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Genome maintenance and human longevity

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Abstract

Accumulation of DNA damage and mutations is considered an important causal factor in age-related diseases. Genetic defects in DNA repair cause premature onset and accelerated progression of aging-related diseases and a shorter life span in humans and mice, providing strong evidence that genome maintenance is a *bona fide* longevity assurance pathway. However, the contribution of genome maintenance to human longevity itself remains to be established. Here, we review the results of human genetics studies, including genome wide association studies, and attempted to catalogue all genes involved in major DNA repair pathways that harbor variants associated with longevity. We hope to provide a comprehensive review to facilitate future endeavors aimed at uncovering the functional role of genome maintenance genes in human longevity.

Introduction

Human longevity is a complex and, most of all, rare phenotype. Indeed, the frequency of those living to be a hundred, i.e., centenarians, in the human population is not more than ~1/5,000 persons. Rarer still are super-centenarians, aged 110+ years, and no more frequent than 1 per 5 million [1]. The genetic contribution to lifespan has been estimated to be about 20–30% from twin and family studies, but it becomes more substantial after age 65 and 85 years, at 36% and 40%, respectively [2]. Centenarians have been a model of human exceptional longevity because they age with enhanced healthspan by delaying, surviving, or escaping age-associated diseases such as cancer, dementia, and cardiovascular disease (CVD) [3•]. Furthermore, centenarians often display unique, healthy metabolic signatures compared to the average elderly individual of between 70 and 90 years old [4,5]. The strong genetic component of extreme longevity is underscored by the observation that offspring of centenarians inherit some of the metabolic signatures and disease profiles from their successful parent(s) [6•], including favorable lipid profiles [7], delayed onset of cognitive impairment [8,9] and reduced cancer incidence [10].

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In a search for longevity genes, centenarians and long-lived humans in general have been the subject of extensive genetic linkage and/or association studies. Linkage analysis generally requires the availability of pedigrees in which the genetic trait of interest, i.e., extreme longevity, segregates with one or more genetic markers. This approach is obviously difficult with late-onset genetic traits. However, using a sib-pair approach, which takes advantage of the presence of a trait in both sibs more often than expected by chance alone, some candidate genes, which could account for inter-individual variance in disease susceptibility, aging rate and lifespan, have indeed been found [11,12].

An approach generally considered superior to linkage analysis when dealing with complex traits is association analysis, which evaluates correlation between a genetic variation and longevity by comparing the frequency of genetic variants in cases (long-lived individuals; nonagenarians or centenarians) and unrelated controls (younger elderly individuals). This can be done genome-wide (genome-wide association analysis; GWAS) or by targeting candidate loci. In general, association analysis has been the method of choice for studying the genetics of extreme longevity because it allows the detection of common variants with small effects. However, by now it seems reasonably clear that the genetic variants controlling extreme longevity are often rare and difficult to detect in GWAS studies. This is due to the fact that the single-nucleotide polymorphisms (SNPs) used in GWAS studies are merely markers for the most frequent common alleles and do not by themselves pinpoint the functional longevity variants, which may be numerous but rare. Until whole genome sequencing has become truly inexpensive, the best alternative to identify human longevity assurance genes is to directly target the functional networks thought to contribute to extreme longevity.

Genome maintenance, longevity assurance pathway

In the quest of human longevity genes, genes involved in the conserved pathways of aging have been popular candidates as they were shown to significantly impact healthspan and lifespan in model organisms across a great evolutionary distance. These pathways include the insulin/insulin like growth factor-1 signaling (IIS), mechanistic target of rapamycin (mTOR), and genome maintenance (GM) pathways [13,14]. The focus of this review is on the role of GM as candidate longevity assurance system in humans.

Two lines of evidence attribute decreased ability to maintain genome integrity to contributing factors of aging. First, low levels of radiation can accelerate the aging process and shorten lifespan in mice [15]. This suggests that DNA damage and mutations induced by various endogenous and exogenous factors can cause aging. A second, stronger line of evidence for the potential importance of genome maintenance as a general longevity assurance system is based on human segmental progeroid syndromes, characterized by the premature appearance of multiple signs of normal aging, and mostly caused by a defect in genome maintenance [16]. The phenotypes and degenerative diseases that these patients develop resemble normal aging but occur at a greatly accelerated pace. This premature aging as well as shorter lifespan due to defective GM in humans can be recapitulated in mouse models harboring mutated genes in affected individuals [17•].

