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Genetics of extreme human longevity to guide drug discovery for healthy ageing

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Supplementary material

Supplementary Table 1. Genome-wide association studies of human ageing.

Study	Ageing-related trait	Cohort size and ethnicity	Genome-wide significant variants ($P < 5E-8$)	Loci/Genes	Ref.
Deelen et al., 2019	Longevity (cases: > 90th or 99th survival percentile; controls: <60th survival percentile)	4 discovery cohorts: 36,745 (11,262 + 25,483) European, 33,444 (5,662 + 27,782) European and East Asian, 41,610 (13,617 + 27,993) European, East Asian and African American, 28,967 (3,484 + 25,483) European	Discovery from European >90th survival percentile: rs7676745, rs429358, rs7412; Discovery from European >99th survival percentile: rs429358, rs7412; Discovery from trans-ethnic >90th survival percentile: rs2069837, rs429358, rs7412; Discovery from trans-ethnic >99th survival percentile: rs2069837, rs429358, rs7412	Discovery from European >90th survival percentile: GPR78, APOE; Discovery from European >99th survival percentile: APOE; Discovery from trans-ethnic >90th survival percentile: IL6, APOE; Discovery from trans-ethnic >99th survival percentile: IL6, APOE	1
Wright et al., 2019	Parental lifespan	540,852 and 579,931 multiethnic	rs1333042, rs10887623, rs9457925, bp75763624, rs931794, bp45411941	ANRIL, WAPL, LPA, SRRM3, CHRNA3/5, APOE	2
Timmers et al., 2019	Parental lifespan	1 million British/European	rs1230666, rs1275922, rs61348208, rs34967069, rs10455872, rs1556516, rs11065979, rs8042849, rs6224, rs12924886, rs142158911, rs429358, rs4970836, rs6744653, rs10211471, rs111333005, rs113160991, rs56179563, rs2519093	MAGI3, KCNK3, HTT, HLA-DQA1, LPA, CDKN2B-AS1, ATXN2/BRAP, CHRNA3/5, FURIN/FES, HP, LDLR, APOE, CELSR2/PSRC1, TREM18, GBX2/ASB18, IGF2R, POM121C, ZC3HC1, ABO	3
Zeng et al., 2018	Longevity (cases: >100 years)	4,477 (2,178 + 2,299) Han Chinese	–	–	4
McDaid et al., 2017	Parental age of death	116,279 British	rs10455872, rs1333045, rs951266, rs4420638	LPA, CDKN2BAS, CHRNA5, APOC1	5
Sebastiani et al., 2017	Longevity (cases: male>95, female>99)	8,329 (2070 + 6259) multiethnic	rs6857, rs769449, rs59007384, rs3764814, rs7976168	APOE, PVRL2, USP42, TMTC2	6
Pilling et al., 2017	Parental lifespan	389,166 British/European	rs602633, rs28383322, rs55730499, rs1556516, rs7137828, rs1317286, rs17514846, rs429358, rs1627804, rs7844965, rs61978928, rs28926173, rs146254978, rs139137459, rs3130507, rs131871514, rs61949650, rs3131621, rs13262617, rs61905747, rs74011415, rs12461964	CLESR2, PSRC1, HLA-DRB1, HLA-DQA1, LPA, CDKN2B-AS1, SH2B3, ATXN2, CHRNA3, FURIN, APOE, APOC1, BEND3, EPHX2, PROX2, MC2R, FPGT, TNNT3, USP2-AS1, PSORSIC3, B3GALT1, MICA, MICB, TOX, ZW10, SEMA6D, EGLN2, CYP2A6, EXOC3L2, MAPK4, C20orf187, CHRNA4	7

