, H.
670 M., Lyytikainen, L. P., Huppertz, C., Willemse, G., Peyrot, W. J., Wu, Y., Kristiansson,
671 K., Demirkan, A., Fornage, M., Hassinen, M., Bielak, L. F., Cadby, G., Tanaka, T., Magi,
672 R., van der Most, P. J., Jackson, A. U., Bragg-Gresham, J. L., Vitart, V., Marten, J.,
673 Navarro, P., Bellis, C., Pasko, D., Johansson, A., Snitker, S., Cheng, Y. C., Eriksson, J.,
674 Lim, U., Aadahl, M., Adair, L. S., Amin, N., Balkau, B., Auvinen, J., Beilby, J., Bergman,
675 R. N., Bergmann, S., Bertoni, A. G., Blangero, J., Bonnefond, A., Bonnycastle, L. L.,
676 Borja, J. B., Brage, S., Busonero, F., Buyske, S., Campbell, H., Chines, P. S., Collins, F.
677 S., Corre, T., Smith, G. D., Delgado, G. E., Dueker, N., Dorr, M., Ebeling, T., Eiriksdottir,
678 G., Esko, T., Faul, J. D., Fu, M., Faerch, K., Gieger, C., Glaser, S., Gong, J., Gordon-
679 Larsen, P., Grallert, H., Grammer, T. B., Grarup, N., van Grootheest, G., Harald, K.,
680 Hastie, N. D., Havulinna, A. S., Hernandez, D., Hindorff, L., Hocking, L. J., Holmens, O.
681 L., Holzapfel, C., Hottenga, J. J., Huang, J., Huang, T., Hui, J., Huth, C., Hutri-Kahonen,
682 N., James, A. L., Jansson, J. O., Jhun, M. A., Juonala, M., Kinnunen, L., Koistinen, H. A.,
683 Kolcic, I., Komulainen, P., Kuusisto, J., Kvaloy, K., Kahonen, M., Lakka, T. A., Launer,
684 L. J., Lehne, B., Lindgren, C. M., Lorentzon, M., Luben, R., Marre, M., Milaneschi, Y.,
685 Monda, K. L., Montgomery, G. W., De Moor, M. H. M., Mulas, A., Muller-Nurasyid, M.,
686 Musk, A. W., Mannikko, R., Mannisto, S., Narisu, N., Nauck, M., Nettleton, J. A., Nolte,
687 I. M., Oldehinkel, A. J., Olden, M., Ong, K. K., Padmanabhan, S., Paternoster, L., Perez,
688 J., Perola, M., Peters, A., Peters, U., Peyser, P. A., Prokopenko, I., Puolijoki, H.,
689 Raitakari, O. T., Rankinen, T., Rasmussen-Torvik, L. J., Rawal, R., Ridker, P. M., Rose,
690 L. M., Rudan, I., Sarti, C., Sarzynski, M. A., Savonen, K., Scott, W. R., Sanna, S.,
691 Shuldiner, A. R., Sidney, S., Silbernagel, G., Smith, B. H., Smith, J. A., Snieder, H.,
692 Stancakova, A., Sternfeld, B., Swift, A. J., Tammelin, T., Tan, S. T., Thorand, B.,
693 Thuillier, D., Vandenput, L., Vestergaard, H., van Vliet-Ostaptchouk, J. V., Vohl, M. C.,
694 Volker, U., Waeber, G., Walker, M., Wild, S., Wong, A., Wright, A. F., Zillikens, M. C.,
695 Zubair, N., Haiman, C. A., Lemarchand, L., Gyllensten, U., Ohlsson, C., Hofman, A.,
696 Rivadeneira, F., Uitterlinden, A. G., Perusse, L., Wilson, J. F., Hayward, C., Polasek, O.,
697 Cucca, F., Hveem, K., Hartman, C. A., Tonjes, A., Bandinelli, S., Palmer, L. J., Kardia, S.
698 L. R., Rauramaa, R., Sorensen, T. I. A., Tuomilehto, J., Salomaa, V., Penninx, B., de

- 699 Geus, E. J. C., Boomsma, D. I., Lehtimaki, T., Mangino, M., Laakso, M., Bouchard, C.,
700 Martin, N. G., Kuh, D., Liu, Y., Linneberg, A., Marz, W., Strauch, K., Kivimaki, M.,
701 Harris, T. B., Gudnason, V., Volzke, H., Qi, L., Jarvelin, M. R., Chambers, J. C., Kooner,
702 J. S., Froguel, P., Kooperberg, C., Vollenweider, P., Hallmans, G., Hansen, T., Pedersen,
703 O., Metspalu, A., Wareham, N. J., Langenberg, C., Weir, D. R., Porteous, D. J.,
704 Boerwinkle, E., Chasman, D. I., Consortium, C., Consortium, E. P.-I., Consortium, P.,
705 Abecasis, G. R., Barroso, I., McCarthy, M. I., Frayling, T. M., O'Connell, J. R., van
706 Duijn, C. M., Boehnke, M., Heid, I. M., Mohlke, K. L., Strachan, D. P., Fox, C. S., Liu, C.
707 T., Hirschhorn, J. N., Klein, R. J., Johnson, A. D., Borecki, I. B., Franks, P. W., North, K.
708 E., Cupples, L. A., Loos, R. J. F., & Kilpelainen, T. O. (2017, Apr). Genome-wide
709 physical activity interactions in adiposity - A meta-analysis of 200,452 adults. *PLoS Genet*, 13(4), e1006528. <https://doi.org/10.1371/journal.pgen.1006528>
710
- 711
- 712 Hao, K., Bosse, Y., Nickle, D. C., Pare, P. D., Postma, D. S., Laviolette, M., Sandford, A.,
713 Hackett, T. L., Daley, D., Hogg, J. C., Elliott, W. M., Couture, C., Lamontagne, M.,
714 Brandsma, C. A., van den Berge, M., Koppelman, G., Reicin, A. S., Nicholson, D. W.,
715 Malkov, V., Derry, J. M., Suver, C., Tsou, J. A., Kulkarni, A., Zhang, C., Vessey, R.,
716 Opiteck, G. J., Curtis, S. P., Timens, W., & Sin, D. D. (2012). Lung eQTLs to help reveal
717 the molecular underpinnings of asthma. *PLoS Genet*, 8(11), e1003029.
718 <https://doi.org/10.1371/journal.pgen.1003029>
719
- 720 Herskind, A. M., McGue, M., Holm, N. V., Sorensen, T. I., Harvald, B., & Vaupel, J. W. (1996,
721 Mar). The heritability of human longevity: a population-based study of 2872 Danish twin
722 pairs born 1870-1900. *Hum Genet*, 97(3), 319-323. <https://doi.org/10.1007/BF02185763>
723
- 724 Huang da, W., Sherman, B. T., & Lempicki, R. A. (2009, Jan). Bioinformatics enrichment tools:
725 paths toward the comprehensive functional analysis of large gene lists. *Nucleic Acids Res*,
726 37(1), 1-13. <https://doi.org/10.1093/nar/gkn923>
727
- 728 Jansen, I. E., Savage, J. E., Watanabe, K., Bryois, J., Williams, D. M., Steinberg, S., Sealock, J.,
729 Karlsson, I. K., Hagg, S., Athanasiu, L., Voyle, N., Proitsi, P., Witoelar, A., Stringer, S.,
730 Aarsland, D., Almdahl, I. S., Andersen, F., Bergh, S., Bettella, F., Bjornsson, S.,
731 Braekhus, A., Brathen, G., de Leeuw, C., Desikan, R. S., Djurovic, S., Dumitrescu, L.,
732 Fladby, T., Hohman, T. J., Jonsson, P. V., Kiddie, S. J., Rongve, A., Saltvedt, I., Sando, S.
733 B., Selbaek, G., Shoai, M., Skene, N. G., Snaedal, J., Stordal, E., Ulstein, I. D., Wang, Y.,
734 White, L. R., Hardy, J., Hjerling-Leffler, J., Sullivan, P. F., van der Flier, W. M., Dobson,
735 R., Davis, L. K., Stefansson, H., Stefansson, K., Pedersen, N. L., Ripke, S., Andreassen,
736 O. A., & Posthuma, D. (2019, Mar). Genome-wide meta-analysis identifies new loci and
737 functional pathways influencing Alzheimer's disease risk. *Nat Genet*, 51(3), 404-413.
