The genetics of human ageing

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Abstract

The past two centuries have witnessed an unprecedented rise in human life expectancy. Sustaining longer lives with reduced periods of disability will require an understanding of the underlying mechanisms of ageing, and genetics is a powerful tool for identifying these mechanisms. Large-scale genome-wide association studies have recently identified many loci that influence key human ageing traits, including lifespan. Multi-trait loci have been linked with several age-related diseases, suggesting shared ageing influences. Moreover, mutations that drive accelerated ageing in prototypical progeria syndromes in humans point to an important role for genome maintenance and stability. Together, these different strands of genetic research are highlighting pathways for the discovery of anti-ageing interventions that may be applicable in humans.

Introduction

Ageing is a seemingly universal biological phenomenon; yet, it is surprisingly difficult to define. In essence, ageing is a term used to describe a correlated set of declines in functioning with advancing chronological age, which generally begins after sexual maturity[1,2]. Characteristic functional changes occur from the molecular and cellular levels, known as 'biological hallmarks' of ageing[2], through to declining physiological homeostasis at the organism level, and lessening abilities to perform everyday physical and cognitive tasks. Ageing also increases the susceptibility to

many common diseases, and death rates rise approximately exponentially with advancing age[3]. The main scientific effort in human ageing, termed 'geroscience'[4], sees ageing as the primary cause of many chronic diseases of later life, including coronary artery disease (CAD), stroke, type 2 diabetes mellitus (T2DM), chronic kidney disease, osteoarthritis, Alzheimer disease, and common cancers (such as breast, prostate and colorectal cancer). Slowing ageing might prevent many of these diseases simultaneously[4], as seen in various experimental interventions in laboratory models that slow and partially reverse features of ageing (Box 1).

Although declining function is characteristic of ageing, rates of decline vary enormously; whereas some people die of age-related disease in their sixties, a few are still active at 100 years of age and beyond. Understanding the genetic factors driving this variability in ageing between people is the main focus of this Review. The scope for experimental studies in human ageing is very limited, and conventional observational studies are often distorted by confounding factors such as smoking or obesity. However, over the past decade, genome-wide association study **[G]** (GWAS)[5] results for many phenotypes relevant to ageing have started to emerge**.** Inherited (that is, germline) variant associations are little affected by confounding and can provide unique biological insights to clarify whether observations in laboratory animals apply to humans. Also, drugs with support from human genetic studies for related effects (reported in GWAS and single gene disorder databases) succeed from phase I trials to final approval twice as often as those without such evidence[6]. Also, even genes with small-effect genetic variants can provide successful drug targets[5]. Therefore identifying specific variants that influence human ageing could help identify suitable targets for antiaging interventions in humans.

In this Review, we start by outlining the limited proxy measures of human ageing currently available. We then discuss recent results from the most robust genetic association studies relevant to human ageing, with a focus on 'multi-trait' variants, that is, variants which affect several ageing-related phenotypes simultaneously, reflecting the view that correlated changes of ageing have common mechanisms. We then describe three key accelerated ageing (progeriod)

genetic disorders in humans and review evidence on the accumulation of somatic mutations **[G]** with advancing age, with these two sections providing insights into underlying DNA damage processes that increase cancer risks and may also contribute to functional declines in ageing. Evidence is accumulating for age-related epigenetic[7], gene expression and splicing[8] changes, but as the causal roles of these changes are uncertain, we do not discuss these topics.

[H1] Proxy phenotypes of ageing

Ideal human ageing phenotypes would measure the underlying biological mechanisms and minimize 'extraneous' environmental factors[9]. At the molecular level, hallmark biological characteristics of ageing include genomic instability (especially DNA damage), telomere attrition, epigenetic alterations, loss of protein homeostasis and deregulated nutrient sensing[2]. At the cellular level, ageing is associated with stem cell exhaustion, mitochondrial dysfunction with falling energy outputs and increased oxidative stress, as well as altered intercellular communications[2]. Unfortunately, few of these hallmarks can currently be measured directly in large enough samples to be analysed in human genetic association studies**.** This means that other age-related phenotypes must serve as proxies.

[H2] Lifespan

Lifespan, the time from birth to death, is an often measured ageing proxy. Longevity (used here to mean relatively long lifespans, with a variety of specific definitions) is an especially popular ageing measure, as some long-lived people, especially centenarians, experience delayed onsets of age-related diseases, with compression of morbidity into a smaller proportion of their lifespans[10]. For example, in one study of centenarians, 32% of men and 15% of women had no age-associated diagnoses at age 100 years[11]. Exceptional longevity has been defined both in terms of arbitrary age cut-off points (for example, ≥85 years, or centenarians), and also by, for example, the longest 10% or 1% of lifespans within a specified cohort[12]. Some studies have focussed on exceptional longevity in the

context of long-lived families, as there is evidence of increased heritability **[G]** of longevity in this context[13].

[H2] Disease and physiological markers

Clinical diagnoses of age-associated chronic diseases and cancers can provide accessible proxy measures of ageing. A summary measure of healthspan **[G]** [14] can be made from the duration of life spent without major age-associated conditions including myocardial infarction, stroke, diabetes and dementia. Other elements can be included in healthspan, such as physical disabilities, cognitive impairments and mental wellbeing.