Inactivation or mutational alteration of GM genes in mice and humans can result in the premature appearance of symptoms of accelerated aging. How about its opposite: would an improved GM capacity promote longevity? One possible way to address this question would be to genetically improve genome maintenance functions in the mouse. Unfortunately, simply overexpressing certain GM genes is often toxic or mutagenic due to imbalance in pathways and currently we lack the critical information as to the type of changes required for improving genome maintenance function. A more reasonable assumption is that genetic variation, often subtle, at loci involved in GM will impact on an individual's ability to sense, process, and repair DNA damage in ways that we cannot, now, fully understand. Ironically, it is not the mouse but the human that is the obvious model system to test such a hypothesis. Normal human populations show great diversity in genotypes related to genome maintenance and it is conceivable that DNA sequence variation at such loci is a critical factor in individual variation of longevity and healthy aging. At the moment, genetic association studies utilizing LLI populations are the best way to test the role of GM genes in human longevity. In a broad sense, GM pathway can be defined to include any genes that are involved in preserving genome integrity [18], but in this review we focus on 120 GM genes implicated in DNA damage signaling, major DNA repair pathways, and telomere maintenance (see Figure 1).

Genetic evidence of genome maintenance in human longevity

There has been a substantial increase in the number of publications reporting positive associations between variants in GM genes and longevity/increased survival in the last couple of years. Most of these reports employed candidate gene approach and only a few reports were from genome-wide approach. Since longevity is a rare phenotype with prevalence of 1 centenarian in 5000 individuals, gene variants that contribute to extreme longevity may be rare and not be detected by GWAS. In fact, initial genome wide association studies (GWAS) involving long-lived individuals have predicted the presence of rare protective variants with strong effects in centenarians as a possible explanation for the failure to detect common variants significantly associated with longevity other than *ApoE* [19–21]. Here, we list and discuss the GWAS results reporting association of gene variants in GM with longevity and the results from candidate gene approaches published since 2007 (summarized in Table 1).

Genome maintenance in GWAS

A GWAS using the Framingham Heart Study (FHS) cohort with 1,173 participants of 618 families was conducted to evaluate the genetic influence on longevity by Yashin et al. [22]. They observed an initial 169 SNPs that were associated with longevity and among these 39 SNPs were identified as longevity SNPs after accounting for familial effect on detection of association. Interestingly, these SNPs in a set of either 169 or 39 showed a joint influence on lifespan: increased number of longevity SNPs in an individual correlated with longer lifespan with a contribution of up to 19–21% to the variance of lifespan, whereas the same number of randomly selected alleles showed no contribution to lifespan variance. The 39 SNPs included 3 SNPs in the GM gene regions; an intronic SNP of *NTHL1*, and intergenic SNPs near *TERFIP3* and *ATRIP*.

Another GWAS reported by Sebastiani et al. was conducted in a case-control study design with 801 centenarians and 914 healthy controls [23]. They found that there only *APOE*/*TOMM40* region showed genome-wide significance in a conventional single SNP analysis, yet there existed regional clusters of associations that individually do not reach genome-wide significance. In an analysis using a genetic risk model that determines a set of SNPs without limiting the number of SNPs, they found a unique combination of 281 SNPs that maximally predict exceptional longevity with 89% sensitivity and specificity in the discovery panel and 85% and 78% sensitivity in the group of older (age 106 or older) subjects from two replication populations. The 281 SNPs from their genetic model included several GM genes, such as *WRN*, *LMNA*, *RAD51L1*, and *RAD51L2*. In addition, two distinct sets of 38 and 24 genes both of which included *WRN* and *LMNA* were linked to Alzheimer's disease (AD) and coronary artery disease (CAD), respectively. Further cluster analysis identified 26 unique genetic signatures of exceptional longevity. Each of these signatures was possessed by 8 to 94 centenarians suggesting each individual has a genetic signature that is shared by some of the centenarians. A common finding between these two GWAS is that there is a collaborative action of multiple genes in determining longevity, which is known to be true for risk of other complex traits.