738 <https://doi.org/10.1038/s41588-018-0311-9>
739
- 740 Jasinska, A. J. (2020, May). Resources for functional genomic studies of health and development
741 in nonhuman primates. *Am J Phys Anthropol*, 171 Suppl 70, 174-194.
742 <https://doi.org/10.1002/ajpa.24051>
743

- 744 Jaul, E., & Barron, J. (2017). Age-Related Diseases and Clinical and Public Health Implications
745 for the 85 Years Old and Over Population. *Front Public Health*, 5, 335.
746 <https://doi.org/10.3389/fpubh.2017.00335>
- 747
- 748 Joshi, P. K., Pirastu, N., Kentistou, K. A., Fischer, K., Hofer, E., Schraut, K. E., Clark, D. W.,
749 Nutile, T., Barnes, C. L. K., Timmers, P., Shen, X., Gandin, I., McDaid, A. F., Hansen, T.
750 F., Gordon, S. D., Giulianini, F., Boutin, T. S., Abdellaoui, A., Zhao, W., Medina-Gomez,
751 C., Bartz, T. M., Trompet, S., Lange, L. A., Raffield, L., van der Spek, A., Galesloot, T.
752 E., Proitsi, P., Yanek, L. R., Bielak, L. F., Payton, A., Murgia, F., Concias, M. P., Biino,
753 G., Tajuddin, S. M., Seppala, I., Amin, N., Boerwinkle, E., Borglum, A. D., Campbell, A.,
754 Demerath, E. W., Demuth, I., Faul, J. D., Ford, I., Gialluisi, A., Gogele, M., Graff, M.,
755 Hingorani, A., Hottenga, J. J., Hougaard, D. M., Hurme, M. A., Ikram, M. A., Jylha, M.,
756 Kuh, D., Ligthart, L., Lill, C. M., Lindenberger, U., Lumley, T., Magi, R., Marques-Vidal,
757 P., Medland, S. E., Milani, L., Nagy, R., Ollier, W. E. R., Peyser, P. A., Pramstaller, P. P.,
758 Ridker, P. M., Rivadeneira, F., Ruggiero, D., Saba, Y., Schmidt, R., Schmidt, H.,
759 Slagboom, P. E., Smith, B. H., Smith, J. A., Sotoodehnia, N., Steinhagen-Thiessen, E.,
760 van Rooij, F. J. A., Verbeek, A. L., Vermeulen, S. H., Vollenweider, P., Wang, Y.,
761 Werge, T., Whitfield, J. B., Zonderman, A. B., Lehtimaki, T., Evans, M. K., Pirastu, M.,
762 Fuchsberger, C., Bertram, L., Pendleton, N., Kardia, S. L. R., Ciullo, M., Becker, D. M.,
763 Wong, A., Psaty, B. M., van Duijn, C. M., Wilson, J. G., Jukema, J. W., Kiemeney, L.,
764 Uitterlinden, A. G., Franceschini, N., North, K. E., Weir, D. R., Metspalu, A., Boomsma,
765 D. I., Hayward, C., Chasman, D., Martin, N. G., Sattar, N., Campbell, H., Esko, T.,
766 Kutalik, Z., & Wilson, J. F. (2017, Oct 13). Genome-wide meta-analysis associates HLA-
767 DQA1/DRB1 and LPA and lifestyle factors with human longevity. *Nat Commun*, 8(1),
768 910. <https://doi.org/10.1038/s41467-017-00934-5>
- 769
- 770 Jun, G. R., Chung, J., Mez, J., Barber, R., Beecham, G. W., Bennett, D. A., Buxbaum, J. D.,
771 Byrd, G. S., Carrasquillo, M. M., Crane, P. K., Cruchaga, C., De Jager, P., Ertekin-Taner,
772 N., Evans, D., Fallin, M. D., Foroud, T. M., Friedland, R. P., Goate, A. M., Graff-
773 Radford, N. R., Hendrie, H., Hall, K. S., Hamilton-Nelson, K. L., Inzelberg, R., Kamboh,
774 M. I., Kauwe, J. S. K., Kukull, W. A., Kunkle, B. W., Kuwano, R., Larson, E. B., Logue,
775 M. W., Manly, J. J., Martin, E. R., Montine, T. J., Mukherjee, S., Naj, A., Reiman, E. M.,
776 Reitz, C., Sherva, R., St George-Hyslop, P. H., Thornton, T., Younkin, S. G., Vardarajan,
777 B. N., Wang, L. S., Wendlund, J. R., Winslow, A. R., Alzheimer's Disease Genetics, C.,
778 Haines, J., Mayeux, R., Pericak-Vance, M. A., Schellenberg, G., Lunetta, K. L., & Farrer,
779 L. A. (2017, Jul). Transethnic genome-wide scan identifies novel Alzheimer's disease loci.
Alzheimers Dement, 13(7), 727-738. <https://doi.org/10.1016/j.jalz.2016.12.012>
- 780
- 781
- 782 Koopmann, T. T., Adriaens, M. E., Moerland, P. D., Marsman, R. F., Westerveld, M. L., Lal, S.,
783 Zhang, T., Simmons, C. Q., Bacsko, I., dos Remedios, C., Bishopric, N. H., Varro, A.,
784 George, A. L., Jr., Lodder, E. M., & Bezzina, C. R. (2014). Genome-wide identification
785 of expression quantitative trait loci (eQTLs) in human heart. *PLoS One*, 9(5), e97380.
786 <https://doi.org/10.1371/journal.pone.0097380>
- 787
- 788 Krautkramer, K. A., Linnemann, A. K., Fontaine, D. A., Whillock, A. L., Harris, T. W., Schleis,
789 G. J., Truchan, N. A., Marty-Santos, L., Lavine, J. A., Cleaver, O., Kimple, M. E., &

- 790 Davis, D. B. (2013, Sep 1). Tcf19 is a novel islet factor necessary for proliferation and
791 survival in the INS-1 beta-cell line. *Am J Physiol Endocrinol Metab*, 305(5), E600-610.
792 <https://doi.org/10.1152/ajpendo.00147.2013>
793
- 794 Kuhns, D. B., Hsu, A. P., Sun, D., Lau, K., Fink, D., Griffith, P., Huang, D. W., Priel, D. A. L.,
795 Mendez, L., Kreuzburg, S., Zerbe, C. S., De Ravin, S. S., Malech, H. L., Holland, S. M.,
796 Wu, X., & Gallin, J. I. (2019, Jan 22). NCF1 (p47(phox))-deficient chronic
797 granulomatous disease: comprehensive genetic and flow cytometric analysis. *Blood Adv*,
798 3(2), 136-147. <https://doi.org/10.1182/bloodadvances.2018023184>
799
- 800 Li, Y., Wang, W. J., Cao, H., Lu, J., Wu, C., Hu, F. Y., Guo, J., Zhao, L., Yang, F., Zhang, Y. X.,
801 Li, W., Zheng, G. Y., Cui, H., Chen, X., Zhu, Z., He, H., Dong, B., Mo, X., Zeng, Y., &
802 Tian, X. L. (2009, Dec 15). Genetic association of FOXO1A and FOXO3A with
803 longevity trait in Han Chinese populations. *Hum Mol Genet*, 18(24), 4897-4904.