Biomarkers, currently mostly of clinical measures such as lipid levels, inflammation, kidney and liver function[15,16] can be combined into indices that predict later clinical outcomes in ageing, and can serve as proxy ageing phenotypes. Various physiological impairments that accompany ageing are measurable, for example, impaired muscle strength[17], cognitive function[18] and gait speed[19]. Measures of disability and frailty — the age-associated increase in vulnerability to stresses and adverse outcomes[20] — have also been developed.

[H2] Challenges in studying ageing

In addition to variations in study design and the vast range of ageing-related phenotypes studied, ageing research is bedevilled by a lack of standard terminology[9]. More fundamentally, the validity of essentially all available measures of ageing itself is debateable. Results of analyses can depend on the specific combination of causal factors driving each phenotype; for example, including smoking-induced cancers in disease measures results in smoking-related genes emerging as important, whereas including common skin cancers will increase the importance of ultra-violet light exposure-related DNA damage pathways. Ultimately, human ageing always occurs in the context of common environmental exposures in studied populations, and what to include and exclude in proxy measures of ageing will likely remain a matter of debate until direct measures of the hallmarks of ageing become available.

[H1] Heritability of ageing traits

To what extent are ageing phenotypes driven by genetic variation between people? Twin or family-based estimates indicate substantial inherited genetic influences. Heritability estimates the ratio of the genetic component to the sum of genetic and other (termed 'environmental') factors, and is specific to each studied population and the environmental exposures current in that population[21]. Widely cited heritability estimates for human longevity from twin studies range from 20% to 30%[22], but in families with a centenarian, estimates increase to 48% in men and 33% in women[10]. However, a recent analysis of millions of family trees estimated the heritability of longevity to be 16% (standard error 0.4%), suggesting that previous studies may have overestimated the heritability of longevity[23]. A second family tree study found evidence for extensive assortative mating inflating heritability estimates, and concluded that the true heritability of longevity is below 10%[24].

Common age-related diseases also have substantial heritable components; for example, hip osteoarthritis is estimated to be 68% heritable[25]; type 2 diabetes mellitus (T2DM) heritability is estimated at 61% to 78%[26]; the heritable component of Alzheimer disease is estimated to be 58% to 79% (depending on the model used)[27]; and cardiovascular disease heritability has been estimated at 45% to 69%[28]. Individual genetic variants have now been identified, mostly by GWAS, that are associated with many ageing phenotypes, and the amount of variation in the trait attributed to these specific genetic differences can be estimated. These genotyped variants cumulatively explained 51.9% of the variation in osteoarthritis of the hip[29], and 18% of T2DM variation[30], but only 8.5% of the variation in parent's age at death[31] and 7.1% of Alzheimer disease[32]. The gap between the higher twin-study-based heritability estimates for each phenotype and the lower estimates from GWAS, often termed the 'missing heritability', is attributed partly to lack of coverage of several types of genetic variation including rare large-effect variants in GWAS, but also to possible overestimates in pedigree-based analyses[33].

Nonetheless, many ageing-related diseases and traits seem to have substantial heritable components. However, heritability estimates do not help identify pathways or mechanisms. For genetics to help reveal biological mechanisms, find new drug targets, and potentially identify individuals for precision medicine treatments, identification of specific human genetic variants associated with ageing phenotypes is needed. Such variants have recently been identified even for traits with modest heritability.

[H1] Candidate gene studies and GWAS

Ageing-related genetic variants have been identified mostly in GWAS, which test statistical associations between millions of germline variants and a phenotype, often in several hundred thousand people[5]. Smaller-scale candidate studies test a subset of variants, but both approaches include multiple statistical tests. As more variants are compared it becomes increasingly likely that some will be statistically significant just by chance[5]. To guard against false-positive findings, stringent statistical significance thresholds are used and 'significant' associations need to be replicated in independent samples. In reviewing ageing studies, we therefore prioritize the strongest available associations (preferably at genome-wide statistical significance[34] $p<5*10^{-8}$), especially those with independent replication.

[H2] Human lifespan and longevity

The most robust identifications of lifespan-related variants currently come from recent, very large cohorts, such as the UK Biobank[35], which includes 500,000 community volunteers. These studies have focused on parental age at death, as offspring health status and survival are associated with parental lifespan. For example, an analysis of Health and Retirement study (USA) data covering participants aged 51-61 years at baseline followed for 18 years, all-cause mortality consistently declined by 19% for each decade their mothers survived beyond age 65 years (14% per decade for fathers)[36]. Also, study participants had progressively lower incidence of cardiovascular disease and cancers[36], as well as reduced rates of cognitive decline[37], with increasing parental survival. A study of 186,151 non-

adopted UK Biobank participants followed for up to 6 years produced similar results, with declines in all-cause mortality of 16% per decade of mothers survival ≥70 years of age (hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.79 to 0.89) and 17% (HR: 0.83; 95% CI: 0.78 to 0.89) for father's survival. Cause specific mortality declined with advancing parental ages especially for Coronary Heart Disease (20% per decade with decades of mother's age ≥70 years: HR: 0.80; 95% CI: 0.68 to 0.95; and 21% for father's HR: 0.79; 95% CI: 0.63 to 0.98), but declines in cancer mortality (HR: 0.92; 95% CI: 0.90 to 0.95) were also present[38].