The group that reported a combinational effect of 281 SNPs from a GWAS performed a meta-analysis using 4 GWAS of Caucasian populations (ELIX, Elixir Pharmaceutical Longevity Study; LLFS, Long Life Family Study; NECS, New England Centenarian Study; SICS, Southern Italian Centenarian Study) and 1 GWAS of Japanese population (JCS, Japanese Centenarian Study) by 3 different genetic models: additive, recessive and dominant model [24]. From the analyses of 4 Caucasian populations, they found 16 SNPs that reached Bonferroni corrected significance including a SNP in *LMNA*. Analysis after addition of Japanese population to these 4 populations identified 6 SNPs with Bonferroni corrected significance which consist of 4 new SNPs including the *WRN* SNP detected in the previous GWAS and 2 SNPs that were found in the 4 Caucasians results. In addition to association with exceptional longevity, the association of *WRN* and *LMNA* with AD and CAD, respectively, in a set of genes was also replicated in this meta-analysis.

Genome maintenance in candidate gene approaches

The most replicated genes that were shown to be associated with longevity in both GWAS and candidate gene studies are *WRN* and *LMNA*. Mutations in these genes cause the two best-characterized progeroid syndromes in humans: Werner syndrome and Hutchinson-Gilford progeria syndrome, respectively. It is notable that a fraction of common variants in these genes are associated with longevity exhibiting a positive effect on lifespan during normal aging, while different mutations in the same genes are implicated in premature aging and shortened lifespan. In two candidate gene studies, *WRN* was shown to be associated with morbidity-free survival at age 65 and with age of death in the Framingham Heart Study, suggesting its role in survival [25] and with longevity in a case-control study of individuals in their 90s and middle-aged controls in 40–50's in a Danish population [26]. SNPs in *LMNA* were investigated by Conneely et al in an association study of Caucasian LLIs and controls [27]. They first searched for variants associated with longevity by genotyping and association analysis of 16 SNPs in the gene region in the discovery

population followed by a replication meta-analysis with 4 additional populations. They identified several longevity associated SNPs, and additionally a longevity associated haplotype of 4 SNPs. Among these 4 *LMNA* SNPs, there were a coding SNP shown to be associated with increased expression of *LMNA* [28] and an intronic SNP shown to be associated with longevity in a GWAS and meta-analysis by Sebastiani et al [23,24].

A functional variant in the *EXO1* promoter has been associated with longevity by Nebel et al [29]. Initially, the authors analyzed 92 non-synonymous SNPs in 49 DNA repair genes for 395 German centenarians and 411 controls and found *EXO1* as the top longevity-associated gene among females. After resequencing analysis of 46 centenarians for fine variation mapping of the gene, subsequent association analysis was performed by using 43 common SNPs and found 17 longevity associated SNPs including 7 potentially functional SNPs in the coding and regulatory region. The authors pursued functional analysis for these 7 variants and found that (1) the longevity-associated allele (C) of a promoter SNP (rs1776180) is associated with *EXO1* mRNA expression in lymphoblastoid cells and (2) this allele increases the *EXO1* promoter activity through lost binding of transcription factor E47 which acts as a repressor of *EXO1* expression in an allele specific manner. This report is one of a very few studies demonstrating functionality of a longevity-associated SNP and the correlation between increased DNA repair gene expression and human longevity.

Similarly, a functional SNP in *ATM* was identified by Chen et al [30]. They first resequenced *ATM* promoter region followed by genotyping and association analysis of discovered SNPs in LLIs (nonagenarians and centenarians) and younger controls. They found that heterozygous genotype (CT) of the SNP rs189037 was enriched in LLIs and that the nucleotide substitution T to C was predicted to gain an activator protein 2α (AP-2α) binding site. Based on this genetic discovery, the authors explored the role of SNP by measuring the gene expression levels in peripheral mononuclear cells carrying each genotype and found that TT carriers showed significantly increased *ATM* expression compared to CC carriers. They showed that T allele resulted in a loss of AP-2α binding that acts as a suppressor of *ATM* gene, leading to increased mRNA expression compared to C allele. In a separate study, the same group has reported that T allele of this SNP is also associated with reduced risk of coronary stenosis and TT genotype was associated with increased *ATM* mRNA levels in peripheral mononuclear cells [31]. The association of rs189037 CT genotype with longevity was replicated in Italian centenarians [32].

