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Genetic Cartography of Longevity in Humans and Mice: Current Landscape and Horizons

Michael Hook¹, Suheeta Roy¹, Evan G. Williams⁵, Maroun Bou Sleiman⁴, Khyobeni Mozhui², James F. Nelson³, Lu Lu¹, Johan Auwerx⁴, and Robert W. Williams¹

¹Department of Genetics, Genomics and Informatics, University of Tennessee Health Science Center, Memphis, TN 38163, USA ²Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN 38163, USA ³Department of Cellular and Integrative Physiology and Barshop Institute for Longevity and Aging Studies, The University of Texas Health Science Center at San Antonio, San Antonio, TX 78229, USA ⁴Interfaculty Institute of Bioengineering, Laboratory of Integrative and Systems Physiology, Institute of Bioengineering, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne CH-1015, Switzerland ⁵Department of Biology, Institute of Molecular Systems Biology, ETH Zurich, Zurich CH-8093, Switzerland

Abstract

Aging is a complex and highly variable process. Heritability of longevity among humans and other species is low, and this has given rise to the idea that it may be futile to search for gene variants that control rates of aging. We argue that the problem is mainly due to low power and the genetic and environmental complexity of longevity. In this review we highlight progress made in mapping genes and molecular networks associated with longevity, paying special attention to work in mice and humans. We summarize 40 years of linkage studies using murine cohorts and 15 years of studies in human populations that have exploited candidate gene and genome-wide association methods. A small but growing number of gene variants contribute to known longevity mechanisms, but a much larger set have unknown functions. We outline these and other challenges and suggest some possible solutions, including more intense collaboration between research communities that use model organisms and human cohorts. Once hundreds of gene variants have been linked to differences in longevity in mammals, it will become feasible to systematically explore gene-by-environmental interactions, dissect mechanisms with more assurance, and evaluate the roles of epistasis and epigenetics in aging. A deeper understanding of complex networks—genetic, cellular, physiological, and social—should position us well to improve healthspan.

*Correspondence to rwilliams@uthsc.edu, Robert W. Williams, Ph.D., Department of Genetics, Genomics and Informatics, University of Tennessee Health Science Center, 71 S Manassas St, Room 407, Memphis TN 38163, Telephone 901 448-7050.

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Keywords

aging; healthspan; heritability; GWAS; QTL analysis

Introduction

Over the past two centuries longevity has increased at an impressive rate, driven by innovations in sanitation, healthcare, nutrition, and social support [1–5]. The proportion of individuals who reach 95 has doubled in the past 25 years, and the peak age of death is now close to 85 worldwide [6]. In some populations there has also been a matched but more gradual increase in age of menopause by one year per decade since 1910 [7–8]. Further improvements in health care and social structure may push lifespan upward, but it is also possible that we are reaching fundamental biological constraints with diminishing prospects of healthy living beyond 100 years [9–10]. The same trends are replicated in laboratory mice—60 years ago, mean lifespan of inbred strains averaged 488 days [11–12]. Genetically identical descendants of these strains now consistently live about 50% longer. This upward shift is almost certainly related to improved husbandry and low rates of infection.

As lifespan increases, causes of death shift from accidents and pathogens to late-onset chronic conditions such as cardiovascular, respiratory, and metabolic diseases, cancer, neurodegeneration, and adverse consequences of pneumonias [6, their Figure 3; 13]. In humans and other species this shift is a result of much weaker selection against heritable factors that reduce post-reproductive longevity—an insight dating back to 1881 [14]. George Williams refined this idea and argued that gene variants may have positive effects on fitness early in life but negative effects later in life: so-called *antagonistic pleiotropy* [15]. Humans and killer whales seem to defy antagonistic pleiotropy for two decades or more after reproductive senescence [16]. Even the roundworm, *C. elegans*, manages to extend lifespan at least twofold beyond the age of reproductive senescence [17]. There is countervailing evidence that post-reproductive vigor and lifespan in some species, including humans, is under positive selection and contributes significantly to fitness by enhancing the success of progeny [18–21]. This provides motivation to find factors that modulate the length of post-reproductive healthspan. While we must continue to fight a rearguard action against age-related chronic diseases, we need to focus much more attention on the deeper genetic, molecular, and cellular processes that modulate longevity, the main topics of this review [22–24].

Variation in longevity among species is pronounced and linked to life history and style of reproduction [18, 22, 25–27]. Weismann proposed that heritable differences driven by millions of years of natural selection are the root cause of this variation [14, 28]. He also pointed out that it was not possible for him “*to indicate the molecular and chemical properties of the cell upon which the duration of its power of reproduction depends: to ask this is to demand an explanation of the nature of heredity—a problem the solution of which may still occupy many generations of scientists.*” And so it has proved. We are still struggling to find and define genetic and molecular causes of aging [29–31]. Since the early 1920s [32], we have known that gene variants influence longevity within species, just as

they must between species. But in humans and other mammals, discovering DNA polymorphisms (also known as chromosomal loci or gene variants) responsible for differences in lifespan has resisted standard mapping methods [early work reviewed by 28, 33–34]. One pessimistic view has been that aging is a consequence of nearly random and irremediable process of stochastic decay driven by somatic mutations in both nuclear and mitochondrial genomes [35]. A more optimistic alternative is that differences in aging rates within species are modulated by genetic variants linked to metabolic states, accuracy of DNA repair, protein processing efficiencies, immune surveillance, and life history—what we and others call the deep causes of aging.

The difference is vital. If aging is fundamentally caused by stochastic molecular decay, there may not be good reasons to look beyond the most prevalent diseases to increase lifespan. In contrast, if longevity is largely a tunable genetic process, as the comparative biology of longevity indicates, then there should be room to push lifespan of humans well into a second century, not just by overcoming chronic disease but by more fundamental interventions that improve general health and vigor. Whether longevity is an integrated hazard function of many diseases or the result of deeper causes, it is not unreasonable to have a goal of good quality life to age 100 [36]—the age at which Jeanne Louise Calment finally put aside her bicycle [37]. She lived another 22.5 years.

Getting at the genetic basis of aging has been hard. We have succeeded in defining a small set of rare mutations in several genes such as *LMNA*, *WRN*, and *SERPINE1* that model some aspects of aging and senescence [38–42], but these variants do not account for normal variability in longevity. Our main aim now is to uncover common sequence variants that influence the kinetics of aging. Many candidate genes have been nominated and tested based on their known roles in DNA repair and cell cycle control, mitochondrial function and metabolism, oxidative stress and proteostasis, and numerous other age-related processes [43–44]. These candidate gene studies often test for enrichment of specific alleles in old cohorts [27, 33]. While this approach may eventually fulfill its promise, hypothesis-driven tests of longevity linked gene variants have generally failed to replicate [45–46]. For example, a large and careful retest of three aged Danish cohorts came up empty-handed after surveying variants in 125 well known genes implicated in aging based on known molecular functions [47]. The conventional excuse for failures of this type is that longevity is a complex, multifactorial phenotype influenced by small contributions from many DNA variants (and of course, many environmental factors), making any one sequence variant exceedingly difficult to validate using simple association studies of this type [48–49]. Compounding this problem, methods are designed to detect only simple additive genetic effects. But there are good reasons to suspect that longevity is modulated by non-linear epistatic interactions, antagonistic pleiotropy [50], and gene-by-environmental interactions (GXE) among multiple loci and gene variants.

Insufficient statistical power is certainly one core problem [51–52], but thanks to rapid growth of elderly populations this should not be a problem much longer. Stepler estimates that there are now ~500,000 centenarians worldwide among a population of ~7.6 billion, and the expectation is that there will be ~3.5 million centenarians by 2050 [53–54]. Eighty-five

percent will be female [55]. We will soon have the access to the very large sample sizes needed to understand genetic and environmental control of longevity [56–58].