Several GWAS have been reported for parents' age at death (or attained age thus far) in UK Biobank alone[31,39,40], and additionally two meta-analyses of UK Biobank with other cohorts have also been published: the "LifeGen consortium" included data from 160,000 study participants from 25 cohorts in addition to UK Biobank[41], and a separate analysis using 300,000 individuals with pedigree data from AncestryDNA[42] was meta-analysed with UK Biobank. The ages at death of the parents (or current age if still alive) studied in the LifeGen analysis[41] varied from 40 to 107 years, while the AncestryDNA[42] lifespans ranged from 40 to 120 years. Six genetic loci were identified in both studies for longer parental lifespan (Table 1), with 12 additional loci identified only in one or other study. Many of the implicated variants have been linked previously to cardio-metabolic conditions (mostly myocardial infarction and diabetes mellitus), with some linked to Alzheimer's disease, autoimmunity and cancer risk[41], thus reflecting the more common causes of death in older people.

Gene–environment interactions were evident for some variants. For example, rs1051730 is in an exon of *CHRNA3* - encoding a nicotinic acetylcholine receptor subunit - and the lifespan-reducing allele is correlated with rs8042849, which increases susceptibility to nicotine dependence[43], and likely reduces lifespan by increasing smoking exposure. Interestingly, this association was stronger for fathers' than mothers' age at death, perhaps due to gender differences in smoking in the parental generation[31]. Effect sizes for all lifespan-associated variants were modest, with the largest per allele effect for the *APOE* ε4 variant accounting for 1.06 years of parental lifespan[41]. The smallest-effect variant

identified by LifeGen was intronic in the *HTT* gene (also known as *Huntingtin*), although the relationship of this variant to Huntington disease mutations is unclear. Of the 18 variants identified, only one (in *APOE*) was exonic and affected the coding sequence, suggesting mainly regulatory effects, as is common for polygenic traits[44].

In a UK Biobank GWAS, sub-analyses of the participants' genotypes in the top 10% of parents' survival (with survival to ≥90 years in mothers and ≥87 years in fathers) produced results similar to overall lifespan analyses[39]: four loci remained associated at genome-wide significance (*APOE*, *CHRNA3*, *LPA* and *CDKN2B-AS1*), with the others remaining nominally significant (all with *p*-values <0.002). Two additional loci (*MC2R* and *USP2-AS1*) were significant for top 10% survival in the analysis of parents' lifespan. In an analysis of centenarian parents the results were consistent, with similar genotype-lifespan effect sizes[39]. Although, numbers here were small - with only 1,181 participants having at least one centenarian parent - meaning only the *APOE* locus was genome-wide significant[39]. Thus, lifespan-associated variants can also be important for longevity, although some variants may be specific to longevity.

[H3] Genetic associations with longevity

GWAS have also directly compared long-lived individuals (aged ≥90 years) to younger controls (aged <65 years, although definitions vary[45–48], as reviewed recently elsewhere[3]). The most recent meta-analysis in 2019 included 11,262 participants who survived beyond the 90th percentile[48]. The most robust findings have been for the *APOE* haplotypes, with *ε4* being less common in long-lived and *APOE ε2* more common (versus the *ε3* haplotype). The two *APOE* haplotypes have similarly inverse associations with Alzheimer's disease[32] and cardiovascular disease[49]. Apolipoprotein E (APOE) is involved in the transport of cholesterol and other lipids to cells; in the brain, this function is important in neural cell membrane and synapse maintenance and repair[50], although the full mechanisms causing Alzheimer disease remain elusive. A recent study showed that the *APOE ε4* haplotype was associated with excess mortality even within the longest lived 1%

of survivors, and that the *ε2/ε2* or *ε2/ε3* haplotypes were associated with modestly decreased mortality within the longest lived 1% of survivors[51]. The recent 2019 meta-analysis of longevity GWAS[48] identified a new locus highlighting *GPR78*: the identified longevity-variants have not previously been identified in GWAS for other traits, but the gene (encoding G Protein-Coupled Receptor 78) has been implicated in traits including lung function[52] in the GWAS catalog[53].

The study of extreme longevity has been refined recently by the finding that heritability is higher in those who are part of long-lived families and that environmental factors seem to be more important in sporadic longevity[13]. A GWAS in 583 'Long Life Family Study' families (covering the long-lived individuals and offspring, which unusually also included predicted longevities) confirmed associations at the *APOE* locus and also identified a variant (rs1927465) between *MYOF* (which encodes myoferlin) and *CYP26A1* (which encodes cytochrome P450 family 26 subfamily A member 1) genes at genome-wide significance[54]. At the time of writing, rs1927465 has not been reported in the GWAS catalogue for other phenotypes.