804 <https://doi.org/10.1093/hmg/ddp459>
805
- 806 Mahajan, A., Taliun, D., Thurner, M., Robertson, N. R., Torres, J. M., Rayner, N. W., Payne, A.
807 J., Steinhorsdottir, V., Scott, R. A., Grarup, N., Cook, J. P., Schmidt, E. M., Wuttke, M.,
808 Sarnowski, C., Magi, R., Nano, J., Gieger, C., Trompet, S., Lecoeur, C., Preuss, M. H.,
809 Prins, B. P., Guo, X., Bielak, L. F., Below, J. E., Bowden, D. W., Chambers, J. C., Kim,
810 Y. J., Ng, M. C. Y., Petty, L. E., Sim, X., Zhang, W., Bennett, A. J., Bork-Jensen, J.,
811 Brummett, C. M., Canouil, M., Ec Kardt, K. U., Fischer, K., Kardia, S. L. R., Kronenberg,
812 F., Lall, K., Liu, C. T., Locke, A. E., Luan, J., Ntalla, I., Nylander, V., Schonherr, S.,
813 Schurmann, C., Yengo, L., Bottinger, E. P., Brandslund, I., Christensen, C., Dedoussis,
814 G., Florez, J. C., Ford, I., Franco, O. H., Frayling, T. M., Giedraitis, V., Hackinger, S.,
815 Hattersley, A. T., Herder, C., Ikram, M. A., Ingelsson, M., Jorgensen, M. E., Jorgensen,
816 T., Kriebel, J., Kuusisto, J., Ligthart, S., Lindgren, C. M., Linneberg, A., Lyssenko, V.,
817 Mamakou, V., Meitinger, T., Mohlke, K. L., Morris, A. D., Nadkarni, G., Pankow, J. S.,
818 Peters, A., Sattar, N., Stancakova, A., Strauch, K., Taylor, K. D., Thorand, B.,
819 Thorleifsson, G., Thorsteinsdottir, U., Tuomilehto, J., Witte, D. R., Dupuis, J., Peyser, P.
820 A., Zeggini, E., Loos, R. J. F., Froguel, P., Ingelsson, E., Lind, L., Groop, L., Laakso, M.,
821 Collins, F. S., Jukema, J. W., Palmer, C. N. A., Grallert, H., Metspalu, A., Dehghan, A.,
822 Kottgen, A., Abecasis, G. R., Meigs, J. B., Rotter, J. I., Marchini, J., Pedersen, O.,
823 Hansen, T., Langenberg, C., Wareham, N. J., Stefansson, K., Gloyn, A. L., Morris, A. P.,
824 Boehnke, M., & McCarthy, M. I. (2018, Nov). Fine-mapping type 2 diabetes loci to
825 single-variant resolution using high-density imputation and islet-specific epigenome
826 maps. *Nat Genet*, 50(11), 1505-1513. <https://doi.org/10.1038/s41588-018-0241-6>
827
- 828 Mahajan, A., Wessel, J., Willems, S. M., Zhao, W., Robertson, N. R., Chu, A. Y., Gan, W.,
829 Kitajima, H., Taliun, D., Rayner, N. W., Guo, X., Lu, Y., Li, M., Jensen, R. A., Hu, Y.,
830 Huo, S., Lohman, K. K., Zhang, W., Cook, J. P., Prins, B. P., Flannick, J., Grarup, N.,
831 Trubetskoy, V. V., Kravic, J., Kim, Y. J., Rybin, D. V., Yaghootkar, H., Muller-Nurasyid,
832 M., Meidner, K., Li-Gao, R., Varga, T. V., Marten, J., Li, J., Smith, A. V., An, P.,
833 Ligthart, S., Gustafsson, S., Malerba, G., Demirkhan, A., Tajes, J. F., Steinhorsdottir, V.,
834 Wuttke, M., Lecoeur, C., Preuss, M., Bielak, L. F., Graff, M., Highland, H. M., Justice, A.
835 E., Liu, D. J., Marouli, E., Peloso, G. M., Warren, H. R., Exome, B. P. C., Consortium,

- 836 M., Consortium, G., Afaq, S., Afzal, S., Ahlqvist, E., Almgren, P., Amin, N., Bang, L. B.,
837 Bertoni, A. G., Bombieri, C., Bork-Jensen, J., Brandslund, I., Brody, J. A., Burtt, N. P.,
838 Canouil, M., Chen, Y. I., Cho, Y. S., Christensen, C., Eastwood, S. V., Eckardt, K. U.,
839 Fischer, K., Gambaro, G., Giedraitis, V., Grove, M. L., de Haan, H. G., Hackinger, S.,
840 Hai, Y., Han, S., Tybjaerg-Hansen, A., Hivert, M. F., Isomaa, B., Jager, S., Jorgensen, M.
841 E., Jorgensen, T., Karajamaki, A., Kim, B. J., Kim, S. S., Koistinen, H. A., Kovacs, P.,
842 Kriebel, J., Kronenberg, F., Lall, K., Lange, L. A., Lee, J. J., Lehne, B., Li, H., Lin, K. H.,
843 Linneberg, A., Liu, C. T., Liu, J., Loh, M., Magi, R., Mamakou, V., McKean-Cowdin, R.,
844 Nadkarni, G., Neville, M., Nielsen, S. F., Ntalla, I., Peyser, P. A., Rathmann, W., Rice,
845 K., Rich, S. S., Rode, L., Rolandsson, O., Schonherr, S., Selvin, E., Small, K. S.,
846 Stancakova, A., Surendran, P., Taylor, K. D., Teslovich, T. M., Thorand, B., Thorleifsson,
847 G., Tin, A., Tonjes, A., Varbo, A., Witte, D. R., Wood, A. R., Yajnik, P., Yao, J., Yengo,
848 L., Young, R., Amouyel, P., Boeing, H., Boerwinkle, E., Bottinger, E. P., Chowdhury, R.,
849 Collins, F. S., Dedoussis, G., Dehghan, A., Deloukas, P., Ferrario, M. M., Ferrieres, J.,
850 Florez, J. C., Frossard, P., Gudnason, V., Harris, T. B., Heckbert, S. R., Howson, J. M.
851 M., Ingelsson, M., Kathiresan, S., Kee, F., Kuusisto, J., Langenberg, C., Launer, L. J.,
852 Lindgren, C. M., Mannisto, S., Meitinger, T., Melander, O., Mohlke, K. L., Moitry, M.,
853 Morris, A. D., Murray, A. D., de Mutsert, R., Orho-Melander, M., Owen, K. R., Perola,
854 M., Peters, A., Province, M. A., Rasheed, A., Ridker, P. M., Rivadineira, F., Rosendaal, F.
855 R., Rosengren, A. H., Salomaa, V., Sheu, W. H., Sladek, R., Smith, B. H., Strauch, K.,
856 Uitterlinden, A. G., Varma, R., Willer, C. J., Bluher, M., Butterworth, A. S., Chambers, J.
857 C., Chasman, D. I., Danesh, J., van Duijn, C., Dupuis, J., Franco, O. H., Franks, P. W.,
858 Froguel, P., Grallert, H., Groop, L., Han, B. G., Hansen, T., Hattersley, A. T., Hayward,
859 C., Ingelsson, E., Kardia, S. L. R., Karpe, F., Kooner, J. S., Kottgen, A., Kuulasmaa, K.,
860 Laakso, M., Lin, X., Lind, L., Liu, Y., Loos, R. J. F., Marchini, J., Metspalu, A., Mook-
861 Kanamori, D., Nordestgaard, B. G., Palmer, C. N. A., Pankow, J. S., Pedersen, O., Psaty,
862 B. M., Rauramaa, R., Sattar, N., Schulze, M. B., Soranzo, N., Spector, T. D., Stefansson,
863 K., Stumvoll, M., Thorsteinsdottir, U., Tuomi, T., Tuomilehto, J., Wareham, N. J.,
864 Wilson, J. G., Zeggini, E., Scott, R. A., Barroso, I., Frayling, T. M., Goodarzi, M. O.,
865 Meigs, J. B., Boehnke, M., Saleheen, D., Morris, A. P., Rotter, J. I., & McCarthy, M. I.
866 (2018, Apr). Refining the accuracy of validated target identification through coding
867 variant fine-mapping in type 2 diabetes. *Nat Genet*, 50(4), 559-571.