What is perhaps surprising is that many other traits that are arguably just as complex as longevity—in particular, metabolic and psychiatric diseases and traits such as body weight and height—have been mapped to numerous genes and loci. In these cases, however, mapping did not rely on the evaluation of small numbers of nominated candidate genes, but rather used unbiased genome-wide association studies (GWAS). As shown in Figure 1, these GWAS require unusually large sample sizes. For example, the analysis of height in humans did not relent to genome-wide analysis until cohorts exceeded 10,000 subjects. Schizophrenia is another good case study and a useful contrast to longevity. While the heritability of schizophrenia is high [59], the idea arose that spontaneous copy number variants were the primary cause [60]. The conundrum was solved by a very large GWAS [61]: with 37,000 subjects, a total of 108 single nucleotide polymorphisms (SNPs) were uncovered. While these SNPs have small effects, they have a significant combinatorial impact. The outcome has been a wealth of leads and unexpected mechanistic insight into the etiology of this complex disease [62].

With aging and lifespan studies, there is the added challenge of defining the most relevant phenotype. There are marked differences in methodology among studies [63], heterogeneity among populations [64–65], and unique genetic effects that may emerge only in extreme age [24, 36, 66]. In some cases, the approach has been to construct a phenotype amalgam based on different health and disease traits such as number of years free of major disease, or psychosocial and emotional functioning [49, 67]. The alternative of using lifespan (i.e., time to all-cause mortality) results in a heterogeneous and noisy phenotype. A complementary approach is to use multisystems measures of frailty [68] or molecular biomarkers. One example is the epigenetic status of specific regions of the genome that can be used as metrics of age in single tissues or cells [69]. Telomere length [42, 70–73], changes in metal isotopes [42, 74], and metabolites such as NAD⁺ [75–76] are other examples of molecular phenotypes of aging being validated in model systems and humans. These and other complementary assays are yielding interesting GWAS hits on what may be considered genetic roots of aging [77], but as has been emphasized by Birney and colleagues [78] it is sometimes difficult to sort out genetic and environmental causes of aging from epigenetic, molecular, and cellular consequences.

In this status report on the genetics of longevity, we focus almost exclusively on forward genetic studies in mouse and human extending back to the dark ages of quantitative trait locus (QTL) mapping [79] and up to the first waves of GWAS in humans [24, 31, 80]. Our review revisits themes covered well by Yuan and colleagues [81]. A side-to-side comparison of our review with theirs is noteworthy and humbling. To give away the main conclusion, there has been painfully slow progress in defining and validating common or rare variants that modulate longevity in mouse or human. We weigh in favor of the simple explanation: that the paucity of longevity hits is primarily the result of inadequate sample size rather than a fundamental problem related to genetic control (or lack thereof) of lifespan. As shown in Figure 1, samples of hundreds of thousands of cases may be mandatory for high yield analysis of the genetics of longevity in humans. As we will see below, the size of mouse

cohorts can be much smaller since almost all studies make use of families of closely related cases or even sets of isogenic strains. GWAS have high mapping precision but low power (hence the need for large sample sizes), while studies using rodents generally have modest mapping precision (1 to 10 Mb) but relatively high power. By combining results from both, we can gain both power and precision to detect gene variants associated with longevity—an approach that has been highly effective in other areas of research [82–84].

Two studies published in 2017 provide an empirical basis for optimism. Both took unusual approaches to the problem: McDaid and colleagues [31] used statistical methods to remove confounds associated with age-related diseases and used very large samples sizes via the UK Biobank; Sebastiani and colleagues [24] accomplished the same goal by studying extremely long-lived humans—so-called supercentenarians—using more modest sample size. Both studies nominated candidate genes and loci that may get at the deep metrics and mechanisms of aging in mammals, and certainly in humans. These variants, in turn, should provide reagents and motivation to dissect molecular controllers and biomarkers of aging, ultimately explaining some of the intrinsic sources of variation in longevity. Genomic methods of mapping and validating DNA variants are becoming so powerful and efficient, and sample sizes so large, that we should soon be able to resolve large numbers of longevity modulators. We should then also be able to move to the opening of Act 2—the analysis of GXE.

Heritability of longevity

Estimates of the heritability of longevity are generally low. Values average about 20% but range widely—from close to 0% to as high as 50% in most natural populations of yeast, nematodes, butterflies, fruit flies, deer, bighorn sheep, and humans [17, 28, 85–89]. Estimates from human cohorts typically hover around 20–30% with heritability increasing among families with exceptional longevity [36, 90–91]. Age at menopause, the best metric of reproductive aging in humans, has a heritability that is significantly higher—about 60–65% [92]. Heritability of traits is often an inverse function of their importance to survival and fitness—the more important a trait, the more it will be scrutinized by natural selection, and the lower its heritability [87; but see counterpoints by 89]. There is an unfortunate tendency to equate heritability with tight genetic control, and to equate genetic control with molecular control. Neither is correct. Traits that are key to survival and fitness are obviously under genetic, molecular, and cellular control—numbers of arms and legs being a silly but useful case in point. But for many key life history traits, the statistical definition of *genetic control* measured by heritability can be exceedingly low. This finding implies that DNA variants have been sanded smooth by selection and that residual sources of variability in longevity are mainly caused by environmental factors or cellular stochastics. There are exceptions to this rule, mainly in the form of balancing selection, but the low heritability of longevity should probably be interpreted as a sign that selection is actively filtering DNA differences that change rates of growth, reproduction, parental investment, and aging. Again, the dramatic variation in longevity among closely related species leaves little room for argument [22, 25, 93].

Heritability of longevity is not a fixed parameter even within a single species or age cohort. Estimates are sensitive to GXE, sex, and even—almost paradoxically—the age of the cohort.

Harsh or volatile environments that increase the range of variation in lifespan will tend to increase heritability estimates. The range of ages over which heritability of longevity or hazard ratios are computed is also an important parameter. Studies of twins demonstrate that the likelihood of survival (or conversely, the risk of death) increases with the age of the cohort, as does the heritability. This makes sense if we consider two extremes. On the one hand, young individuals who have just become sexually mature should have a risk of death that is determined largely by environmental factors or bad luck, not by gene variants. At this stage of maturation, human monozygotic and dizygotic twins do not differ much in their risk or survival concordance [94]. On the other hand, individuals older than 60 will have a risk of death that is determined to a progressively greater degree by genetic influences on rates of senescence and risks of chronic disease. Above 60 years-of-age, hazard ratios of monozygotic twins are much more similar to each other than those of dizygotic twins [94].

Nor is heritability necessarily fixed even with a given set of genomes and environment. Heritability can be boosted by using large families of inbred or isogenic lines and can easily be raised to 30–50% by resampling the same genome many times [79, 95–96]. We have used data from two recent longevity studies of mice—that of Yuan, Bogue, and colleagues [12, 97] and our own ongoing study of the BXD strains [98]—to compute heritabilities of longevity based on strain means. Estimates range from 25 to 45%, extending up to 55% in the case of BXD females placed on a high fat diet. Goodrick [99] and Rikke and colleagues [96] provide an even higher estimate—up to 85% for the effective heritability of strain means [100].

Collectively, these estimates of heritability of longevity in panels of inbred strains of mice are much higher than those for other species—from yeast to human—for three reasons: (1) tight control of the environment and food sources, and negligible pathogen exposure; (2) longevity is computed as a mean, median, or hazard function based on large numbers of genetically identical cases (usually 5 to 20 samples/genome); and (3) families of fully inbred strains collectively incorporate twice the genetic variance of outcrossed populations because they lack heterozygous loci [101]. With sufficiently deep resampling of isogenic cohorts, the effective heritability of longevity can be pushed surprisingly close to 1.0 in a well-controlled environment. The ability to boost heritability in these ways makes families of inbred strains a welcome complement to studies of more complex outcrossed natural populations, including humans. It also means that relatively small sample sizes may be effective in mapping longevity loci.