A much studied set of extreme longevity-associated variants have been reported in the *FOXO3A* gene, which encodes a transcription factor that influences energy metabolism, cell cycle regulation and inflammation, and is important in modulating the effect of calorie restriction on longevity in model organisms[55]. In the longest lived 1% of survivors, 17 *FOXO3A* variants were more common compared with controls (n=2,072 aged ≥96 years versus <96 years); the strongest association was found for the variant rs4946935 (odds ratio 1.20 for extreme longevity, $p=3.2*10^{-5}$)[56]. However, none of these 17 *FOXO3A* variants affected death rates for the younger 99% of lifespans, which is consistent with no *FOXO3A* variants reaching genome-wide significance in the large parents lifespan GWAS discussed above[39,41].

The evidence on mostly candidate gene variants has also been reviewed (comparing groups aged ≥85 years including centenarians versus those aged <85 years, most <60 years)[57], with seven claimed longevity variants found to be weakly or not associated with survival to age ≥85 years. It has been argued that different

populations may have different exceptional longevity variants due to particular environmental exposures and ancestry-specific genetic differences[58], providing a possible explanation for the limited replication of claimed exceptional longevity variants. Another explanation might be the relatively modest sample sizes (often fewer than 10,000 long-lived individuals), or potential false-positive findings of some associations.

None of the variants identified thus far as being associated with (extreme) longevity seem essential (that is, not all long-lived people harbour them) and none seem sufficient to achieve longevity (all are fairly common in groups who die earlier). This finding is consistent with the notion that the heritable component in the longest 10% for survival is a quantitative trait[13] likely affected by large numbers of small effect variants.

[H2] Reproductive lifespan in women

Women are unusual compared with other female mammals in having a total lifespan that is substantially longer than their reproductive lifespan. In a GWAS of age at menopause[59], 56 variants were identified, with approximately two-thirds of loci implicated in the DNA damage response (DDR)[60]. As discussed below, unrepaired DNA damage might be a major driver of overall ageing. Also, some of the menopause associated variants have effects on the hypothalamic–pituitary axis, which controls many hormone levels. A polygenic risk score **[G]** for each individual in a study population can be calculated by summing the number of risk-increasing alleles (weighted by published effect size) each participants carries: a genetic risk score for age at menopause was not associated with parental lifespan[31] in the UK Biobank. Menopause associated variants may therefore have limited effects on human ageing more generally.

[H2] Muscle strength

Decreasing muscle strength is a common feature of ageing and is associated with increased risks of cardiovascular disease and mortality, even in those aged <60 years[61]. A GWAS of the full range of strength (measured as grip strength)[62] identified several lead variants in or near genes implicated in the structure and

function of skeletal muscle fibres, neuronal maintenance and signal transduction in the central and peripheral nervous systems. Whether low muscle strengths in older people are driven by the same variants is unclear, but a targeted study of the human leukocyte antigen (HLA)-mediated autoimmunity-associated region reported associations with low muscle strength in 60- to 70-year-olds[63] without autoimmune disease.

[H2] Cognitive impairment

Normal ageing is often associated with impairment in some cognitive tests, even in the absence of dementia. Cognitive impairment has a number of risk factors, such as hypertension, that are potentially treatable if caught early[64]. The largest recent genetic study of general cognitive function in >300,000 people identified >100 loci, implicating genes expressed in the brain, but also including loci associated with traits such as hypertension, suggesting systemic effects on cognition[65]. A recent genetic analysis of decline in cognitive ability in 1,091 people found that the *APOE ε4* allele alone was the strongest predictor compared to polygenic risk scores for CAD, educational attainment and other traits[66]. Another study in 1,176 men in their 50s[67] found that genetic risk of Alzheimer disease was associated with mild cognitive impairments. Although these studies were limited by small sample sizes, cognitive impairment is evidently a complex multifactorial process in which inherited variation has a role in addition to lifestyle and other health-related factors [68].

[H2] Age-related disease variants

Many GWAS of age-related diseases have been reported, with thousands of variants now identified[5]. One of the earliest successful GWAS identified variants influencing age-related macular degeneration (AMD)[69], the most common cause of blindness in the western world. Two larger-effect loci were found: one mapped to *CFH*, which encodes complement factor H in the complement inflammation cascade, and *ARMS2* (also known as *HTRA1*), which is involved in extracellular matrix turnover. Both variants were associated with more than 2.5-fold differences

in AMD risk in a recent large study[70]. The effect sizes of these variants contrast with many other common disease-associated variants, for which effect sizes are typically small, often with <10% differences in risk[5].

[H2] Genetic variation across common diseases

The duration of the disease-free period of life (that is, 'healthspan') is an important measure of the physical health aspects of ageing well, and was recently studied in UK Biobank participants aged 37–73 years[14]. All available age-associated diagnoses were included and a notable variant found to be associated with healthspan had previously been implicated in skin cancers[71]. As skin cancers represent the most common cancer type[72], the prominence of skin cancer variants in the results of this composite healthspan measure is unsurprising. However, skin cancer risk is related to high levels of sun exposure[73], which is a highly variable behavioural exposure, especially between older people. Thus, composite measures may highlight common exposures rather than necessarily identifying shared ageing mechanisms.