<https://doi.org/10.1038/s41588-018-0084-1>
868
869
870 Malik, R., Chauhan, G., Traylor, M., Sargurupremraj, M., Okada, Y., Mishra, A., Rutten-Jacobs,
871 L., Giese, A. K., van der Laan, S. W., Gretarsdottir, S., Anderson, C. D., Chong, M.,
872 Adams, H. H. H., Ago, T., Almgren, P., Amouyel, P., Ay, H., Bartz, T. M., Benavente, O.
873 R., Bevan, S., Boncoraglio, G. B., Brown, R. D., Jr., Butterworth, A. S., Carrera, C.,
874 Carty, C. L., Chasman, D. I., Chen, W. M., Cole, J. W., Correa, A., Cotlarciuc, I.,
875 Cruchaga, C., Danesh, J., de Bakker, P. I. W., DeStefano, A. L., den Hoed, M., Duan, Q.,
876 Engelter, S. T., Falcone, G. J., Gottesman, R. F., Grewal, R. P., Gudnason, V.,
877 Gustafsson, S., Haessler, J., Harris, T. B., Hassan, A., Havulinna, A. S., Heckbert, S. R.,
878 Holliday, E. G., Howard, G., Hsu, F. C., Hyacinth, H. I., Ikram, M. A., Ingelsson, E.,
879 Irvin, M. R., Jian, X., Jimenez-Conde, J., Johnson, J. A., Jukema, J. W., Kanai, M.,
880 Keene, K. L., Kissela, B. M., Kleindorfer, D. O., Kooperberg, C., Kubo, M., Lange, L. A.,
881 Langefeld, C. D., Langenberg, C., Launer, L. J., Lee, J. M., Lemmens, R., Leys, D.,

- 882 Lewis, C. M., Lin, W. Y., Lindgren, A. G., Lorentzen, E., Magnusson, P. K., Maguire, J.,
883 Manichaikul, A., McArdle, P. F., Meschia, J. F., Mitchell, B. D., Mosley, T. H., Nalls, M.
884 A., Ninomiya, T., O'Donnell, M. J., Psaty, B. M., Pulit, S. L., Rannikmae, K., Reiner, A.
885 P., Rexrode, K. M., Rice, K., Rich, S. S., Ridker, P. M., Rost, N. S., Rothwell, P. M.,
886 Rotter, J. I., Rundek, T., Sacco, R. L., Sakaue, S., Sale, M. M., Salomaa, V., Sapkota, B.
887 R., Schmidt, R., Schmidt, C. O., Schminke, U., Sharma, P., Slowik, A., Sudlow, C. L. M.,
888 Tanislav, C., Tatlisumak, T., Taylor, K. D., Thijs, V. N. S., Thorleifsson, G.,
889 Thorsteinsdottir, U., Tiedt, S., Trompet, S., Tzourio, C., van Duijn, C. M., Walters, M.,
890 Wareham, N. J., Wassertheil-Smoller, S., Wilson, J. G., Wiggins, K. L., Yang, Q., Yusuf,
891 S., Consortium, A. F., Cohorts for, H., Aging Research in Genomic Epidemiology, C.,
892 International Genomics of Blood Pressure, C., Consortium, I., Starnet, Bis, J. C., Pastinen,
893 T., Ruusalepp, A., Schadt, E. E., Koplev, S., Bjorkegren, J. L. M., Codoni, V., Civelek,
894 M., Smith, N. L., Tregouet, D. A., Christophersen, I. E., Roselli, C., Lubitz, S. A., Ellinor,
895 P. T., Tai, E. S., Kooner, J. S., Kato, N., He, J., van der Harst, P., Elliott, P., Chambers, J.
896 C., Takeuchi, F., Johnson, A. D., BioBank Japan Cooperative Hospital, G., Consortium,
897 C., Consortium, E.-C., Consortium, E. P.-I., International Stroke Genetics, C.,
898 Consortium, M., Neurology Working Group of the, C. C., Network, N. S. G., Study, U. K.
899 Y. L. D., Consortium, M., Sanghera, D. K., Melander, O., Jern, C., Strbian, D.,
900 Fernandez-Cadenas, I., Longstreth, W. T., Jr., Rolfs, A., Hata, J., Woo, D., Rosand, J.,
901 Pare, G., Hopewell, J. C., Saleheen, D., Stefansson, K., Worrall, B. B., Kittner, S. J.,
902 Seshadri, S., Fornage, M., Markus, H. S., Howson, J. M. M., Kamatani, Y., Debette, S.,
903 & Dichgans, M. (2018, Apr). Multiancestry genome-wide association study of 520,000
904 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet*, 50(4),
905 524-537. <https://doi.org/10.1038/s41588-018-0058-3>
906
907 McDaid, A. F., Joshi, P. K., Porcu, E., Komljenovic, A., Li, H., Sorrentino, V., Litovchenko, M.,
908 Bevers, R. P. J., Rueger, S., Reymond, A., Bochud, M., Deplancke, B., Williams, R. W.,
909 Robinson-Rechavi, M., Paccaud, F., Rousson, V., Auwerx, J., Wilson, J. F., & Katalik, Z.
910 (2017, Jul 27). Bayesian association scan reveals loci associated with human lifespan and
911 linked biomarkers. *Nat Commun*, 8, 15842. <https://doi.org/10.1038/ncomms15842>
912
913 Melzer, D., Pilling, L. C., & Ferrucci, L. (2020, Feb). The genetics of human ageing. *Nat Rev
914 Genet*, 21(2), 88-101. <https://doi.org/10.1038/s41576-019-0183-6>
915
916 Menon, A. G., Morreau, H., Tollenaar, R. A., Alphenaar, E., Van Puijenbroek, M., Putter, H.,
917 Janssen-Van Rhijn, C. M., Van De Velde, C. J., Fleuren, G. J., & Kuppen, P. J. (2002,
918 Dec). Down-regulation of HLA-A expression correlates with a better prognosis in
919 colorectal cancer patients. *Lab Invest*, 82(12), 1725-1733.