In addition to achieving high heritability and high power with relatively modest sample sizes, it is also possible to use families of inbred strains or isogenic lines to study biomarkers of aging under many different, but tightly controlled diets, treatments, and stressors [96, 98, 102]. But there are also disadvantages of using inbred strains in longevity studies, the foremost being that individuals are homozygous across their entire genome. While this increases the genetic variance, it may also increase the burden of diseases influenced strongly by recessive alleles. This could in principle compromise average longevity compared to either outbred populations [103] or four-parent F2 intercross progeny of the type used in the *Interventions Testing Program* [104–107]. However, at least in the case of the LXS family of mice that has been so well characterized in several different environments

[96, 102], the family of inbred strains manages to live to an average age of 825 days (44 strains), and some strains live to an average of 1200 days even on a conventional unrestricted diet (e.g., LXS46). This lifespan rivals that of dwarf mice on caloric restriction [108], and is exceeded only by a handful (literally) of *Ghr* knockout mice [109] and outbred mice. For the record, the current record age reached by any mouse is an individual from the Diversity Outbred population that reached 1730 days (Dr. Steven Munger, personal communication).

What happens to the heritability of longevity after the reproductive phase of life?

Antagonistic pleiotropy [15] posits that alleles that have positive effects on growth and reproductive success early in life may accelerate senescence after reproduction [110]. In contrast, alleles that slow growth and reproduction may increase lifespan as well as sensitivity [111] or resilience to stress [112]. Following in the footsteps of Weismann, there is also evidence of direct competition between the germline and somatic tissues that can shorten or extend life [113–115]. In contrast, there is not much direct evidence for antagonistic pleiotropy in humans, although the *APOE* gene is a reasonable candidate [116–117], and sex hormone genes also may fall into this category—essential for reproductive performance but with deleterious effects when expressed later in life [118]. There may be countervailing pressure that has to do with persistent parental and grandparental investment in the fitness of progeny [18–19, 21]. There are also good reasons to suspect that plasticity of life history traits, such as age of reproduction and peak parental investment, will be under strong balancing selection in a normally volatile world with many ecological niches for single species [119]. Even in the absence of antagonistic pleiotropy, selection will inevitably be relaxed after the main phase of reproduction, and this will contribute to the steep increase in incidence of chronic diseases and the steep rise in mortality described by Gompertz nearly 200 years ago [120]. The good news is that this steep rise in mortality should be accompanied by a steep rise in heritability, implying that conscious attention to both alleles and environments should enable significant enhancement of healthspan.

In conclusion, the heritability of longevity is low compared to that of most chronic diseases, and even traits such as height, body weight, and schizophrenia. This low heritability goes a long way to explaining the comparative difficulty of mapping longevity, a finding highlighted well by the longevity points we have added in Figure 1. In humans, very large sample sizes will generally be required (hundreds of thousands of centenarians would be ideal). But as we show in the next section, when working with families of isogenic strains, cohorts of as few as 30–40 have proved effective [79, 96, 102, 121–122] because heritability can be maximized.

Mapping longevity loci in mouse

Mice are the preeminent mammalian model of aging. Reasons are simple—an impressive wealth of genetic and genomic resources and tools [97, 123–124], coupled with small size, fast reproduction, short lifespan, high tolerance for inbreeding, and of course, an impressive set of methods to modify genomes [125–127]. These many advantages enable extensive and detailed investigation into both the genetics and the molecular biology of aging—from the first studies of lifespan by Roderick and Storer [11] to the latest studies from the *Interventions Testing Program* (ITP) [128]. Mice, like other mammals, share ~95% of

protein-coding genes with humans [129], but their much shorter lifespan makes longevity studies practical [e.g., 96, 102]. This latter factor is critical in efficiently mapping loci, and even DNA variants, influencing lifespan and aging as a function of experimental manipulations [81, 104, 107, 130].

A range of murine resource types have been used to map variation in longevity. The first study by Smith and Walford used a panel of congenic strains on a C57BL/10 background that harbored different versions of the major histocompatibility (MHC or *H2*) locus on chromosome (Chr) 17 [130]. Yunis and colleagues analyzed longevity in a conventional backcross [79] and then followed up with an analysis of longevity across 20 BXD recombinant inbred strains [121]. More recently, an expanded panel of BXD strains ($n \sim 75$) has been used in a second phase of longevity studies investigating two diets—6% versus 60% calories from fat [131]. Rikke and colleagues have also used the LXS recombinant inbred strains, in their case derived from a cross between ILS and ISS parental strains [96]. They also used matched sets on two diets—a conventional *ad libitum* diet or an intense dietary restriction. Surprisingly, few studies have used standard F2 intercrosses to map longevity in mice [132–133], the main challenge being able to achieve sufficient power using an intercross in which every case is genetically unique. But sample sizes of more than 1000 intercross progeny, heterogeneous stock, or outbred mice should soon yield results.

By far the largest and most systematic study of lifespan variation in mice is the ITP, a resource that is ideal for mapping QTLs for longevity. The ITP was initiated in 2004 [104, 134–135] and has made use of an intercross between C57BL/6J x BALB/cByJ F1 females and C3H/HeJ x DBA/2J F1 males [136]. Each of the F2 progeny is genetically unique, and this does impose design limitations, but the benefit is excellent consilience with human populations. The F2 mice generated by the ITP have been used primarily for non-genetic studies of the impact of dietary interventions on lifespan [107, 128, 137–138]. For example, smaller F2 progeny tend to live longer than larger siblings, and have lower levels of thyroid hormone T4, growth hormone mediator IGF1, and leptin [139]. A small cohort of these F2 animals was used in an early mapping study of longevity [132], but in an era when marker resources were modest. The ITP cohort is now so large ($n \sim 15,000$ cases) that it is now well powered to detect longevity QTLs [98].

How replicable are results from longevity studies using mouse models? Longevity estimates generated by Roderick and Storer [11] correlate well with data generated 48 years later by Yuan and colleagues ($r = 0.88$), although lifespan increased from 520 to 754 days. Gelman and colleagues [121] studied longevity in 15 strains in common with Lang et al. [140], and again the correlation is high ($r = 0.77$). In this case, longevity values also replicate (Gelman et al.: 711 days, $n = 23$ strains, all females; Lang et al.: 704 days, $n = 23$ strains, all females). Differences in longevity between sexes can be large [141]. The correlation of male-female lifespan in Lang's study of the BXD strains is 0.40, and males actually outlived females by two months. The ITP has shown that longevity of males is particularly sensitive to housing despite best efforts to standardize husbandry [106, 137–138]. Finally, dietary interventions can completely disrupt patterns of longevity. Correlations across the LXS strains on restricted or unrestricted diet are merely -0.02 and 0.15 for females and males, respectively

($n = 41$ strains, median longevity). In sum, we should be prepared for potentially strong environmental and sex effects on longevity.

Over the past four decades, 16 studies have been carried out to define QTLs for longevity in mice—a surprisingly modest number given the importance and inherent interest of this topic [79, 96, 121–122, 130, 132–133, 140–148]. The first genetic analysis by Smith and Walford [130] exploited congenic strains and very large sample sizes ($n = 120$ per congenic strain) to test whether longevity is modulated by sequence variants in the major histocompatibility complex (MHC, *H2*) on Chr 17. The answer in this study was yes, but as the authors point out, longevity linkage results will depend strongly on the environment. Genotypes in this critical region controlling the adaptive immune response after infection should be a determinant of longevity when pathogen levels are high. Standards of animal care have changed greatly over the past 40 years—in particular, the introduction of specific-pathogen-free colonies. To the best of our knowledge, none of the more recent studies have detected a longevity locus on Chr 17.