Due to the lifespan extension effects of increased gene activity or expression in model organisms, sirtuins have been of particular interest in human longevity studies. SNPs in *SIRT1* and *SIRT3* were shown to be associated with human longevity. The most recent association between *SIRT1* with long-term survival of a general population was reported by Figarska et al in a cohort followed for 18 years [33]. In a tag SNP approach utilizing representative marker SNPs co-inherited with other SNPs within a region, they found a SNP upstream of *SIRT1* is associated with reduced all-cause mortality in both males and females. The minor allele of this SNP showed more profound protective effect against the mortality risk in overweight/obese individuals and better glucose tolerance in male individuals. Another *SIRT1* association with longevity was reported in a case-control study utilizing nonagenarians and centenarians to investigate the genetic role of *SIRT1* and *XRCC6* on

telomere maintenance [34]. Longer telomere length was associated with both *XRCC6* and *SIRT1* SNPs whereas longevity was associated only with *SIRT1* SNP. A possible interaction of the two genes was examined, but the genetic influence of *SIRT1* and *XRCC6* SNPs on either telomere length or longevity were independent of each other. In the case of *SIRT3*, there are 2 studies reporting association with longevity. An intronic SNP in *SIRT3* was associated with longevity in a large scale study using SNPs in 2.5Mb region covering 11p15.5 for 4 European populations consisting of 1,321 centenarians and 1,140 controls [35]. However the authors concluded that this association is not robust enough because following replication and additional meta-analysis did not show association. Another study reported a *SIRT3* SNP associated with both female longevity in a prospective analysis and enhanced *SIRT3* protein levels in peripheral mononuclear cells [36].

Telomere shortening is a risk factor for cancer and aging. Recently, the link between telomere length and human lifespan has been reported [37,38]. Among telomere maintenance genes, telomerase coding gene *TERT* and RNA component *TERC* were the most studied candidate genes. Atzmon et al. showed that a synonymous SNP and three haplotypes in the *TERT* gene were associated with longevity. In addition, one haplotype was associated with longer telomere length [39]. By utilizing offspring of centenarians in the study design, this study demonstrated that the telomere length is heritable, and contributes to healthy aging and longevity in humans. Seorenson et al performed association analyses of 4 *TERT* SNPs that were used for haplotyping in Atzmon et al.'s study and reported no significant association of the *TERT* haplotypes with longevity or leukocyte telomere length (LTL) but marginally significant decrease in mortality. They also studied 2 *TERC* SNPs previously associated with LTL in 2 GWAS [40,41] using 4 Danish cross-sectional populations [42]. In this study, they found that A allele of the *TERC* SNP rs3772190 was associated with short LTL in males and reduced survival of individuals with age 80. The same A allele showed an unexpected association with longevity in the comparison of allele frequency between centenarians and the group of elderly individuals with age <80. The authors speculate the small sample number used for longevity association may be the cause of contrasting result, though there could be a complex regulation or interaction between genetics and environments confounding this association result. There is a VNTR in *TERT* region that was tested for association with longevity and LTL by Concetti et al [43]. This VNTR was known to increase the putative promoter activity of antisense transcript of *TERT* in a previous study [44]. The authors divided the study population into 3 groups by their age for cross-sectional comparisons. The length variation of a VNTR, MNS16A, was associated with longevity only between two older groups such that MNS16A*L, a longer form, is depleted in oldest group (female >91, male >88). Carriers of this allele showed significant telomere attrition along with the increased age, suggesting that the allele may be implicated in decreased telomere length maintenance due to the hampered *TERT* expression by increased anti-sense transcripts, thus negatively influencing the lifespan.

Soerenen et al. investigated longevity-association of 1,273 tag SNPs in 148 genes involved in three major candidate pathways of aging [26] including GH/Insulin/IGF-1 signaling, pro/antioxidant mechanism, and DNA repair signaling for a Danish cohort of 1,089 oldest-old (age 92–93) and 736 middle-aged subjects. Among DNA repair genes, 5 genes (*RAD52*,

WRN, *RAD23B*, *POLB*, *NTLH1*) were associated with longevity and 3 genes (*MLH1*, *H2AFX*, and *XRCC5*) were associated with survival of 11 years of follow-up. The association of these genes in Danish individuals was not replicated in German and Dutch populations. However, a supportive non-significant tendency was observed for *RAD52*.