920 <https://doi.org/10.1097/01.lab.0000043124.75633.ed>
921
922 Michailidou, K., Lindstrom, S., Dennis, J., Beesley, J., Hui, S., Kar, S., Lemacon, A., Soucy, P.,
923 Glubb, D., Rostamianfar, A., Bolla, M. K., Wang, Q., Tyrer, J., Dicks, E., Lee, A., Wang,
924 Z., Allen, J., Keeman, R., Eilber, U., French, J. D., Qing Chen, X., Fachal, L., McCue, K.,
925 McCart Reed, A. E., Ghousaini, M., Carroll, J. S., Jiang, X., Finucane, H., Adams, M.,
926 Adank, M. A., Ahsan, H., Aittomaki, K., Anton-Culver, H., Antonenkova, N. N., Arndt,
927 V., Aronson, K. J., Arun, B., Auer, P. L., Bacot, F., Barrdahl, M., Baynes, C., Beckmann,

928 M. W., Behrens, S., Benitez, J., Bermisheva, M., Bernstein, L., Blomqvist, C.,
929 Bogdanova, N. V., Bojesen, S. E., Bonanni, B., Borresen-Dale, A. L., Brand, J. S.,
930 Brauch, H., Brennan, P., Brenner, H., Brinton, L., Broberg, P., Brock, I. W., Broeks, A.,
931 Brooks-Wilson, A., Brucker, S. Y., Bruning, T., Burwinkel, B., Butterbach, K., Cai, Q.,
932 Cai, H., Caldes, T., Canzian, F., Carracedo, A., Carter, B. D., Castelao, J. E., Chan, T. L.,
933 David Cheng, T. Y., Seng Chia, K., Choi, J. Y., Christiansen, H., Clarke, C. L.,
934 Collaborators, N., Collee, M., Conroy, D. M., Cordina-Duverger, E., Cornelissen, S., Cox,
935 D. G., Cox, A., Cross, S. S., Cunningham, J. M., Czene, K., Daly, M. B., Devilee, P.,
936 Doheny, K. F., Dork, T., Dos-Santos-Silva, I., Dumont, M., Durcan, L., Dwek, M.,
937 Eccles, D. M., Ekici, A. B., Eliassen, A. H., Ellberg, C., Elvira, M., Engel, C., Eriksson,
938 M., Fasching, P. A., Figueroa, J., Flesch-Janys, D., Fletcher, O., Flyger, H., Fritschl, L.,
939 Gaborieau, V., Gabrielson, M., Gago-Dominguez, M., Gao, Y. T., Gapstur, S. M.,
940 Garcia-Saenz, J. A., Gaudet, M. M., Georgoulias, V., Giles, G. G., Glendon, G.,
941 Goldberg, M. S., Goldgar, D. E., Gonzalez-Neira, A., Grenaker Alnaes, G. I., Grip, M.,
942 Gronwald, J., Grundy, A., Guenel, P., Haeberle, L., Hahnen, E., Haiman, C. A.,
943 Hakansson, N., Hamann, U., Hamel, N., Hankinson, S., Harrington, P., Hart, S. N.,
944 Hartikainen, J. M., Hartman, M., Hein, A., Heyworth, J., Hicks, B., Hillemanns, P., Ho,
945 D. N., Hollestelle, A., Hooning, M. J., Hoover, R. N., Hopper, J. L., Hou, M. F., Hsiung,
946 C. N., Huang, G., Humphreys, K., Ishiguro, J., Ito, H., Iwasaki, M., Iwata, H.,
947 Jakubowska, A., Janni, W., John, E. M., Johnson, N., Jones, K., Jones, M., Jukkola-
948 Vuorinen, A., Kaaks, R., Kabisch, M., Kaczmarek, K., Kang, D., Kasuga, Y., Kerin, M.
949 J., Khan, S., Khusnutdinova, E., Kiiski, J. I., Kim, S. W., Knight, J. A., Kosma, V. M.,
950 Kristensen, V. N., Kruger, U., Kwong, A., Lambrechts, D., Le Marchand, L., Lee, E., Lee,
951 M. H., Lee, J. W., Neng Lee, C., Lejbkowicz, F., Li, J., Lilyquist, J., Lindblom, A.,
952 Lissowska, J., Lo, W. Y., Loibl, S., Long, J., Lophatananon, A., Lubinski, J., Luccarini,
953 C., Lux, M. P., Ma, E. S. K., MacInnis, R. J., Maishman, T., Makalic, E., Malone, K. E.,
954 Kostovska, I. M., Mannermaa, A., Manoukian, S., Manson, J. E., Margolin, S., Mariapun,
955 S., Martinez, M. E., Matsuo, K., Mavroudis, D., McKay, J., McLean, C., Meijers-
956 Heijboer, H., Meindl, A., Menendez, P., Menon, U., Meyer, J., Miao, H., Miller, N., Taib,
957 N. A. M., Muir, K., Mulligan, A. M., Mulot, C., Neuhausen, S. L., Nevanlinna, H., Neven,
958 P., Nielsen, S. F., Noh, D. Y., Nordestgaard, B. G., Norman, A., Olopade, O. I., Olson, J.
959 E., Olsson, H., Olswold, C., Orr, N., Pankratz, V. S., Park, S. K., Park-Simon, T. W.,
960 Lloyd, R., Perez, J. I. A., Peterlongo, P., Peto, J., Phillips, K. A., Pinchev, M., Plaseska-
961 Karanfilska, D., Prentice, R., Presneau, N., Prokofyeva, D., Pugh, E., Pylkas, K., Rack,
962 B., Radice, P., Rahman, N., Rennert, G., Rennert, H. S., Rhenius, V., Romero, A., Romm,
963 J., Ruddy, K. J., Rudiger, T., Rudolph, A., Ruebner, M., Rutgers, E. J. T., Saloustros, E.,
964 Sandler, D. P., Sangrajrang, S., Sawyer, E. J., Schmidt, D. F., Schmutzler, R. K.,
965 Schneeweiss, A., Schoemaker, M. J., Schumacher, F., Schurmann, P., Scott, R. J., Scott,
966 C., Seal, S., Seynaeve, C., Shah, M., Sharma, P., Shen, C. Y., Sheng, G., Sherman, M. E.,
967 Shrubsole, M. J., Shu, X. O., Smeets, A., Sohn, C., Southey, M. C., Spinelli, J. J.,
968 Stegmaier, C., Stewart-Brown, S., Stone, J., Stram, D. O., Surowy, H., Swerdlow, A.,
969 Tamimi, R., Taylor, J. A., Tengstrom, M., Teo, S. H., Beth Terry, M., Tessier, D. C.,
970 Thanassisithichai, S., Thone, K., Tollenaar, R., Tomlinson, I., Tong, L., Torres, D., Truong,
971 T., Tseng, C. C., Tsugane, S., Ulmer, H. U., Ursin, G., Untch, M., Vachon, C., van
972 Asperen, C. J., Van Den Berg, D., van den Ouwendal, A. M. W., van der Kolk, L., van
973 der Luijt, R. B., Vincent, D., Vollenweider, J., Waisfisz, Q., Wang-Gohrke, S., Weinberg,

- 974 C. R., Wendt, C., Whittemore, A. S., Wildiers, H., Willett, W., Winqvist, R., Wolk, A.,
975 Wu, A. H., Xia, L., Yamaji, T., Yang, X. R., Har Yip, C., Yoo, K. Y., Yu, J. C., Zheng,
976 Zheng, Y., Zhu, B., Ziogas, A., Ziv, E., Investigators, A., ConFab, A. I., Lakhani, S.
977 R., Antoniou, A. C., Droit, A., Andrulis, I. L., Amos, C. I., Couch, F. J., Pharoah, P. D. P.,
978 Chang-Claude, J., Hall, P., Hunter, D. J., Milne, R. L., Garcia-Closas, M., Schmidt, M. K.,
979 Chanock, S. J., Dunning, A. M., Edwards, S. L., Bader, G. D., Chenevix-Trench, G.,
980 Simard, J., Kraft, P., & Easton, D. F. (2017, Nov 2). Association analysis identifies 65
981 new breast cancer risk loci. *Nature*, 551(7678), 92-94.