Tanaka et al., 2017	Parental longevity (cases: mother>91 or father>87)	5,716 American (European and African descent)	–	–	8
Joshi et al., 2017	Parental lifespan	606,059 European and African	rs34831921, rs55730499, rs8042849, rs429358, rs10198124	HLA-DQA1, HLA-DRB1, LPA, CHRNA3, CHRNA5, APOE	9
Pilling et al., 2016	Parental longevity (cases: mother≥98, father≥95) and lifespan	42,273 (1,339 + 40,934) 'white' British and 75,244 'white' British	rs62227724, rs528161076, rs75824829, rs4709783	AP5Z1	10
Zeng et al., 2016	Longevity (cases: >100)	4,477 (2,178 + 2,299) Han Chinese	rs2069837, rs2440012	IL6, ANKRD20A9P	11
Joshi et al., 2016	Parental mortality	272,081 British	rs10519203, rs429358	CHRNA3/5, APOE	12
Flachsbart et al., 2016	Longevity (cases: mean age = 99.0)	7,826 (1,458 + 6,368) German	rs2075650	APOE, TOMM40	13
Fortney et al., 2015	Longevity (cases: >95; ≥90)	2 discovery cohort: 1,715 (801 + 914) Caucasian and 23,451 (7,330 + 16,121) European	rs2075650, rs4420638	APOE, TOMM40	14
Broer et al., 2015	Longevity (cases: ≥90)	9,793 (6,036 + 3,757) Caucasian	rs1416280	GRIK2	15
Yashin et al., 2015	Lifespan	679 female and multiethnic	rs12949468, rs4639950, rs7894051, rs2292664, rs2229188	TLK2, C1QTNF5, ECHS1, RIMBP2, CYP51A1	16
Deelen et al., 2014	Longevity (cases: ≥85)	23,850 (7,729 + 16,121) European	rs2149954, rs4420638	EBF1, APOE	17
Edwards et al., 2013	Aging (cases: >80 and successful aging)	263 (74 + 189) Amish	–	–	18
Sebastiani et al., 2012	Longevity (cases: ≥95)	1,715 (801 + 914) Caucasian	rs2075650	APOE, TOMM40	19
Deelen et al., 2011	Longevity (cases: ≥89)	2,073 (403 + 1,670) European	rs2075650	APOE, TOMM40	20
Walter et al., 2011	Aging (time to event)	25,007 European	–	–	21
Malovini et al., 2011	Longevity (cases: >90)	963 (410 + 553) European	–	–	22
Nebel et al., 2011	Longevity (cases: >94)	1,848 (763 + 1,085) European	rs4420638	APOC1	23
Newman et al., 2010	Longevity (cases: >90)	3,791 (1,836 + 1,955) European	–	–	24

Yashin et al., 2010	Lifespan	1,173 multiethnic	–	–	25
Poduslo et al., 2010	Aging (cases: >79; controls: AD patients)	316 (89 + 227) European and African American	rs12474609	LRP1B	26

Notes: For case-control studies, the age criteria for cases are included in the parentheses and the cohort size is shown as 'the total number of samples (the number of cases + the number of controls)'.

Supplementary Table 2. Independent loci with significant longevity- or lifespan-association. #

<i>N</i> 1 †	<i>N</i> 2 ‡	Locus (SNP ID)	Chr.	Position (hg38)	LD in <i>R</i> ² , all population §	References	In Figure 2? Reasons if not
1		rs146254978	1	74402115		7	Small study
2	1	rs602633	1	109278889	See Supplementary Table 2.2	7	Non-independent SNP
		rs4970836	1	109279175		3	Yes
3		rs1230666	1	113630788		3	Yes
4		rs6744653	2	628524		3	Yes
5		rs1275922	2	26710019		3	Yes
6		rs10198124	2	35216373		9	Beta not available
7		rs12474609	2	140963573		26	Small study
8		rs10211471	2	236173211		3	Yes
9		rs61348208	4	3087837		3	Yes
10		rs7676745	4	8563820		1	Yes
11		rs2149954	5	158393594		17	Yes
12		rs3130507	6	31179699		7	Different effect size measurement
13		rs3131621	6	31457722		7	Different effect size measurement
14	2	rs34831921	6	32622991	See Supplementary Table 2.14	9	Non-independent SNP
		rs34967069	6	32623471		3	Yes
		rs28383322	6	32625019		7	Non-independent SNP
15		rs1416280	6	102438768		15	Small study
16		rs1627804	6	107079224		7	Different effect size measurement
17		rs111333005	6	160066164		3	Yes
18		rs9457925	6	160427711		2	Yes
19	3	rs55730499	6	160584578	See Supplementary Table 2.19	7,9	Non-independent SNP
		rs10455872	6	160589086		3,5	Yes
20		rs4709783	6	163874119		10	Yes
21		rs528161076	7	4787884		10	Yes
22		rs3764814	7	6150149		6	Small study
23	4	rs2069837	7	22728408		1,11	Yes
24		rs113160991	7	75465064		3	Yes
25		rs28689051	7	76134306		2	Yes
26		rs2229188	7	92134309		16	Small study
27		rs56179563	7	130045757		3	Yes
28		rs13262617	8	58925574		7	Different effect size measurement
29	5	rs1556516	9	22100177	See Supplementary Table 2.29	3,7	Yes