An alternative to examining composite measures of disease is to examine common loci associated with several different diseases of ageing. This approach is in line with the geroscience view that biological mechanisms of ageing underlie many of the diseases that occur in later life. All the most common diseases of ageing, including Alzheimer disease, CAD, chronic kidney disease, osteoarthritis, stroke, T2DM, and common cancers, have been extensively studied in GWAS. Of note, this list excludes diseases with known dominant environmental risk factors, for example, lung cancer and chronic obstructive pulmonary disease, risks of both being strongly related to smoking. When analysed, 961 genome-wide significant variant associations had been reported for our list of included common age-related conditions (Supplementary tables 1 and 2, see the GWAS catalog for a continuously updated database of GWAS findings). As biological pathways of ageing likely affect susceptibility to many of these diseases of later life, finding genetic variants associated with several pathways simultaneously should help reveal underlying ageing mechanisms.

[H3] Genetic correlation

One approach to explore shared genetic effects is to estimate genetic correlation — the degree of genetic overlap between pairs of traits — using GWAS results[74,75] (Fig. 1, Supplementary table 3). This method uses linkage disequilibrium (LD) **[G]** information in conjunction with the variant–trait associations to compute cross-trait LD score regression estimates of shared heritability (genetic correlation), and is well suited to analyses of complex traits with many thousands of small-effect variants that do not necessarily reach genome-wide significance[74]. Our analyses show that CAD, osteoarthritis, T2DM and stroke GWAS results correlated negatively with parental longevity, with 40–60% overlap (see Supplementary Table 3 for details) suggesting strong shared mechanisms. Alzheimer disease GWAS results had a moderate negative correlation with lifespan, but breast cancer and prostate cancer variants were not correlated with lifespan (Supplementary Table 3) suggesting that shared variants across diseases of ageing are important but not for all phenotypes.

[H3] Genetic risk score associations

An alternative approach to revealing shared mechanisms is to test whether a polygenic risk score for a biomarker is associated with a phenotype. For example, increasing parental lifespan was associated with lower genetic risk of raised LDL-cholesterol levels and systolic blood pressure[31]. Also, a 7-month shortening in parental lifespan per unit of genetically determined increasing body mass index (BMI) has been reported[40]. This adverse effect of increased BMI contrasts with claims that being obese or overweight is beneficial in older people[76] but is consistent with the success of calorie restriction in lengthening survival in animal models (Box 1). Also, high numbers of senescent cells accumulate in adipose tissue with age, especially around internal organs[77,78]. The paradoxical obesity claims seem to be generated in part by weight loss resulting from serious disease in older people. In other words, older people with obesity have to be fairly healthy to maintain their obesity. Longer-term observational analyses minimizing the

effects of diseases that cause weight loss show that 65–74-year-olds with obesity are at higher risk of dementia[79] and have higher death rates[80]. However, whether avoiding obesity is important to reach centenarian status remains unclear[81].

[H1] Shared genetic effects on ageing phenotypes

As noted, there were 961 genome-wide significant variant–trait associations across selected age-related diseases (Supplementary table 2). Given our focus on variants that affect several age-related diseases simultaneously — as these are more likely to reveal underlying ageing mechanisms — we searched for loci associated with three or more of selected age-related traits (with variants separated by <250 kb). We found 22 such ageing multi-trait loci; of these, 12 loci had variants in LD (R^2>0.6) with each other (Supplementary tables 4 and 5). One of those loci was *APOE*, which as described above has been associated with Alzheimer disease, CAD, as well as exceptional longevity and parental lifespan. Two other loci (*LPA* and *LDLR)* contain variants influencing blood lipid levels[82] and cardiovascular traits[49]. The disease associations of the remaining nine multi-trait loci are more diverse (Fig. 2) and therefore more likely linked to ageing mechanisms, as we discuss below.

[H2] The *CDKN2A/B* and *CAS8* loci

The *CDKN2A/B* locus (also known as the 9p21 locus) contains genes that produce the p16ink4a, p14arf and p15ink4b tumour suppressor proteins (Fig. 3) and the long non-coding RNA (lncRNA) *CDKN2B-AS1* (also known as *ANRIL*), which regulates *CDKN2A/B* expression[83]. Variants in or near these genes have been associated with multiple diseases, including cardiovascular conditions[49], T2DM[30], cancers[84,85], endometriosis[86], glaucoma and related optic disc traits[87], as well as blood cell count[88] and parental lifespan[41] (see further details and references in Supplementary table 6). Cell senescence is often accompanied by expression of $p16^{ink4a}$ (*CDKN2A*), and clearance of *CDKN2A*-expressing cells in mice[89] attenuated age-related deterioration in the eye, kidney, heart, and fat, with no

overtly adverse effects [see Box 1]. Efforts to develop interventions to remove senescent cells in humans are being actively pursued[90].

Interestingly, the disease-associated variants in the *CDKN2A/B* locus are not in coding areas (Fig. 3, see Supplementary table 6 for details), and there is limited overlap in variants associated with different traits: for example, variants associated with vascular disease, such as rs944797[49], are not associated with diabetes mellitus[30], and vice versa. This locus may therefore be an example of genetic variation influencing cell-type-specific regulation of genes important in human ageing.