982 <https://doi.org/10.1038/nature24284>
983
- 984 Mitchell, B. D., Hsueh, W. C., King, T. M., Pollin, T. I., Sorkin, J., Agarwala, R., Schaffer, A. A.,
985 & Shuldiner, A. R. (2001, Sep 1). Heritability of life span in the Old Order Amish. *Am J
986 Med Genet*, 102(4), 346-352. <https://doi.org/10.1002/ajmg.1483>
987
- 988 Miyoshi, N., Fujino, S., Ohue, M., Yasui, M., Takahashi, Y., Sugimura, K., Tomokuni, A., Akita,
989 H., Kobayashi, S., Takahashi, H., Omori, T., Miyata, H., & Yano, M. (2018, Jul). The
990 POU5F1 gene expression in colorectal cancer: a novel prognostic marker. *Surg Today*,
991 48(7), 709-715. <https://doi.org/10.1007/s00595-018-1644-9>
992
- 993 Moreno-Grau, S., de Rojas, I., Hernandez, I., Quintela, I., Montreal, L., Alegret, M., Hernandez-
994 Olasagarre, B., Madrid, L., Gonzalez-Perez, A., Maronas, O., Rosende-Roca, M.,
995 Mauleon, A., Vargas, L., Lafuente, A., Abdelnour, C., Rodriguez-Gomez, O., Gil, S.,
996 Santos-Santos, M. A., Espinosa, A., Ortega, G., Sanabria, A., Perez-Cordon, A.,
997 Canabate, P., Moreno, M., Preckler, S., Ruiz, S., Aguilera, N., Pineda, J. A., Macias, J.,
998 Alarcon-Martin, E., Sotolongo-Grau, O., consortium, G. A., consortium, D., Alzheimer's
999 Disease Neuroimaging, I., Marquie, M., Monte-Rubio, G., Valero, S., Benaque, A.,
1000 Clarimon, J., Bullido, M. J., Garcia-Ribas, G., Pastor, P., Sanchez-Juan, P., Alvarez, V.,
1001 Pinol-Ripoll, G., Garcia-Alberca, J. M., Royo, J. L., Franco, E., Mir, P., Calero, M.,
1002 Medina, M., Rabano, A., Avila, J., Antunez, C., Real, L. M., Orellana, A., Carracedo, A.,
1003 Saez, M. E., Tarraga, L., Boada, M., & Ruiz, A. (2019, Oct). Genome-wide association
1004 analysis of dementia and its clinical endophenotypes reveal novel loci associated with
1005 Alzheimer's disease and three causality networks: The GR@ACE project. *Alzheimers
1006 Dement*, 15(10), 1333-1347. <https://doi.org/10.1016/j.jalz.2019.06.4950>
1007
- 1008 Morris, J. A., Kemp, J. P., Youlten, S. E., Laurent, L., Logan, J. G., Chai, R. C., Vulpescu, N. A.,
1009 Forgetta, V., Kleinman, A., Mohanty, S. T., Sergio, C. M., Quinn, J., Nguyen-Yamamoto,
1010 L., Luco, A. L., Vijay, J., Simon, M. M., Pramatarova, A., Medina-Gomez, C.,
1011 Trajanoska, K., Ghirardello, E. J., Butterfield, N. C., Curry, K. F., Leitch, V. D., Sparkes,
1012 P. C., Adoum, A. T., Mannan, N. S., Komla-Ebri, D. S. K., Pollard, A. S., Dewhurst, H.
1013 F., Hassall, T. A. D., Beltejar, M. G., andMe Research, T., Adams, D. J., Vaillancourt, S.
1014 M., Kaptoge, S., Baldock, P., Cooper, C., Reeve, J., Ntzani, E. E., Evangelou, E.,
1015 Ohlsson, C., Karasik, D., Rivadeneira, F., Kiel, D. P., Tobias, J. H., Gregson, C. L.,
1016 Harvey, N. C., Grundberg, E., Goltzman, D., Adams, D. J., Lelliott, C. J., Hinds, D. A.,
1017 Ackert-Bicknell, C. L., Hsu, Y. H., Maurano, M. T., Croucher, P. I., Williams, G. R.,
1018 Bassett, J. H. D., Evans, D. M., & Richards, J. B. (2019, Feb). An atlas of genetic

- 1019 influences on osteoporosis in humans and mice. *Nat Genet*, 51(2), 258-266.
1020 <https://doi.org/10.1038/s41588-018-0302-x>
- 1021
- 1022 Ng, B., White, C. C., Klein, H. U., Sieberts, S. K., McCabe, C., Patrick, E., Xu, J., Yu, L.,
1023 Gaiteri, C., Bennett, D. A., Mostafavi, S., & De Jager, P. L. (2017, Oct). An xQTL map
1024 integrates the genetic architecture of the human brain's transcriptome and epigenome. *Nat
1025 Neurosci*, 20(10), 1418-1426. <https://doi.org/10.1038/nn.4632>
- 1026
- 1027 Nica, A. C., Parts, L., Glass, D., Nisbet, J., Barrett, A., Sekowska, M., Travers, M., Potter, S.,
1028 Grundberg, E., Small, K., Hedman, A. K., Bataille, V., Tzenova Bell, J., Surdulescu, G.,
1029 Dimas, A. S., Ingle, C., Nestle, F. O., di Meglio, P., Min, J. L., Wilk, A., Hammond, C. J.,
1030 Hassanali, N., Yang, T. P., Montgomery, S. B., O'Rahilly, S., Lindgren, C. M.,
1031 Zondervan, K. T., Soranzo, N., Barroso, I., Durbin, R., Ahmadi, K., Deloukas, P.,
1032 McCarthy, M. I., Dermitzakis, E. T., Spector, T. D., & Mu, T. C. (2011, Feb 3). The
1033 architecture of gene regulatory variation across multiple human tissues: the MuTHER
1034 study. *PLoS Genet*, 7(2), e1002003. <https://doi.org/10.1371/journal.pgen.1002003>
- 1035
- 1036 Nyholt, D. R., Yu, C. E., & Visscher, P. M. (2009, Feb). On Jim Watson's APOE status: genetic
1037 information is hard to hide. *Eur J Hum Genet*, 17(2), 147-149.
1038 <https://doi.org/10.1038/ejhg.2008.198>
- 1039
- 1040 Okabe, H., Satoh, S., Kato, T., Kitahara, O., Yanagawa, R., Yamaoka, Y., Tsunoda, T.,
1041 Furukawa, Y., & Nakamura, Y. (2001, Mar 1). Genome-wide analysis of gene expression
1042 in human hepatocellular carcinomas using cDNA microarray: identification of genes
1043 involved in viral carcinogenesis and tumor progression. *Cancer Res*, 61(5), 2129-2137.
1044 <https://www.ncbi.nlm.nih.gov/pubmed/11280777>
- 1045
- 1046 Pilling, L. C., Atkins, J. L., Bowman, K., Jones, S. E., Tyrrell, J., Beaumont, R. N., Ruth, K. S.,
1047 Tuke, M. A., Yaghootkar, H., Wood, A. R., Freathy, R. M., Murray, A., Weedon, M. N.,
1048 Xue, L., Lunetta, K., Murabito, J. M., Harries, L. W., Robine, J. M., Brayne, C., Kuchel,
1049 G. A., Ferrucci, L., Frayling, T. M., & Melzer, D. (2016, Mar). Human longevity is
1050 influenced by many genetic variants: evidence from 75,000 UK Biobank participants.
1051 *Aging (Albany NY)*, 8(3), 547-560. <https://doi.org/10.18632/aging.100930>
- 1052
- 1053 Pilling, L. C., Kuo, C. L., Sicinski, K., Tamosauskaite, J., Kuchel, G. A., Harries, L. W., Herd, P.,
1054 Wallace, R., Ferrucci, L., & Melzer, D. (2017, Dec 6). Human longevity: 25 genetic loci
1055 associated in 389,166 UK biobank participants. *Aging (Albany NY)*, 9(12), 2504-2520.