In several cases, different cohorts made using the same parental strains have been used repeatedly to refine longevity QTL maps. The best example of a progressive improvement in power and precision is work that has been carried out since 1979 using C57BL/6J (B6) and DBA/2J (D2) parental strains and their progeny. The first analysis of longevity by Yunis and colleagues [79 1984] preceded the introduction of modern genetic mapping resources, and the authors were able to test only three markers in a backcross of 388 cases (Figure 2). Remarkably, two of their markers were highlighted as predictors of differences in longevity. Only one of these would now be considered significant after corrections for multiple tests—that linked to the brown locus, *Tyrp1*, on Chr 4. Gelman and colleagues [121] replicated this longevity analysis within the same laboratory, but now using BXD recombinant inbred strains also made by crossing B6J to D2. With a more comprehensive set of 101 markers, they linked variation in lifespan to loci on Chrs 1, 2, 7, and 12, but did not confirm linkage to *Tyrp1* (Figure 2). de Haan and colleagues [143] revisited Gelman's data after noticing a curious distribution in the range of lifespan within isogenic strains: high variation in age of death in nine strains, moderate variation in seven strains, and low variation in eight strains. Using this new phenotype they were able to map a locus on Chr 11 that may control variability of longevity within strain (Figure 2). These traits can now be remapped in GeneNetwork (www.genenetwork.org) simply by linking to the appropriate BXD phenotype trait identifier. For example, the longevity variability data is listed in GeneNetwork as BXD phenotype trait 19422, and it is easy to validate the Chr 11 locus. Using the latest genotypes, this trait has a linkage peak with a logarithm of odds (LOD) score of 4.8 between *Meis1* (*unc-62*) to the exportin 1 gene, *Xpo1*. Both genes are strong biological candidates [149–150]. One caveat: the statistic that they used—range of lifespan within strain—is an unusual and noisier trait than conventional longevity statistics, such as the mean or median lifespan. It will soon be possible to test whether this trait can be replicated in much larger BXD aging cohorts.

Lang and colleagues [140] also generated independent longevity data for 23 BXD strains—17 common to Gelman—and they report a QTL on Chr 7, as well as a locus on Chr 11 for median lifespan (Figure 2). We have not been able to replicate their results at a genome-wide

significance level using much higher densities marker maps (see GeneNetwork BXD phenotype traits 12563 and 12564). We suspect that the map method that they used—composite interval mapping—explains this failure. This method is generally not recommended with such small sample size, because it is easy to test too many alternative models.

Finally, Houtkooper and colleagues [122] remapped the Gelman BXD longevity data (GeneNetwork BXD phenotypes 17475, 10148, 10112) but now using 3800 markers and treating outlier data appropriately for mapping. They were able to refine the initial Chr 2 locus to a comparatively short interval of about 5 Mb (see GeneNetwork BXD group trait 17475). Validation studies of genes in this interval using *C. elegans* and mouse aging transcriptome data sets highlighted the mitochondrial ribosomal protein S5 (*Mrps5*) as the single best candidate. Inactivating this gene in worm extended lifespan significantly and also triggered a mitochondrial unfolded protein response (UPR^{mt}). While linkage between a specific sequence variant in mouse and direct control of lifespan is still not yet established, our working hypothesis is that sequence differences near *Mrps5* influence the UPR^{mt} and thereby longevity. The role of this family of mitochondrial genes in human longevity is an open question, but there is evidence that the mitochondrial ribosome—consisting of about 74 protein coding genes in all—is associated with differences in neurocognitive aging in older women [151].

The LXS panel of recombinant inbred strains has also been used effectively and collaboratively to map longevity QTLs. Liao [102] and Rikke and colleagues [96] aged mice at two sites and collectively have defined loci on Chrs 7, 9, and 15 affecting lifespan, fertility, and metabolic efficiency in response to dietary restriction. None of these loci has yet been linked to genes or mechanisms, but the Chr 15 locus has been fine-mapped to a small interval using congenic strains [152]. One concluding note on current mouse longevity QTL data: it is now practical to remap and reanalyze many of the older data sets using GeneNetwork [124]. For example, while the first wave mapping studies used up to 1000 markers [96, 140], it is now possible to remap both BXD and LXS longevity data using far denser and more reliable maps. Remapping was the first step that led to the discovery of *Mrps5* by Houtkooper and colleagues [122]. As part of this review, we remapped all longevity traits in Rikke et al. [96] and now detect an apparently new female longevity locus (normal *ad libitum* diet) on Chr 1 at about 80 Mb (Figure 2, and see GeneNetwork LXS group, trait 10156).

Mapping longevity gene variants in humans

While interest in genetic determinants of longevity in humans has grown significantly as gene mapping methods have become more powerful, there are still comparatively few robustly mapped, replicated natural variants that modulate longevity. Only the *TOMM40/APOE/APOC1* gene cluster (19q13.11–19q13.32) and the *FOXO3* gene (6q21) can make this claim [46, 91, 153–154]. Apolipoprotein E (*APOE*) has two isoforms known to influence longevity through their association with disease, *APOE e2* and *APOE e4* [48]. *APOE e2* promotes longevity largely by decreasing risk of cardiovascular disease and Alzheimer disease whereas *APOE e4* does the opposite, limiting longevity [155–158].

Similarly, the $\epsilon 2$ allele is enriched in centenarians whereas the $\epsilon 4$ allele is diminished [159–160]. Inheriting two copies of the *APOE* $\epsilon 4$ allele reduces the odds of achieving exceptional longevity by 45–65% [161]. The effects of these isoforms are robust and have attained genome-wide significance in at least 10 human GWAS studies of longevity and age-related disease (Table 1). Interestingly, recent work has shown the $\epsilon 4$ isoform may be beneficial in non-industrialized settings [116–117]. The forkhead box O3 (*FOXO3*) gene has a more modest association with longevity but has also crossed the significance threshold in a recent GWAS [153]. *FOXO3* is linked to insulin/insulin-like growth factor 1 signaling [162–163] and is a compelling true longevity gene. Other than *APOE* and *FOXO3*, there are also a number of candidates that are statistically significant, but not yet validated (Table 1). These include *GRIK2* [153], *RAD50/IL3* [164], and *MINPP1* [80].

A recent study by McDaid and colleagues [31] developed a new approach to discover longevity loci. They took advantage of the many SNPs linked to age-related disease and adjusted for these effects to detect underlying polymorphisms that modulate lifespan. The team was able to use an exceptionally large general population cohort rather than focusing on only the oldest of the old. Sixteen SNPs were highlighted as genome-wide significant and 11 were replicated in five independent cohorts. This study is also one of the first to bridge between mouse and human longevity data. Gene expression in the LXS mice was analyzed to evaluate the three strongest human candidate genes—*RMB6*, *SULT1A1*, and *CHRNA5*. Increased lifespan was associated with lower mRNA levels of *RMB6* in mouse prefrontal cortex. A caloric restricted diet known to extend lifespan in mice was associated with increased *SULT1A1* expression. These joint approaches using data from several species has promise to define new loci.

The point of mapping gene variants that control longevity is to use them as validated entry points to defining mechanisms of aging—the topic of next section. While mapping is not a necessary prelude to studying mechanism, it has the advantage of being relatively unbiased, and can help find common gene variants that are modulators of lifespan and healthspan. A complementary and powerful approach is to systematically inactivate genes one at a time across the genome [165]. This approach has been most effective in small organisms such as yeast, nematode, and fruit fly. For example, Magwire and colleagues [111] used transposon mutagenesis to define 58 loci that increase longevity (on average about 12%) in Canton-S derived isogenic lines. They defined many non-linear interactions among mutations and significant differences between sexes. There are two minor downsides to this approach. First, most experiments of this type test mutations on one genetic background, which will limit generality of specific gene effects. Second, induced mutations can inactivate genes effectively, but they are unlikely to replicate the effects of natural variants for longevity that are likely to be under intense selection.

From mapping to mechanisms

One of the major goals of aging research is to understand mechanisms well enough to reduce age-related disease burden, improve vigor, and extend healthspan and lifespan. As mentioned above, mapping does not get us there; it just points—we hope—in the right direction. We know a great deal about the molecular and cellular biology of longevity from

classical experimental approaches in model organisms that we outline below. But the point of this section is to encourage thought about how to effectively bridge between two major approaches to longevity—the highly effective reductionist paradigm and the more holistic and unbiased systems genetics approach. The reductionist approach looks for large effects of mutations and perturbations using constrained experimental designs (usually one genotype); the systems approach uses a more open-ended discovery design and large genetically complex cohorts. We need to bridge between these approaches, their communities, and most importantly, their key discoveries [166]. QTLs and GWAS hits for longevity need to be combined with everything we know about mechanisms of longevity. Mapping longevity should ideally not be unbiased, but should take advantage of all of the prior information we have on disease process and normal aging in all organisms.