Another multi-trait locus of potential importance for ageing is *CASC8* (cancer susceptibility candidate 8), which is a lncRNA containing variants associated with breast[84], prostate[85] and colorectal[91] cancers. A T2DM-associated variant is located nearby (<250 kb) in *CASC11*[30]. Both *CASC8* and *CASC11* are upstream of *MYC*, an oncogene known to be regulated by lncRNAs[92]. This observation suggests a similar mechanism to that of the lncRNA *CDKN2B-AS1*, whereby genetic variants affect regulation of senescence-related genes via lncRNAs.

[H2] Telomere-related genetic variants

Four unique genetic variants mapped to the telomerase gene *TERT* were associated with breast, colorectal and prostate cancer risk in GWAS[84,85,91]. Telomerase is involved in telomere maintenance, the end fragments of chromosomes which shorten with each cell cycle. Telomere shortening is a major contributor to replicative senescence[93] and therefore a biological hallmark of ageing. In humans, telomere length measured in blood has a strong inherited genetic component, with heritability estimates of 34–82%[94]. GWAS have linked 16 inherited variants to human leukocyte telomere length[95], including variants in the genes encoding telomerase and telomere-protective protein genes (*TERC, TERT, NAF1, OBFC1* and *RTEL1*)[96]. A Mendelian randomization **[G]** study of genetic variants associated with longer telomeres reported reduced risks of CAD and interstitial lung disease but increased risks of several forms of cancer[95], suggesting

a trade-off between risks of cancer and chronic age-related disease. No association was found between genetic predisposition to longer telomeres and parental longevity[31], suggesting that the positive and negative effects on health might cancel themselves out for overall survival. A recent analysis suggested that telomere variants were also not associated with the top 1% of parental longevity, or measures of cognitive or physical function in older UK Biobank participants[97].

[H2] SH2B3: a partial *Drosophila* homologue

In humans, the *SH2B3 gene* encodes lymphocyte adaptor protein LNK, which is an intracellular modulator of the erythropoietin receptor, the stem cell factor receptor c-Kit and JAK2[98]. GWAS have implicated the *SH2B3* locus and nearby genes (*ATXN2*, *BRAP*) in many diseases[49,91,99]. The likely causal variant in *SH2B3* associated with shorter parental longevity[39,100] is a missense variant (rs3184504-T) predicted to disrupt LNK protein functioning. The T allele is more common in autoimmune and cardiovascular conditions[101] and myeloproliferative cancers[98], as well as breast, colorectal and lung cancers[102] (compared to the 'normal' functioning C allele). By contrast, the C allele of rs3184504 is more common in those reaching the longest lived 10%[39] and 1% of lifespan[103]. The INTERVAL GWAS of human blood protein levels found that the rs3184504 C allele is associated with reduced levels of vascular cell adhesion protein 1 (VCAM-1), which functions in leukocyte recruitment in the cellular immune response, in angiogenesis[104], and influences development and spread of cancers[105]. Interestingly, the rs3184504 C allele is also associated with increased cardiovascular risk[49,99] but decreased cancer risk[91], again suggesting a trade-off between chronic disease and cancer mechanisms in ageing (Supplementary table 2).

In *Drosophila melanogaster,* the *SH2B* gene is an insulin-like growth factor (IGF-1) and energy balance signalling modulator, and an *SH2B* loss-of-function mutant was long-lived in starvation conditions, through increased carbohydrate stores[106]. Modifications to the IGF pathway in model organisms, from worms to mice, produce dramatic lifespan extension akin to those seen in dietary restriction experiments[107,108] (Box 1). However, whereas the human *SH2B1* and *SH2B2*

homologues of *SH2B* are important for IGF-1 signalling, *SH2B3* is not an important IGF-1 regulator[109]. The *SH2B3* locus is therefore clearly important in human ageing but likely through more specialized mechanisms than those targeted in *SH2B* model organisms for ageing, underlining the need for caution in generalizing from ancestral genes in model organisms to humans.

[H2] The HLA region and ABO blood groups

The histocompatibility complex gene group on chromosome 6 encodes *HLA* genes, which mediate chronic inflammatory pathways in autoimmune and infectious diseases[110]. Genetic variants near *HLA-DQA1* are associated with lifespan[41], Alzheimer disease[32], prostate cancer[85] and T2DM[30], and also alter levels of the circulating inflammation marker C-reactive protein[111]. An HLA variant has also been linked to low muscle strength[63], suggesting a role in the development of physical impairments in human ageing. These associations suggest that overlaps exist between autoimmune inflammatory mechanisms and the chronic inflammation commonly seen in ageing.

Somewhat similar are the ABO antigens, which determine blood group types. ABO antigens are expressed on a wide range of tissues and cell surfaces, and are important in infectious disease susceptibility, tumorigenesis and cardiovascular disease[112]. Genetic variants in the *ABO* locus have been associated with T2DM[30], breast cancer[84] and stroke[99] as well as altered levels of the circulating inflammation marker C-reactive protein[111]. In each study, the O (recessive) blood type was protective later in life (compared to the other blood groups) but also seemed to increase the risk of haemorrhages at younger ages[112], an apparent example of antagonistic pleiotropy **[G]** (Box 2).