1056 <https://doi.org/10.18632/aging.101334>
- 1057
- 1058 Porcu, E., Rueger, S., Lepik, K., e, Q. C., Consortium, B., Santoni, F. A., Reymond, A., &
1059 Kutalik, Z. (2019, Jul 24). Mendelian randomization integrating GWAS and eQTL data
1060 reveals genetic determinants of complex and clinical traits. *Nat Commun*, 10(1), 3300.
1061 <https://doi.org/10.1038/s41467-019-10936-0>
- 1062

- 1063 Rall, S. C., Jr., Weisgraber, K. H., & Mahley, R. W. (1982, Apr 25). Human apolipoprotein E.
1064 The complete amino acid sequence. *J Biol Chem*, 257(8), 4171-4178.
1065 <https://www.ncbi.nlm.nih.gov/pubmed/7068630>
1066
1067 Ryu, S., Atzmon, G., Barzilai, N., Raghavachari, N., & Suh, Y. (2016, Apr). Genetic landscape
1068 of APOE in human longevity revealed by high-throughput sequencing. *Mech Ageing Dev*,
1069 155, 7-9. <https://doi.org/10.1016/j.mad.2016.02.010>
1070
1071 Schunkert, H., Konig, I. R., Kathiresan, S., Reilly, M. P., Assimes, T. L., Holm, H., Preuss, M.,
1072 Stewart, A. F., Barbalic, M., Gieger, C., Absher, D., Aherrahrou, Z., Allayee, H.,
1073 Altshuler, D., Anand, S. S., Andersen, K., Anderson, J. L., Ardiissino, D., Ball, S. G.,
1074 Balmforth, A. J., Barnes, T. A., Becker, D. M., Becker, L. C., Berger, K., Bis, J. C.,
1075 Boekholdt, S. M., Boerwinkle, E., Braund, P. S., Brown, M. J., Burnett, M. S.,
1076 Buyschaert, I., Cardiogenics, Carlquist, J. F., Chen, L., Cichon, S., Codd, V., Davies, R.
1077 W., Dedoussis, G., Dehghan, A., Demissie, S., Devaney, J. M., Diemert, P., Do, R.,
1078 Doering, A., Eifert, S., Mokhtari, N. E., Ellis, S. G., Elosua, R., Engert, J. C., Epstein, S.
1079 E., de Faire, U., Fischer, M., Folsom, A. R., Freyer, J., Gigante, B., Girelli, D.,
1080 Gretarsdottir, S., Gudnason, V., Gulcher, J. R., Halperin, E., Hammond, N., Hazen, S. L.,
1081 Hofman, A., Horne, B. D., Illig, T., Iribarren, C., Jones, G. T., Jukema, J. W., Kaiser, M.
1082 A., Kaplan, L. M., Kastelein, J. J., Khaw, K. T., Knowles, J. W., Kolovou, G., Kong, A.,
1083 Laaksonen, R., Lambrechts, D., Leander, K., Lettre, G., Li, M., Lieb, W., Loley, C.,
1084 Lotery, A. J., Mannucci, P. M., Maouche, S., Martinelli, N., McKeown, P. P., Meisinger,
1085 C., Meitinger, T., Melander, O., Merlini, P. A., Mooser, V., Morgan, T., Muhleisen, T.
1086 W., Muhlestein, J. B., Munzel, T., Musunuru, K., Nahrstaedt, J., Nelson, C. P., Nothen,
1087 M. M., Olivieri, O., Patel, R. S., Patterson, C. C., Peters, A., Peyvandi, F., Qu, L.,
1088 Quyyumi, A. A., Rader, D. J., Rallidis, L. S., Rice, C., Rosendaal, F. R., Rubin, D.,
1089 Salomaa, V., Sampietro, M. L., Sandhu, M. S., Schadt, E., Schafer, A., Schillert, A.,
1090 Schreiber, S., Schrezenmeir, J., Schwartz, S. M., Siscovick, D. S., Sivananthan, M.,
1091 Sivapalaratnam, S., Smith, A., Smith, T. B., Snoep, J. D., Soranzo, N., Spertus, J. A.,
1092 Stark, K., Stirrups, K., Stoll, M., Tang, W. H., Tennstedt, S., Thorgeirsson, G.,
1093 Thorleifsson, G., Tomaszewski, M., Uitterlinden, A. G., van Rij, A. M., Voight, B. F.,
1094 Wareham, N. J., Wells, G. A., Wichmann, H. E., Wild, P. S., Willenborg, C., Witteman, J.
1095 C., Wright, B. J., Ye, S., Zeller, T., Ziegler, A., Cambien, F., Goodall, A. H., Cupples, L.
1096 A., Quertermous, T., Marz, W., Hengstenberg, C., Blankenberg, S., Ouwehand, W. H.,
1097 Hall, A. S., Deloukas, P., Thompson, J. R., Stefansson, K., Roberts, R., Thorsteinsdottir,
1098 U., O'Donnell, C. J., McPherson, R., Erdmann, J., Consortium, C. A., & Samani, N. J.
1099 (2011, Mar 6). Large-scale association analysis identifies 13 new susceptibility loci for
1100 coronary artery disease. *Nat Genet*, 43(4), 333-338. <https://doi.org/10.1038/ng.784>
1101
1102 Sebastiani, P., Gurinovich, A., Bae, H., Andersen, S., Malovini, A., Atzmon, G., Villa, F., Kraja,
1103 A. T., Ben-Avraham, D., Barzilai, N., Puca, A., & Perls, T. T. (2017, Oct 12). Four
1104 Genome-Wide Association Studies Identify New Extreme Longevity Variants. *J
1105 Gerontol A Biol Sci Med Sci*, 72(11), 1453-1464. <https://doi.org/10.1093/gerona/glx027>
1106

- 1107 Seo, J., Kim, M. H., Hong, H., Cho, H., Park, S., Kim, S. K., & Kim, J. (2019, Dec 15). MK5
1108 Regulates YAP Stability and Is a Molecular Target in YAP-Driven Cancers. *Cancer Res*,
1109 79(24), 6139-6152. <https://doi.org/10.1158/0008-5472.CAN-19-1339>
- 1110
- 1111 Shaffer, J. M., & Smithgall, T. E. (2009, Mar). Promoter methylation blocks FES protein-
1112 tyrosine kinase gene expression in colorectal cancer. *Genes Chromosomes Cancer*, 48(3),
1113 272-284. <https://doi.org/10.1002/gcc.20638>
- 1114
- 1115 Stankunas, K., Shang, C., Twu, K. Y., Kao, S. C., Jenkins, N. A., Copeland, N. G., Sanyal, M.,
1116 Selleri, L., Cleary, M. L., & Chang, C. P. (2008, Sep 26). Pbx/Meis deficiencies
1117 demonstrate multigenetic origins of congenital heart disease. *Circ Res*, 103(7), 702-709.