p53 is a key tumor suppressor gene, loss of which can cause various types of tumors. The role of a common non-synonymous SNP in this gene, rs1042522 (Arg72Pro), has been shown to exhibit functional differences: Arg has an increased ability of p53 to localize to mitochondria and increase cell death, while substitution of the allele to Pro results in reduced apoptotic potential of the protein and increased cell cycle arrest [45,46]. This SNP has been exhaustively studied for association with an array of diseases including cancer, age-related or age-independent diseases [45–52]. The impact of the SNP on longevity, however, is still ambiguous due to contradicting association results among different studies. Ørsted et al. reported that the Pro allele of this SNP contributes to longevity or increased survival after diagnosis of cancer without being associated with reduced cancer risk [53]. The authors used a large cohort consisting of 9,219 individuals aged 20–95 and investigated survival of these individuals at 12 years after initial recruitment. Recently, the opposite allele (Arg) was reported to be associated with female longevity in Central Italy by Pietro et al [54]. In this study, subjects are divided into 3 sub-groups by their age for a cross-sectional comparison and longevity association was found between the group of 73–91 year-old and the group of older than 91 years in females. The contradicting results between these two studies may be due to different study design (longitudinal vs. cross-sectional and gender stratification) or due to adaptation of these different ethnic groups in distinct geographical regions.

Perspectives

More than 1,600 published GWAS reported significant ($p < 5 \times 10^{-8}$) associations of >5,000 SNPs for more than 200 traits/diseases (<http://www.genome.gov>). However, each locus has a surprisingly low to modest effect and there is a wide gap between the population variation in traits explained by the results of GWAS (usually less than 10%) and heritability estimates (often more than 50%) [55]. Interestingly, the frequency of a set of alleles identified by GWAS to increase the risk of the major diseases that contribute to human mortality was almost identical between long-lived individuals and younger controls [21,56]. These results suggest that the genome of the long-lived may harbor longevity-promoting alleles that protect against age-related diseases that contribute to population mortality, rather than the absence of alleles promoting such diseases. Furthermore, these results predict the presence of rare variants with strong effects in long-lived individuals as a possible explanation for the failure to detect common variants significantly associated with longevity other than *ApoE* [19–21]. Since extreme longevity is a rare phenotype, only an exhaustive and comprehensive approach will ensure that no rare but important SNP escapes attention. Coupled with the rapid advances in ultra-high-throughput sequencing technologies, it is now feasible to comprehensively analyze all sequence variants in genome maintenance genes segregating with a longevity phenotype.

The candidate gene approach has been widely used to analyze possible associations between genetic variants in GM pathway genes and longevity based on *a priori* knowledge of the role of GM pathway in healthspan and lifespan. As noted in this review, however, these associations were overall poorly replicated. To complete a genetic study with solely a statistical end point is unsatisfactory in view of the uncertainties associated with the statistical interpretation. To minimize possible errors and spurious association, an integrated approach is required to assess the phenotypical relevance of gene variations and to overcome the statistical limitations. Once the potential phenotypically relevant variations from the population data through association analysis are identified, it is critical to verify the functions of their gene products at the molecular level. Moreover, although functional variants are likely to be rare [57], these rare SNPs are not queried in most case-control studies because of the insufficient statistical power when sample sizes are limited. So far, this candidate approach combined with functional analysis has been successfully applied to identify functional rare variants in the insulin like growth factor-1 receptor (*IGF1R*) gene that are enriched in Ashkenazi Jewish centenarians as compared to younger controls and cause defects in IGF1R signaling, gene regulation, and cell cycle control in response to IGF-1 treatments in short-term cell culture models [58,59], supporting the role of IGF-1 signaling in human longevity. In principle, these approaches can be applied to genome maintenance genes.

The vast majority of the variants detected by GWAS are located in the genome that does not code for known proteins, referred to as gene deserts, and understanding their functional consequences and causality is largely incomplete and at best rudimentary [60,61]. Recent development of tools to incorporate ENCODE driven data sets including ChIP-seq data to predict functional variants will greatly facilitate future endeavors to identify causal variants in the regulatory regions and to elucidate the molecular mechanisms underlying the association with longevity. Understanding the mechanisms by which longevity-associated genome maintenance gene variants contribute to human longevity will be critically important to facilitate the development of strategies to delay aging and promote health span.

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Figure 1. Schematic representation of genes involved in genome maintenance as candidate longevity assurance genes selected for this review

The genes in which heritable mutations have been found to be associated with accelerated aging in humans are labeled in red. The genes with longevity association listed in this review are indicated in bold with asterisk (*). NHEJ, non-homologous end joining; HR, homologous recombination repair; DSB, double-strand break; NER, nucleotide excision repair; GGR, global-genome repair; TCR, transcription-coupled repair; BER, base excision repair.

repair; MMR, mismatch repair. Genes are grouped as much as possible to represent the pathway.