[H2] Obesity, T2DM and cancer loci

Variants in the *TCF7L2* locus are linked to T2DM[30], breast[84] and colorectal cancer[91]. TCF7L2 is involved in β-cell proliferation and insulin production[113], and variants in this locus are also associated with increased obesity[114], which itself is a driver of T2DM and many cancers[115]. There are also other multi-trait loci linked

to T2DM and multiple cancers, including *ZMIZ1*[30,84,91], *VEGFA*[30,85], and *FTO*[30,84] (Supplementary table 5). These loci highlight the importance of adiposity as an accelerator of ageing, which is consistent with the accumulation of senescent cells in adipose tissue[77] and the success of caloric restriction in lengthening life in many laboratory models (Box 1).

[H1] Inferring mechanisms of aging from mutations

The integrity and maintenance of the genome appears to be strongly connected with aging and longevity. Mutations in genes that affect DNA repair capacity and DNA maintenance cause progerias, and there is evidence that the accumulation of somatic DNA mutations may be associated with phenotypes of aging and contribute to chronic diseases.

[H2] Single-gene disorders of accelerated ageing

Segmental progerias are genetic diseases that exhibit many clinical manifestations similar to those that develop with ageing but which manifest earlier in life[116]. Prototypical examples of these syndromes are Werner syndrome (Online Mendelian Inheritance of Man (OMIM) #277700), Hutchinson–Gilford progeria (OMIM #176670) and Cockayne syndrome (OMIM #216400). The study of these conditions can provide important hints on the genetic and biological mechanisms that drive the ageing process.

[H3] Clinical phenotypes

Patients with Werner syndrome develop normally but lack a pubertal growth spurt and later develop skin atrophy, loss of subcutaneous adipose tissue, loss and greying of hair, T2DM, cataracts, osteoporosis, early loss of fertility, severe arteriosclerosis, peripheral neuropathy and cancer[117]. Interestingly, cells from patients with Werner syndrome exhibit a shortened replicative lifespan[118]. Patients with Hutchinson–Gilford progeria are normal at birth but then grow slowly and develop baldness, loss of eyelashes and eyebrows, prominent eyes, convex nasal bridge and a small jaw, loss of subcutaneous fat, musculoskeletal abnormalities

and premature cardiovascular pathology[119]. Patients with Cockayne syndrome display photosensitivity and developmental failure after 1 year of age, underrepresented subcutaneous adipose tissue, premature decline of cognitive function and cardiovascular pathology, leading to a median survival of approximately 12 years[120].

[H3] Genetics

Interestingly, all three syndromes arise from genetic mutations that affect genomic structure and function through DNA repair, nuclear architecture and the fidelity of DNA replication[121]. In particular, Werner syndrome is caused by mutations of the *WRN* gene, which encodes a member of the RecQ family of helicases that is involved in DNA recombination, replication and telomere maintenance[117]. Over 90% of Hutchinson–Gilford progeria cases are caused by de novo heterozygous mutations in the *LMNA* gene, which encodes the proteins lamin A and lamin C through alternative splicing[122]. Lamin A and C are assembled to form a matrix on the inner surface of the nuclear membrane the integrity of which is important for DNA maintenance, such as DNA double-strand break repair[122]. Of note, in Hutchinson–Gilford progeria, a point mutation within *LMNA* exon 11 leads to the production of *progerin,* a mutant protein responsible for the fragility of the nuclear envelope, with rearrangement of heterochromatin similar to what is often see in fibroblast nuclei from older persons[123]. Small amounts of progerin accumulate with normal ageing and may contribute to age-related cardiovascular diseases[124]. Finally, Cockayne syndrome is caused by mutations in the *ERCC8* and *ERCC6* genes, which encode the CSA and CSB proteins, which play central roles in transcription-coupled nucleotide excision repair that occurs at specific secondary DNA structures[125].

Overall, prototypical progerias suggest that a progressive loss of genetic and genomic integrity may contribute to the ageing process. So far, data on progerias suggest that mechanisms of DNA repair and maintenance are important for health maintenance, but whether they configure true accelerated aging syndromes remains questionable. A key question that follows is whether common

variants mapped to these same progeria genes are important for the common traits in the general population. The GWAS catalog[53] reports that variants in the Werner syndrome-associated *WRN* gene are associated with cognitive function and educational attainment[126]; variants in the Hutchinson-Gilford-associated *LMNA* gene are associated with white blood cell counts[52] and height[52]; and variants in the Cockayne syndrome-associated *ERCC8* gene affect age at smoking initiation[127]. No variants in *ERCC6* have reached genome-wide significance in studies published in the GWAS catalog (as of 19 July 2019).

[H3] Hereditary haemochromatosis

Other lower penetrance genetic disorders also provide insights into the mechanisms of ageing. A prototypic example is iron overload due to hereditary haemochromatosis, which causes widespread oxidative damage[128]. The main homozygous *HFE* p.C282Y mutations (present in approximately 1 in 150 people of Northern European ancestry) is associated with increased incidence of arthritis, T2DM and liver disease[129], typically after age 40 years, as well as low muscle strength and chronic pain in 60–70 year olds[130]. Treatment (withdrawing blood) is effective and safe but often delayed because early manifestations are mistaken for 'normal' ageing. This mutation probably became common during the transition from hunter–gatherer to agricultural living, when low meat intake made increased dietary iron absorption advantageous, especially for pregnant women. This disease therefore supports the antagonistic pleiotropy theory of ageing, being a variant selected to enhance reproduction but that has adverse effects later in life (Box 2). More work is needed to identify other mutations with later life effects[131], including rare mutations.