		rs1333042	9	22103814		2	Non-independent SNP
		rs1333045	9	22119196		5	Non-independent SNP
30		rs2519093	9	133266456		3	Yes
31		rs75824829	9	135376756		10	Yes
32		rs10887623	10	86555424		2	Yes
33		rs7894051	10	133370917		16	Small study
34		rs61905747	11	113769120		7	Different effect size measurement
35		rs4639950	11	119345845		16	Small study
36		rs139137459	11	119399248		7	Yes
37		rs7976168	12	83044780		6	Different effect size measurement
38	6	rs7137828	12	111494996	See Supplementary Table 2.38	7	Non-independent SNP
		rs11065979	12	111621753		3	Yes
39		rs2292664	12	130437119		16	Small study
40		rs2440012	13	18865983		11	Small study
41		rs1043332229	13	31297377		7	Different effect size measurement
42		rs61949650	13	64262356		7	Different effect size measurement
43		rs61978928	14	74855011		7	Different effect size measurement
44		rs74011415	15	47367997		7	Different effect size measurement
45	7	rs10519203	15	78521704	See Supplementary Table 2.45	12	Non-independent SNP
		rs8042849	15	78525587		3,9	Yes
		rs931794	15	78533838		2	Non-independent SNP
		rs951266	15	78586199		5	Non-independent SNP
		rs1317286	15	78603787		7	Non-independent SNP
46		rs17514846	15	90873320		7	Different effect size measurement
47		rs6224	15	90880313		3	Yes
48		rs12924886	16	72041694		3	Yes
49		rs12949468	17	62516455		16	Small study
50		rs28926173	18	13886720		7	Yes
51		rs142158911	19	11079858		3	Yes
52		rs12461964	19	40835324		7	Different effect size measurement
53	8	rs6857	19	44888997	See Supplementary Table 2.53	6	Non-independent SNP
		rs2075650	19	44892362		14,19,20,27	Non-independent SNP
		rs59007384	19	44893408		6	Non-independent SNP
		rs769449	19	44906745		6	Non-independent SNP
		rs429358	19	44908684		1-3,7,9,12	Yes

		rs7412	19	44908822		1	Yes
		rs4420638	19	44919689		5,14,17,23	Non-independent SNP
54		rs74444983	19	45242349		7	Different effect size measurement
55		rs62227724	22	44128027		10	Yes

Notes:

Among 72 SNPs listed in Supplementary Table 1.

† The index of independent longevity-associated loci.

‡ The index of independent longevity-associated loci that have been replicated in multiple studies.

§ LD among multiple associated SNPs in a locus.

Supplementary Table 2.2. LD in R^2 .

	rs602633
rs4970836	0.9584

Supplementary Table 2.14. LD in R^2 .

	rs34831921	rs34967069	rs28383322
rs34831921	-	0.9658	0.4096
rs34967069		-	0.4
rs28383322			-

Supplementary Table 2.19. LD in R^2 .

	rs10455872
rs55730499	0.8122

Supplementary Table 2.29. LD in R^2 .

	rs1556516	rs1333042	rs1333045
rs1556516	-	0.9936	0.3548
rs1333042		-	0.3549
rs1333045			-

Supplementary Table 2.38. LD in R^2 .

	rs11065979
rs7137828	0.9041

Supplementary Table 2.45. LD in R^2 .

	rs10519203	rs8042849	rs931794	rs951266	rs1317286
rs10519203	-	0.7819	0.5168	0.447	0.3315
rs8042849		-	0.3848	0.3539	0.2528
rs931794			-	0.4623	0.3305
rs951266				-	0.6688
rs1317286					-

Supplementary Table 2.53. LD in R^2 .

	rs6857	rs2075650	rs59007384	rs769449	rs429358	rs7412	rs4420638
rs6857	-	0.4919	0.3253	0.4701	0.2739	0.0066	0.2117
rs2075650		-	0.3348	0.4296	0.1973	0.002	0.1428
rs59007384			-	0.195	0.1377	0.1083	0.1193
rs769449				-	0.3859	0.0056	0.3076
rs429358					-	0.0139	0.3387
rs7412						-	0.0037
rs4420638							-

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