Model organisms have been vital to this goal of identifying and understanding the molecular, cellular, and environmental factors affecting longevity and thereby improving lifespan. Studies in *S. cerevisiae* [167], *C. elegans* [168–169], *D. melanogaster* [111, 170], and most recently killifish [171] have all made major contributions toward understanding mechanisms that modulate longevity. An in-depth discussion of all these evolutionarily conserved biological processes and factors is beyond our scope; instead we refer readers to comprehensive overviews by Kenyon [172], Houtkooper and colleagues [173], López-Otín and colleagues [174], and Riera and colleagues [175].

In the following short sections, we enumerate some of the major intertwined mechanisms of senescence and longevity along with sets of gene variants highlighted in genetic studies.

1. Nutrient-sensing pathways that regulate aging

Insulin/IGF-1 and FOXO pathway—The first and possibly best characterized pathway to influence aging in organisms ranging from yeast to mammals is the insulin/IGF-1 pathway [172, 176]. Extensive research has shown that cumulative regulation of many genes through DAF-16, a FOXO transcription factor; HSF-1, the heat-shock transcription factor; and SKN-1, a Nrf-like xenobiotic response factor in the insulin/IGF1 signaling pathway prolongs the lifespan of *C. elegans* and *Drosophila melanogaster* by as much as two-fold [reviewed by 172]. In mammals, the relation between insulin/IGF1 signaling and longevity becomes more complex owing to the involvement of multiple insulin and IGF receptors, and because of the crucial role for insulin in regulation of glucose homeostasis. The insulin/IGF-1 pathway is a good candidate for mediating longevity through dietary restriction in worms, flies, and mice under specific conditions [177].

While polymorphisms in many core genes in these extended networks have been tested repeatedly [e.g., 47], most do not control normal variation in longevity in human populations. In humans, only variants in the *FOXO3* gene have been consistently replicated as associated with longevity across multiple populations, with the minor allele *AA* genotype being associated with increased lifespan [153, 178].

TOR signaling—The mechanistic target of rapamycin (mTOR) is a serine/threonine protein kinase that functions in two distinct complexes regulating different downstream processes—mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [179]. Under

conditions favorable for growth, TOR signaling modulates protein translation, protein homeostasis, and cellular growth and has been implicated as a controller of longevity in diverse species. Interest in understanding the physiological role and molecular targets of the TOR pathway has surged since the discovery that rapamycin treatment extends life in yeast, nematodes, flies, and mice via mTOR inhibition [180]. The TOR network has also been consistently linked to dietary restriction that reduces mTORC activity, which in turn increases lifespan in many organisms ranging from yeast to mice [172]. Sataranatarajan and colleagues report that rapamycin shortened the lifespan of the leptin receptor *db* mutant mouse—a reminder that genes and the networks they influence are unlikely to be universally beneficial [181]. Selman and colleagues showed increased lifespan in a mouse model of decreased mTOR signaling—ribosomal S6 kinase 1 knockout mice (*S6k1^{-/-}*) [182]. Similarly, mTOR knockout strains (*Mtor^{+/-}* and *Mlst8^{+/-}*) and hypomorphic homozygous *Mtor^l* mice have increased lifespans [183–184]. mTORC1 promotes mRNA translation and protein synthesis by activating ribosomal protein S6 kinases (RPS6KA1) and inhibiting eukaryotic translation initiation factor 4E-binding protein 1 (EIF4EBP1) [179]. However, no associations have been detected yet for mTOR complex gene variants (*MTOR*, *RPTOR*, *RICTOR*, and *RPS6KA1*) with extreme human longevity [185].

Sirtuins—Sirtuins, a protein family of metabolic sensors, have gained recognition over the last two decades as crucial regulators of evolutionary conserved pathways related to aging in a wide variety of organisms ranging from yeast to mammals [186]. The role of sirtuins in aging was first identified in yeast [187]. Since then, several research groups have showed that *Sir2* overexpression in *C. elegans* [188] and *Drosophila* [189] results in extending lifespan in a dose-dependent manner. Mammals have seven homologs of the yeast *Sir2* gene (*SIRT1* to *SIRT7*). All homologs contain the highly conserved NAD-dependent sirtuin core domain. This domain targets multiple cellular substrates and influences a broad range of cellular functions, including multiple metabolic and neuronal pathways. Experiments in mouse have shown that sirtuins are modulated by diet; thus, sirtuins could be therapeutic targets to enhance healthspan [190]. *SIRT1*, the best-characterized mammalian sirtuin, controls mitochondrial function by deacetylation of targets like *TRP53*, *PPARGC1A*, and *FOXO* [191]. There is compelling evidence that enhancing sirtuin activity leads to decreased cancer risk and is protective against metabolic dysfunction associated with aging [191–192]. *SIRT3*, which localizes to mitochondria, appears to be required for dietary restriction-mediated longevity through deacetylation of mitochondrial proteins [193]. *SIRT6* is a key modulator of healthy aging, and mice deficient in *SIRT6* have a reduced lifespan. Overexpression promotes genomic stability [194], promotes DNA repair, and suppresses genomic instability [195]. Deficiencies in mice lead to age-associated degenerative abnormalities and early death.

Lack of lifespan extension in *Sirt1^{-/-}* mice on caloric restriction, as well as the paucity of associations between polymorphisms in *SIRT1* and human lifespan, has cast doubts on the relevance of *SIRT1* as a key longevity gene [196]. Association studies of lifespan and *SIRT3* are inconsistent [197–199]. In the Iowa cohort of the Established Population for Epidemiologic Studies of the Elderly, homozygous minor allele *TT* genotypes for *SIRT5* and

SIRT6 were associated with a shorter lifespan, after controlling for age-related risk factors [200].

AMP kinase signaling—SIRT1 and AMPK are co-regulated; they interact and share many common target molecules. AMPK (adenosine monophosphate-activated protein kinase) is a highly conserved cellular energy sensor that is activated when cellular energy reserves are low, and also maintains metabolic energy balance [201]. AMPK is a key mediator of several signaling networks linked to aging and is activated by a wide array of small molecules, making it a potential therapeutic target for pro-longevity drugs such as metformin, resveratrol, rapamycin, aspirin, as well as a key mediator of several signaling pathways linked to aging [202–203]. However, many of these effects are indirect and are yet to be fully elucidated by work in model organisms. AMPK activity may be an important contributing factor in networks linking autophagy [204], dysregulated intracellular lipid metabolism, and reduced mitochondrial function associated with aging [205]. AMPK activity controls the function of several signaling networks associated with aging: FOXO/*daf-16* [172, 206], SIRT1 [207], TOR [179], and CRTC_s [208]. AMPK-induced deacetylation by SIRT1 modulates the activity of downstream targets, including the peroxisome proliferator-activated receptor- γ coactivator 1 α (PPARGC1A) and the forkhead transcription factors, FOXO1 and FOXO3. Treatment of mice with resveratrol, famously linked to cardiovascular benefits and cancer preventive properties of red wine, activates the NAD⁺–SIRT1 network and induces genes impacting oxidative phosphorylation and mitochondrial biogenesis [209]. The beneficial effect of S6K1 deficiency on lifespan might involve AMPK activation [182].