Table 1

Longevity associated genes in genome maintenance pathway

Study	Gene	SNP	Nature of var	Associated allele(s)	p-Value	Description of association	Study subjects
Lunetta KL et al. 2007 [25]	WRN	rs2543600	Intergenic	NA	$0.03/4.2 \times 10^{-6}$	Morbidity-free survival at age 65/Age and death	1,345 Framingham Study
Østved DD et al. 2008 [53]	TP53	rs1042522	Coding (R72P)	CG (Arg/Pro) CC (Pro/Pro)	0.003 0.002	Longevity (increased median survival of 2-3 years) and survival after cancer diagnosis	9,219 (20-95), 12yrs follow-up, Danish
Lescai F et al. 2008 [35]	SIRT3	rs939915	Intronic	A	0.0145	Longevity, indicated not to be robust by the authors	1,321 centenarians vs 1,140 controls, German, Italian, French
Nebel A et al. 2009 [29]	EXO1	rs735943 rs1776180 [‡]	Coding (H354R) Promoter	A C	5.90×10^{-4} $0.0023/0.053$	Longevity $\varnothing$ discovery/replication Higher EXO1 mRNA expression	Discovery: 395 centenarians vs 411 controls, German. Replication: 455 centenarians vs 109 controls, French
Atzmon G et al. 2010 [39]	TERT	rs33954691	Coding (H1013H)	T	0.0049	Longevity and telomere length	123 Ashkenazi Jewish (43-105 yrs)
		Haplotype of rs35226131, rs35837567, rs33954691, rs2853690	intronic Coding (A305A) Coding (H1013H) intronic	TGTC T G T C	0.008		
Polosak J et al. 2010 [62]	XPB	rs13181	Coding (K751Q)	AC	0.0047	Longevity and XPD mRNA expression	413 young vs. 149 centenarians (99-107), Polish
Chen T et al. 2010 [30]	ATM	rs189037	5'UTR/intronic	CT	0.004	Longevity and ATM mRNA expression	789 long-lived vs. 886 controls, Chinese
Yashin AI et al. 2010 [22]	NTHL1 TERFIP3 ATRIP	rs2516739 rs6813479 rs9876781	Intronic Intergenic (38kb downstream) Intergenic (0.8kb upstream)	NA NA NA	1×10^{-6} 1×10^{-6} 1×10^{-6}	Longevity, GWAS	1,173 Framingham study
Soerensen M et al. 2011 [42]	TERC	rs3772190	13kb upstream	A	0.016/0.014	Longevity / short telomere length $\varnothing^*$	127 centenarians vs 578 controls (<80), Danish (58-100+)
Kim S et al. 2012 [34]	SIRT1	rs7896005	intronic	G	0.0056 [*] /0.0085	Longevity/telomere length (recessive model)	Discovery: LAHS, 224 nonagenarians vs 293 controls, Replication: GCS, 170 centenarians vs 220 controls, Caucasian