1118 <https://doi.org/10.1161/CIRCRESAHA.108.175489>
- 1119
- 1120 Timmers, P. R., Mounier, N., Lall, K., Fischer, K., Ning, Z., Feng, X., Bretherick, A. D., Clark,
1121 D. W., e, Q. C., Agbessi, M., Ahsan, H., Alves, I., Andiappan, A., Awadalla, P., Battle,
1122 A., Bonder, M. J., Boomsma, D., Christiansen, M., Claringbould, A., Deelen, P., van
1123 Dongen, J., Esko, T., Fave, M., Franke, L., Frayling, T., Gharib, S. A., Gibson, G.,
1124 Hemani, G., Jansen, R., Kalnapanakis, A., Kasela, S., Kettunen, J., Kim, Y., Kirsten, H.,
1125 Kovacs, P., Krohn, K., Kronberg-Guzman, J., Kukushkina, V., Kutilik, Z., Kahonen, M.,
1126 Lee, B., Lehtimaki, T., Loeffler, M., Marigorta, U., Metspalu, A., van Meurs, J., Milani,
1127 L., Muller-Nurasyid, M., Nauck, M., Nivard, M., Penninx, B., Perola, M., Pervjakova, N.,
1128 Pierce, B., Powell, J., Prokisch, H., Psaty, B. M., Raitakari, O., Ring, S., Ripatti, S.,
1129 Rotzschke, O., Rueger, S., Saha, A., Scholz, M., Schramm, K., Seppala, I., Stumvoll, M.,
1130 Sullivan, P., Teumer, A., Thiery, J., Tong, L., Tonjes, A., Verlouw, J., Visscher, P. M.,
1131 Vosa, U., Volker, U., Yaghootkar, H., Yang, J., Zeng, B., Zhang, F., Agbessi, M., Ahsan,
1132 H., Alves, I., Andiappan, A., Awadalla, P., Battle, A., Bonder, M. J., Boomsma, D.,
1133 Christiansen, M., Claringbould, A., Deelen, P., van Dongen, J., Esko, T., Fave, M.,
1134 Franke, L., Frayling, T., Gharib, S. A., Gibson, G., Hemani, G., Jansen, R., Kalnapanakis,
1135 A., Kasela, S., Kettunen, J., Kim, Y., Kirsten, H., Kovacs, P., Krohn, K., Kronberg-
1136 Guzman, J., Kukushkina, V., Kutilik, Z., Kahonen, M., Lee, B., Lehtimaki, T., Loeffler,
1137 M., Marigorta, U., Metspalu, A., van Meurs, J., Milani, L., Muller-Nurasyid, M., Nauck,
1138 M., Nivard, M., Penninx, B., Perola, M., Pervjakova, N., Pierce, B., Powell, J., Prokisch,
1139 H., Psaty, B. M., Raitakari, O., Ring, S., Ripatti, S., Rotzschke, O., Rueger, S., Saha, A.,
1140 Scholz, M., Schramm, K., Seppala, I., Stumvoll, M., Sullivan, P., Teumer, A., Thiery, J.,
1141 Tong, L., Tonjes, A., Verlouw, J., Visscher, P. M., Vosa, U., Volker, U., Yaghootkar, H.,
1142 Yang, J., Zeng, B., Zhang, F., Shen, X., Esko, T., Kutilik, Z., Wilson, J. F., & Joshi, P. K.
1143 (2019, Jan 15). Genomics of 1 million parent lifespans implicates novel pathways and
1144 common diseases and distinguishes survival chances. *Elife*, 8.
1145 <https://doi.org/10.7554/eLife.39856>
- 1146
- 1147 Võsa, U., Claringbould, A., Westra, H. J., Bonder, M. J., Deelen, P., & Franke, L. (2018).
1148 Unraveling the polygenic architecture of complex traits using blood eQTL meta-analysis.
1149 <https://doi.org/https://doi.org/10.1101/447367>
- 1150
- 1151 Wang, Y., Wang, J., Zhang, L., Karatas, O. F., Shao, L., Zhang, Y., Castro, P., Creighton, C. J.,
1152 & Ittmann, M. (2017, Aug 15). RGS12 Is a Novel Tumor-Suppressor Gene in African

- 1153 American Prostate Cancer That Represses AKT and MNX1 Expression. *Cancer Res*,
1154 77(16), 4247-4257. <https://doi.org/10.1158/0008-5472.CAN-17-0669>
- 1155
- 1156 Wei, M., Brandhorst, S., Shelehchi, M., Mirzaei, H., Cheng, C. W., Budniak, J., Groshen, S.,
1157 Mack, W. J., Guen, E., Di Biase, S., Cohen, P., Morgan, T. E., Dorff, T., Hong, K.,
1158 Michalsen, A., Laviano, A., & Longo, V. D. (2017, Feb 15). Fasting-mimicking diet and
1159 markers/risk factors for aging, diabetes, cancer, and cardiovascular disease. *Sci Transl
1160 Med*, 9(377). <https://doi.org/10.1126/scitranslmed.aai8700>
- 1161
- 1162 Westra, H. J., Peters, M. J., Esko, T., Yaghootkar, H., Schurmann, C., Kettunen, J., Christiansen,
1163 M. W., Fairfax, B. P., Schramm, K., Powell, J. E., Zhernakova, A., Zhernakova, D. V.,
1164 Veldink, J. H., Van den Berg, L. H., Karjalainen, J., Withoff, S., Uitterlinden, A. G.,
1165 Hofman, A., Rivadeneira, F., Hoen, P. A. C., Reinmaa, E., Fischer, K., Nelis, M., Milani,
1166 L., Melzer, D., Ferrucci, L., Singleton, A. B., Hernandez, D. G., Nalls, M. A., Homuth,
1167 G., Nauck, M., Radke, D., Volker, U., Perola, M., Salomaa, V., Brody, J., Suchy-Dicey,
1168 A., Gharib, S. A., Enquobahrie, D. A., Lumley, T., Montgomery, G. W., Makino, S.,
1169 Prokisch, H., Herder, C., Roden, M., Grallert, H., Meitinger, T., Strauch, K., Li, Y.,
1170 Jansen, R. C., Visscher, P. M., Knight, J. C., Psaty, B. M., Ripatti, S., Teumer, A.,
1171 Frayling, T. M., Metspalu, A., van Meurs, J. B. J., & Franke, L. (2013, Oct). Systematic
1172 identification of trans eQTLs as putative drivers of known disease associations. *Nat
1173 Genet*, 45(10), 1238-1243. <https://doi.org/10.1038/ng.2756>
- 1174
- 1175 Willcox, B. J., Donlon, T. A., He, Q., Chen, R., Grove, J. S., Yano, K., Masaki, K. H., Willcox,
1176 D. C., Rodriguez, B., & Curb, J. D. (2008, Sep 16). FOXO3A genotype is strongly
1177 associated with human longevity. *Proc Natl Acad Sci U S A*, 105(37), 13987-13992.
1178 <https://doi.org/10.1073/pnas.0801030105>
- 1179
- 1180 Zeng, Y., Nie, C., Min, J., Liu, X., Li, M., Chen, H., Xu, H., Wang, M., Ni, T., Li, Y., Yan, H.,
1181 Zhang, J. P., Song, C., Chi, L. Q., Wang, H. M., Dong, J., Zheng, G. Y., Lin, L., Qian, F.,
1182 Qi, Y., Liu, X., Cao, H., Wang, Y., Zhang, L., Li, Z., Zhou, Y., Wang, Y., Lu, J., Li, J.,
1183 Qi, M., Bolund, L., Yashin, A., Land, K. C., Gregory, S., Yang, Z., Gottschalk, W., Tao,
1184 W., Wang, J., Wang, J., Xu, X., Bae, H., Nygaard, M., Christiansen, L., Christensen, K.,
1185 Franceschi, C., Lutz, M. W., Gu, J., Tan, Q., Perls, T., Sebastiani, P., Deelen, J.,
1186 Slagboom, E., Hauser, E., Xu, H., Tian, X. L., Yang, H., & Vaupel, J. W. (2016, Feb 25).
1187 Novel loci and pathways significantly associated with longevity. *Sci Rep*, 6, 21243.
1188 <https://doi.org/10.1038/srep21243>
- 1189
- 1190