2. Mitochondrial function and reactive oxygen species effects

A decline in mitochondrial function contributes to normal aging through multiple distinct processes, including oxidative damage, inflammation, and senescence [210]. Reactive oxygen species (ROS), generated as a by-product of the mitochondrial respiratory system and intracellular metabolism in peroxisomes, were initially implicated as one of the causative factors of aging. Increased ROS levels may be detrimental and lead to cell death and acceleration in aging and age-related diseases; genetic studies in *C. elegans*, *Drosophila*, and mice have implicated enhanced stress resistance or reduced free radical production with increased lifespan [211]. Senescent cells are associated with high levels of intracellular ROS and accumulated oxidative damage to DNA and proteins [212]. However, that theory has been largely refuted, and several studies have shown that mitochondria can cope with physiological levels of oxidative damage [213–216]. Such ROS levels are most likely essential for regulation of cell cycle progression, cell signaling, and apoptosis, while increased ROS production over a certain level has a detrimental effect on cell physiology [217–218]. Lifespan extension by mild inhibition of mitochondrial respiration is evolutionarily conserved. Some key factors required to mediate this longevity response include dietary restriction, increased HIF1 activity, induction of homeobox protein CEH-23, and mitochondrial unfolded protein response (UPR) [219]. Impairment of the mitochondrial translation by a drop in mitochondrial ribosomal protein S5 (*MRPS5*) level initiates UPR^{mt} activation and results in increased longevity in both worms and mice [122].

Many of the longevity genes, including *AKT* (glucose uptake), *EIF4EBP1*, and *RPS6KA1* (protein synthesis, autophagy), *SIRT* (mitochondrial function), and *FOXO3* (oxidative stress defense), have multiple effects with intertwined actions in overlapping metabolic networks that often affect mitochondrial function [173]. Associations between mtDNA and longevity differ from the SNP-based associations seen in the nuclear genome. Several small and underpowered studies have associated mtDNA variation with human longevity in Japanese [220], Chinese Uygur [221], Italian [222], French [223], Irish [224] and Finnish [220] populations.

3. DNA damage and genomic instability

Perturbations in genomic stability might have negative outcomes, including cancer, reduced lifespan, and premature aging. Genomic DNA is subjected to incessant chemical, physical, and biological abuse, resulting in tens of thousands of molecular lesions per cell per day [225]. DNA damage can result from endogenous processes, such as hydrolysis, oxidation and alkylation, or exposure to radiation or environmental mutagens. Most DNA lesions are rapidly corrected by a sophisticated network of genome maintenance systems. Unrepaired DNA damage, both nuclear [226] and mitochondrial, leads to mutations, loss and gain of sequence, and aging [227–228]. The RecQ helicase family participates in maintaining genomic stability and is conserved across organisms [229]. In humans, sequencing of genes involved in DNA repair revealed that SNPs in the *WRN* helicase gene are associated with shorter lifespan. GWAS studies have identified markers associated with longevity at loci involved in genome maintenance, including *WRN*, *LMNA*, *CDKN2A/CDKN2B*, *FOXO1*, and *FOXO3* [41, 230].

4. Proteostasis imbalance

Protein homeostasis is maintained by tightly regulated action of intricate cellular systems that are gradually compromised with age, leading to an increase in accumulation of damaged and misfolded proteins. Loss of proteostasis contributes to many age-related pathologies, including neurodegenerative diseases such as Alzheimer's and Parkinson's disease [231]. Most cellular proteins fold directly after translation in the cytosol while membrane and secreted proteins fold in the endoplasmic reticulum. Presence of misfolded proteins in these cellular compartments is detected by chaperone networks, which initiate a proteostasis response to restore cellular homeostasis. The cytosolic response is initiated by the heat shock response (HSR) regulated by stress-activated heat shock factor1 (HSF1) which induces transcription of chaperones and other protective genes [232]. In worms, reduction of HSF1 induces accelerated aging. In response to endoplasmic reticulum (ER) stress, unfolded protein response UPR^{ER} is mediated by three signaling cascades modulated by IRE1, PERK, and ATF6, leading to several outcomes including reduced translation rates and transcriptional upregulation of many chaperones [233]. Prolonged stress triggers apoptosis. In mitochondria, both the integrated stress response and UPR^{mt} are activated to protect from proteotoxic stress, initiating a mitonuclear cascade that leads to transcription of protective genes [234–235]. Damaged proteins are degraded by the two principal proteolytic systems: the ubiquitin–proteasome system and the autophagic–lysosomal system. Their efficiency declines with age, supporting the idea that protein clearance mechanisms are directly linked to aging and age-associated diseases [236].

Activation of UPR^{mt} correlates with longevity across organisms in yeast, worms, flies, and mice [237]. A QTL for lifespan on Chr 2 in the BXD family of mice is thought to correspond to polymorphisms in mitochondrial ribosomal protein S5 (*Mtps5*). Expression correlates inversely with longevity in mouse, as it does in *C. elegans* [122]. Although no association has yet been found between mitochondrial ribosomal proteins (MRPs) and human lifespan, pathway-level genetic analysis points toward association between the *MRP* family and cognitive decline in women, independent of the *APOE* locus [151] and protein aggregation in *C. elegans* [238].

5. Telomere length

Telomeres are complex nucleoprotein structures at the tips of eukaryotic chromosomes made up of repetitive sequences bound by shelterin complex proteins (*TRF1*, *TRF2*, *TIN2*, *POT1*, *TPPI*, *RAP1*) [239]. The erosion of telomeres during DNA replication can trigger the onset of cellular senescence [240], but linkage between telomere length, aging, and reproductive success are complex and depend on species and life history [e.g., 241]. Common laboratory strains such as B6 mice have a mean telomere length of ~50 kb, whereas the wild-derived CAST/EiJ has shorter (~15 kb) telomeres comparable to that of humans [242]. Telomere length is inherited as a unique genotype, and short telomeres are sufficient on their own to cause degenerative diseases associated with aging even in the presence of normal levels of telomerase [243]. Heritability of telomere length has been demonstrated in human studies, but it is still unclear whether telomere shortening is a risk factor for telomere-mediated disease [244].

The most prevalent genes implicated in monogenic inherited telomere disorders (about 90% of cases) are *TERT* (telomerase reverse transcriptase) and *TERC* (telomerase RNA). Rare mutations in these genes cause autosomal dominant disease leading to significant morbidity after maturity [42, 245]. Taking a candidate gene approach, Atzmon and colleagues identified a common *TERT* haplotype that is associated with both exceptional longevity and telomere length in a cohort of Ashkenazi centenarians and their offspring [246]; a finding that has been replicated with variable success [247, see, <http://genomics.senescence.info/longevity/gene.php?id=TERT>)..

6. Epigenetics

There is no doubt that the epigenome ages at multiple levels (e.g., histones and heterochromatins, noncoding RNAs, DNA methylation) [248–250]. DNA methylation has received the most attention because this modification can be most readily quantified by existing technology. The most widely used epigenetic clock is calculated using 353 specific CpG sites that are distributed across the human genome, and this age biosignature has been more closely related to “biological age” rather than “chronological age” and is predictive of human health and longevity [251–253]. This powerful approach for predicting the biological aging rate has now been extended to mouse [254].

The mechanistic basis of epigenetic changes as a function of age remain unclear. Genetic variation is causally linked to phenotypes, but interpreting associations with epigenetic markers can be problematic. Unlike GWAS hits, the direction of causality between DNA

methylation and aging is ambiguous [78, 255]. Epigenetic data are also more liable to noise and confounding variables; for instance, the increase in cellular heterogeneity with aging could contribute to some of the age-related signal in DNA methylation. An optimal scenario would be when evidence from both genetic and epigenetic studies converge on a common gene variant that modulates the epigenome. A possible example is the enhancer of zest homolog 2 (*Ezh2*) gene that codes for the core catalytic subunit of the polycomb repressive complex. Polycombs are highly conserved multimeric proteins that control epigenetic status during embryonic development, cell differentiation, and stem cell proliferation, and potentially aging [256]. The *Ezh2* locus in the BXD family is highly polymorphic and is associated with *cis*-acting variation in expression of the *Ezh2* transcript. Work by de Haan and colleagues identified *Ezh2* as a candidate for hematopoietic stem cell aging, and overexpression of this gene rescues stem cell aging [257–259]. On the epigenetics front, CpG sites that undergo age-dependent changes in DNA methylation, including the 353 age-informative sites used to calculate the human epigenetic age, are enriched in genes targeted by the polycomb complex [251, 260–262]. This is an example in which the integration of genomic and epigenomic data can shed light on some of the mechanistic aspects of an aging epigenome. A multi-omic approach and careful integration of epigenomic and genomic approaches will be a powerful ally to the genetic cartography of aging and longevity.