Study	Gene	SNP	Nature of var	Associated allele(s)	p-Value	Description of association	Study subjects
Sebastiani P et al. 2012 [23]	WRN	rs1800392	Coding (L787L)	NA	0.0130	Exceptional longevity in a given set of 281 SNPs, tested by using genetic risk modeling linked to Alzheimer's and coronary artery diseases, <i>GWAS</i>	Discovery : NECS, 801 centenarians vs 914 controls Replication : ELIX, 253 old vs 341; NECS, 60 centenarians vs 2863 control,
	WRN	rs3024239	Intronic	NA	0.0023		
	RAD51L3	rs3816754	Intronic	NA	0.0013		
	RAD51L1	rs4902538	Intronic	NA	0.0040		
	RAD51L1	rs1033686	Intronic	NA	0.0054		
Conneely KN et al. 2012 [27]	LMNA	rs915179	Intronic	NA	2.4×10^{-5}	Longevity, stage1/stage2 (replication by meta-analysis using 4 additional independent populations)	Stage 1 : 837 LLIs (95) vs 443 controls (50), Caucasian Stage 2 : NECS 545 LLIs (96–113) vs 193 controls (55–92), French 558 LLIs (99) vs 546 controls (18–70), SICS 455 LLIs (90–109) vs 450 controls (18–46), Ashkenazi Jewish 354 LLIs (95–109) vs 348 controls (43–90)
	LMNA	rs3814314	7kb upstream	NA	0.017/0.039		
	LMNA	rs915179	Intronic	NA	0.014/0.020		
	LMNA	rs2485662	Intronic	NA	0.054/0.026		
	LMNA	rs508641	Intronic	NA	0.014/0.044		
Soerensen M et al. 2012 [26]	RAD52 WRN RAD23B POLB NTHL1 MLH1 XRCC5 (Ku80) H2AFX	rs1468772	6.5kb downstream	NA	0.034/0.0056	Longevity, case-control Longevity, case-control Longevity, case-control Longevity, case-control Longevity, case-control Early death, longitudinal Early death, longitudinal No. of days lived, longitudinal	Discovery : 1,089 oldest old (91.2–93.8) vs 736 middle aged (46–55), Danish. Replication : 1,613 LLIs (98.4±2.7) vs 1,104 control (67.2±4.1), German; 536 (85) with 10.4 yrs follow-up, Leiden85-plus
		rs915179	Intronic	NA	1.1×10^{-4}		
		rs13251813	Intronic	NA	2.1×10^{-4} /0.02		
		rs1805329	Intronic	NA	0.0225		
		rs2953983	Coding (A1140V)	NA	0.0309		
	H2AFX	rs3211994	Downstream	NA	0.0056 /0.009	Longevity, case-control Longevity, case-control Longevity, case-control Longevity, case-control Longevity, case-control Early death, longitudinal Early death, longitudinal No. of days lived, longitudinal	Discovery : 1,089 oldest old (91.2–93.8) vs 736 middle aged (46–55), Danish. Replication : 1,613 LLIs (98.4±2.7) vs 1,104 control (67.2±4.1), German; 536 (85) with 10.4 yrs follow-up, Leiden85-plus
		rs13320360	Intronic	NA	0.0036		
		rs705649	Upstream	NA	0.017		
		rs2509049	Intronic	NA	0.029		
		rs1468772	6.5kb downstream	NA	0.0045 /0.0037		
Sebastiani P et al. 2013 [24]	WRN	rs1800392	Coding (L787L)	AC/CC	0.0007	Exceptional longevity, meta-analysis	NECS, 801 old (95–119) vs 914 younger (53–90); ELIX, 253 old (89–114) vs 341 controls; SICS, 410 old (90–109) vs 553 young; LLFS, 738 old (95–110) vs 356 younger (44–95); JCS, 513 centenarians (110–114) vs 561 controls (19–89)
	LMNA	rs915179	Intronic	G	0.0001		
Concetti F et al. 2013 [43]	TERT	MNS16A (VNTR)	1.2kb downstream	MNS16A*L	0.020/0.002	Negative influence on longevity and telomere length	200 old (>91) vs 539 younger (73–91), Central Italian
Han et al. 2013 [63]	PMS2	Novel	Coding (Y318C)	G	0.02	Longevity	390 centenarians vs 410 controls, Ashkenazi Jewish
Piacentini et al. 2013 [32]	ATM	rs189037	5'UTR/intronic	CT	0.037	Longevity	67 centenarians vs 150 controls (67.2±0.1), Italian
Albani D et al. 2013 [36]	SIRT3	rs4980329 rs11555236	Intronic Coding (S159S)	AA TT	0.02 0.03	Longevity, measured by survival function	549 individuals (>70) from TRELONG, Italian

Study	Gene	SNP	Nature of var	Associated allele(s)	p-Value	Description of association	Study subjects
Di Pietro F et al. 2013 [54]	TP53	rs1042522	Codnig (R72P)	G(Arg)	0.008	Longevity $\bar{Q}$	100 Group3 (>91) vs 280 Group2 (73–91)
Figarska SM et al. 2013 [33]	SIRT1	rs12778366	1.3kb upstream	C	0.015	Mortality from 18yrs follow-up and better glucose tolerance $\bar{O}^{\dagger}$	1,390 subjects, Dutch

* P-value after multiple correction;
 $\bar{Q}$ association only in female;
 $\bar{O}^{\dagger}$ association only in male;

$\dagger$ Functional SNP, **LLIs**, Long Lived Individuals; **LHAS**, Louisiana Healthy Aging Study; **GCS**, Georgia Centenarian Study; **SICS**, Southern Italian Centenarian Study; **NECS**, New England Centenarian Study; **LLFS**, Long Life Family Study, **ELIX**, Elixir Pharmaceutical Longevity Study; **JCS**, Japanese Centenarian Study; **TRELONG**, Treviso Longeva