Future directions

Progress in unraveling the genetics of longevity is on the threshold of a new phase, poised to burst out from the gloom of an infinitesimal model of gene action—thousands of polymorphisms with undetectable effects—to the clarity of a large collection of validated gene variants. The development of powerful genetics, genomics, and bioinformatics tools is enabling a more comprehensive and perhaps even more objective systems analysis of longevity networks. By combining discovery-based methods with mechanistic analyses and systematic studies of GXE, it is highly likely that over the next decade many new genes, networks, and mechanisms will be connected to longevity and aging-related diseases.

We need to make better progress using both huge human cohorts and model organisms, including mouse—our most effective mammalian model. Boosting sample sizes is an obvious and often effective strategy, but this may not be enough. A better strategy at this point is to integrate across species, models, and experiments. Model organisms have already proved their worth in longevity research. However, the lack of more intimate collaboration between human and model organism researchers remains a barrier. We have seen some strong results from collaboration across species with yeast, mouse, or *C. elegans* serving as instigators and corroborators of key discoveries [31, 122, 167]. Yeast, *C. elegans*, *Drosophila*, naked mole rats, killifish, and mice can help trace networks and mechanisms of longevity, and provide unrivalled access to the next frontier—GXE interactions and aging. Our hope is that the next version of this review will not only summarize a much more numerous set of longevity gene variants, but showcase new mechanisms that explain how genetic, epigenetic, cellular, and hormonal systems interact with environment and lifestyle to modify rates of aging. Finally, mechanisms are not enough. We need to aim, and aim rapidly, at developing and testing interventions that both increase vigor and reduce diseases and functional deficits that accompany aging

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Abbreviations

B6	C57BL/6J mouse strain
Chr	chromosome
D2	DBA/2J mouse strain
ER	endoplasmic reticulum
F1	filial 1 generation
F2	filial 2 generation
GWAS	genome-wide association study
GXE	gene-by-environmental interaction
HDL	high-density lipoprotein
HSR	heat shock response
ITP	Interventions Testing Program
LOD	logarithm of odds
Mb	megabase
MHC or H2	major histocompatibility complex
mtDNA	mitochondrial DNA
NAD	nicotinamide adenine dinucleotide
QTL	quantitative trait locus
ROS	reactive oxygen species
SNP	single nucleotide polymorphism
UPR	unfolded protein response
UPR^{ER}	unfolded protein response of endoplasmic reticulum
UPR^{mt}	unfolded protein response of mitochondria

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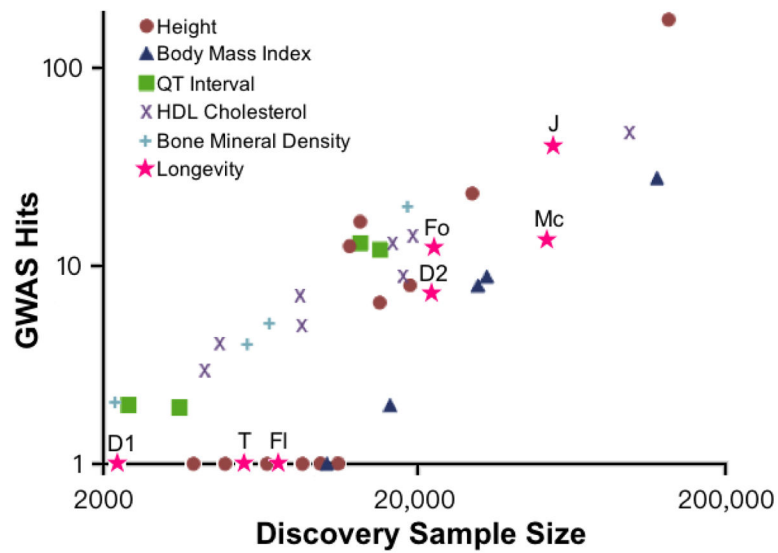


Figure 1.

Illustration of the effect of sample size (x-axis) on the yield of genome-wide association study (GWAS) findings (y-axis). Variation in human height (red dots) is a highly complex trait with moderate heritability that was refractory to GWAS at sample sizes below ~10,000 subjects. Longevity studies (stars) were refractory until sample sizes reached ~20,000. Longevity points: Deelen et al. (*D1*) [263], Deelen et al. (*D2*) [264], Tanaka et al. (*T*) [265], Flachsbar et al. (*FI*) [164], Joshi et al. (*J*) [266], and McDaid et al. (*Mc*) [31]. Redrawn with additions from Visscher et al. [267].

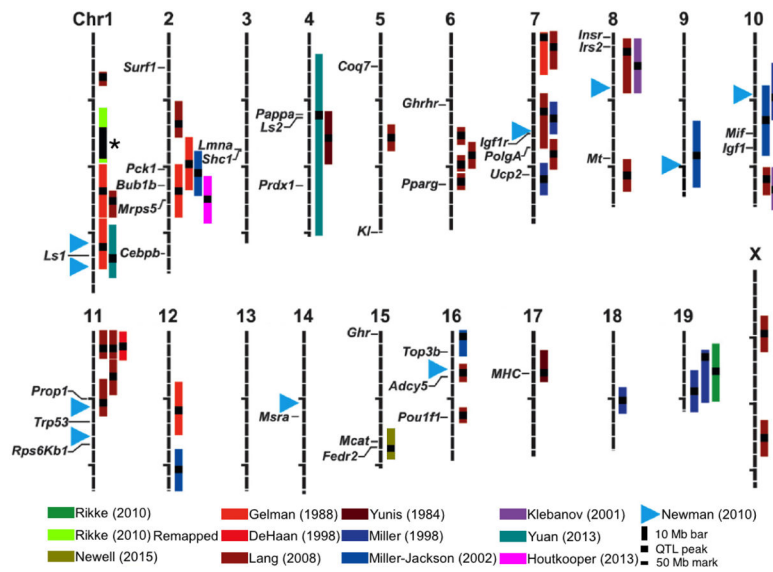


Figure 2.

QTLs for mouse longevity adapted from Yuan and colleagues [81] with added peaks from Houtkooper et al. [122], Yuan et al. [133], and Newell et al. [152]. We have also added a locus on Chr 1 at about 80 Mb detected by remapping data from Rikke et al. [96] via GeneNetwork LXS phenotype 10156 (asterisk to right of Chr 1). Length of colored bars represents the 95% confidence interval or a 40 Mb interval centered on the peak.

Table 1
Selected Genome-Wide Significant Results of Human Longevity GWAS/Linkage Studies

Study	Discovery Cohort	Cohort Size	Chromosome (Linked Loci)	RS or Nearest Marker	LOD	p-value	Linked Longevity Genes	NS
Puca et al., 2001 [268]	SR	308 (137 Sib)	Chr 4 (4q25)	D4S1564	3.26	-	-	-
Reed et al., 2004 [269]	NAS-NRC VTR	190 (95 Sib)	NGWSF	-	-	-	-	7
Beekman et al., 2006 [63]	LLS	379 (164 Sib)	NGWSF	-	-	-	-	-
Lunetta et al., 2007 [230]	FHS	1,345	NGWSF	-	-	-	-	1
Boyden & Kunkel, 2010 [270]	NECS	632 (279 Sib)	Chr 3 (3p24.2-22.3)	rs28150	4.02	-	<i>TOP2B</i>	-
			Chr 9 (9q31.3-34.2)	rs536861	3.89	-	<i>TLR4; DBC1</i>	-
			Chr 12 (12q24.31-24.33)	rs1732462	4.05	-	-	-
Newmann et al., 2010 [80]	CHARGE	3,791 (2 Rep)	NGWSF	-	-	-	-	136
Deelen et al., 2011 [263]	LLS	2,073 (3 Rep)	Chr 19 (19q13.32)	rs2075650	-	3.39E-17	<i>TOMM40/APOE/APOC1</i>	0
Edwards et al., 2011 [64]	CAMP	263	Chr 6	rs1409014	4.49	-	<i>BMP5</i>	-
			Chr 7	rs517258	3.11	-	-	-
			Chr 14	rs764602	4.17	-	<i>BMP4</i>	-
Malovini et al., 2011 [271]	SR	963	NGWSF	-	-	-	-	67
Nebel et al., 2011 [272]	SR	1,848 (2 Rep)	Chr 19	rs4420638	-	1.80E-10	<i>TOMM40/APOE/APOC1</i>	15
Walter et al., 2011 [49]	CHARGE	16,995 (4 Rep)	NGWSF	-	-	-	-	101
Kerber et al., 2012 [273]	UPDB	325	NGWSF	-	-	-	-	1
Sebastiani et al., 2012 [274]	NECS	5,114 (2 Rep)	Chr 19 (19q13.32)	rs2075650	-	1.03E-08	<i>TOMM40/APOE/APOC1</i>	27
Beekman et al., 2013 [275]	GEHA	4,445 (2118 Sib)	Chr 14 (14q11.2)	rs10484218 - rs977870	3.47	-	-	-
			Chr 17 (17q12-q22)	rs2429990 - rs12947910	3.71	-	-	-
			Chr 19 (19p13.3 - 13.11)	rs432001 - rs919333	3.76	-	-	-
			Chr 19 (19q13.11-q13.32)	rs7250748 - rs10403760	3.57	9.60E-08	<i>TOMM40/APOE/APOC1</i>	-
			Chr 8 (8p11.21-q13.1) M	rs801100 - rs4368961	3.61	-	-	-
			Chr 15 (15q12-q14) F	rs1871009 - rs580839	3.16	-	-	-
			Chr 19 (19q13.33-q13.41) M	rs1236093 - rs1661965	4.97	-	-	-
Edwards et al., 2013 [65]	CAMP	263	Chr 6 (6q25-27)	rs1247322 - rs1247363	3.2	-	<i>PLG/MAP3K4</i>	-
			Chr 6 (6q25-27)	rs16892673 - rs16892700	3.2	-	<i>PARK2</i>	-
Deelen et al., 2014 [264]	MCC ^a	23,850 (6 Rep)	Chr 5 (5q33.3)	rs2149954	-	1.74E-08	<i>EBF1</i>	6
			Chr 19 (19q13.32)	rs4420638	-	3.40E-36	<i>TOMM40/APOE/APOC1</i>	-

Study	Discovery Cohort	Cohort Size	Chromosome (Linked Loci)	RS or Nearest Marker	LOD	p-value	Linked Longevity Genes	NS
Broer et al., 2015 [153]	CHARGE	9,793	Chr 6	rs2802292	-	1.85E-10	<i>FOXO3</i>	20
Minster et al., 2015 [276]	LLFS	3,140 (2 Rep)	Chr 9 (9p24.2-p23) F	rs2075650	-	2.40E-10	<i>TOMM40/APOE/APOC1</i>	-
Flachsbarth et al., 2016 [164]	IkGP	7,826 (3 Rep)	NGWSF	-	3.36	-	-	-
Fortney et al., 2016 [277]	MCC ^b	25,166 (4 Rep)	Chr 19	rs2075650	-	2.40E-13	<i>TOMM40/APOE/APOC1</i>	10
Joshi et al., 2016 [266]	UKB	116,425 (3 Rep)	Chr 19 (19q13) F	rs429358	-	4.20E-15	<i>TOMM40/APOE/APOC1</i>	33
Pilling et al., 2016 [278]	UKB	75,224	Chr 15 (15q24) M	rs10519203	-	4.80E-11	<i>CHRNA3/5</i>	2,913
			Chr 7	rs528161076	-	3.40E-08	<i>AP5Z1</i>	
			Chr 9	rs75824829	-	4.00E-08	<i>C9orf62</i>	
			Chr 15 ^d	rs1051730	-	3.00E-08	<i>CHRNA3</i>	
			Chr 22	rs62227724	-	3.00E-08	-	
Tanaka et al., 2016 [265]	HRS	5,716 (2 Rep)	Chr 18	rs35715456	-	2.89E-08	<i>SMAD7</i>	-
Zeng et al., 2016 [279]	CLHLS	4,965 (4 Rep)	Chr 7	rs2069837	-	4.05E-08	<i>IL6</i>	9
			Chr 13	rs2440012	-	4.89E-08	<i>ANKRD20A9P</i>	
McDaid et al., 2017 [31]	UKB	116,279 (5 Rep)	Chr 6	rs10455872	-	1.60E-08	<i>LPA</i>	12
			Chr 9	rs1333045	-	1.77E-08	<i>CDKN2BAS</i>	
			Chr 15	rs951266	-	4.33E-10	<i>CHRNA5</i>	
			Chr 19	rs4420638	-	4.33E-08	<i>TOMM40/APOE/APOC1</i>	
Sebastiani et al., 2017 [24]	MCC ^c	8,329 (2 Rep)	Chr 7	rs3764814	-	5.00E-15	<i>USP42</i>	44
			Chr 12	rs7976168	-	4.00E-09	<i>TMTC2</i>	
			Chr 19	rs6857	-	2.00E-27	<i>TOMM40/APOE/APOC1</i>	
			Chr 19	rs769449	-	1.00E-23	<i>TOMM40/APOE/APOC1</i>	
			Chr 19	rs59007384	-	5.00E-15	<i>TOMM40/APOE/APOC1</i>	
Singh et al., 2017 [280]	LLFS	3,876 (1 Rep)	Chr 1 (1p13.3)	rs201856309	-	1.67E-09	<i>NBPF6; NBPF5</i>	68
			Chr 2 (2p22.1)	rs116083259	-	1.17E-08	<i>CAPN9; Clorf198</i>	
			Chr 10 (10p15)	rs61019025	-	4.65E-08	<i>KLF6</i>	

Chr, chromosome; QTL, quantitative trait locus; RS, representative single-nucleotide polymorphism; LOD, logarithm of odds score; NS, number of suggestive findings per study ($p < 5E-5$) or indicated by authors; Sib, number of siblings present in study; Rep, number of replication samples in study; NGFSW, no genome-wide significant findings; -, data was not reported or not available; SR, self-recruited cohort; M, found only in male subjects; F, found only in female subjects; LLS, Leiden Longevity Study; NAS-NRC VTR, National Academy of Sciences-National Research Council Veteran Twin Registry; FHS, Framingham Heart Study; NECS, New England Centenarian Study; CHARGE, CHARGE Consortium; CAMP, Collaborative Aging and Memory Project; UPDB, Utah Population Database; GEHA, Genetics of Healthy Aging Study; MCC, Multiple Combined Cohorts; LLS, Long Life Family Study; IKGP, 1,000 Genome Project; UKB, UK Biobank; HRS Health and Retirement Study; CLHLS, Chinese Longitudinal Healthy Longevity Surveys

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^bBelfast Elderly Longitudinal Free-living Ageing Study, Calabria cohort, CEPH centenarian cohort, Danish longevity study I & II, deCODE, Estonian Biobank, Genetics of Healthy Aging Study, German longevity study, Leiden 85-plus study, Leiden Longevity Study, Newcastle 85+ Study, PROspective Study of Pravastatin in the Elderly at Risk, Rotterdam Study, TwinGene

^dNew England Centenarian Study, 90PLUS Cohort

^cSouthern Italian Centenarian Study, Long Life Family Study, Longevity Gene Project, New England Centenarian Study

^d35 other variants were of genome-wide significance; rs1051730 deemed most significant due to its previous link smoking fewer cigarettes and lower risk of lung cancer