[H2] Somatic mutations in human ageing

As several of the progerias (and age at menopause) are caused by genes involved in DNA repair and genomic stability, an obvious related question is whether accumulation of somatic mutations are important drivers of ageing[132]. There is now increasing evidence from single-cell and small sample size sequencing studies

that unrepaired or incompletely repaired somatic mutations accumulate with ageing, including in oncogenes, and can lead to clonal expansion **[G]** of mutated cells[133]. Stem cells generate new cells used for tissue repair, remodelling or renovation, and therefore somatic mutations in stem cells have the highest potential for clonal expansion. A study of small intestine, colon and liver samples from human donors aged 3–87 years showed an accumulation of approximately 40 somatic mutations per year in stem cells[134]. A study of human B lymphocyte somatic mutations, in both coding and regulatory regions, found <500 per cell in neonates, rising to >3,000 per cell in centenarians[135]. Similar accumulations of somatic mutations with age have also been reported for satellite cells in muscle[136]. Similarly, sequencing of oesophageal micro-samples showed age-associated accumulation of mutations, with middle-aged and elderly donors having cancer-associated mutation clones (including in the *TP53* cancer control gene and *NOTCH1*, which encodes a tissue development regulator) covering a majority of the epithelium, with evidence that the burden of mutations is higher in heavy drinkers and smokers[137,138]. There is some evidence that clonal expansion of somatic mutations in haematopoietic stem cells is associated with a higher risk of cardiovascular diseases and leukaemia[139], but whether it is also linked to biological ageing has not been demonstrated. However, it remains unclear how important these somatic mutations are for longevity; one study of 864 people aged 80–105 years found that somatic mutations in genes linked to clonal expansion of hematopoietic stem cells did not compromise 10-year survival[140].

[H3] Acquired mitochondrial genetic variants

Mitochondria have their own DNA (mtDNA), a circular 16.5 kb double-stranded loop of DNA that encodes 13 protein subunits of the electron transport chain and is uniquely inherited from mother to offspring[141]. Each cell contains many mitochondria and each one contains many mtDNA copies; therefore, multiple mutations can coexist in the same cell, a phenomenon known as heteroplasmy[142]. Maternally inherited mtDNA variants can cause mitochondrial diseases[143]. Interestingly, mitochondrial inherited diseases are often characterized by

progeroid characteristics, such as neurodegenerative and neuromuscular manifestations[144], suggesting that mitochondrial dysfunction may contribute to ageing. Indeed, de novo mtDNA mutations occur at random and accumulate unrepaired in several tissues at a rate substantially higher than nuclear DNA, probably because of the direct exposure to reactive oxygen species (ROS), lack of true histones and limited DNA repair mechanisms[145–147]. If the mutational load reaches a certain threshold it can affect the efficiency of oxidative phosphorylation and increase the production of ROS, especially in individuals who already have inherited mtDNA mutations[148]. This accumulation of mtDNA variants may cause many of the phenotypes of ageing, including metabolic, neurodegenerative and neoplastic diseases[148]. In support of this hypothesis, a knock-in mouse mutation that compromises the proofreading ability of mtDNA polymerase and results in massive accumulation of mtDNA mutations with age was associated with reduced lifespan and early development of ageing phenotypes[149]. Indeed, the frequency and quantity of mtDNA mutations is higher in organs of patients with chronic diseases that specifically affect those organs but is particularly evident in neurodegenerative diseases, such as Alzheimer, Parkinson and Huntington diseases[150,151].

Conclusions and future perspectives

Despite still being in the early phases of genetic discovery in human ageing, the available evidence supports major insights. The emerging picture (Fig. 4) is one of human ageing being driven by the balance of damage and repair processes, influenced by both environmental exposures and genetic variation between people. The hallmark pathways of ageing were identified mainly from animal models[152], but a role for some of these mechanisms is evident in GWAS results: several multi-trait loci including *CDKN2A/B, SH2B3*, *TERT*, as well as inflammation and obesity-related variants, are linked to hallmark pathways of ageing. In some cases, variants in these loci result in trade-offs between cancer and chronic disease risks. DNA repair mechanisms have emerged as important for female reproductive ageing as well as key progeria syndromes, and evidence is

accumulating that unrepaired somatic mutations may be of fundamental importance in human ageing.

In addition to the multi-trait loci, many variants showing disease-specific effects are also important in how humans age. For example, the vascular disease effects of lipid-altering variants or the cartilage-specific variants involved in osteoarthritis[29] suggest that both shared ageing mechanisms and disease-specific mechanisms are important in human ageing. Disease-specific genetic and environmental risks help explain the great variability of ages of disease onsets and comorbidities seen across older populations.

Will knowledge of ageing-related genetic variation ever yield personal predictions for later life? A whole-genome risk score from the 1 million lifespan parental longevity GWAS, comparing individuals in the top and bottom deciles, was associated with 3–5 year increased life expectancy[41]. This observation is promising, although this variation constitutes only a small proportion of the variation seen in human lifespan. Also, better control of potentially modifiable health risks that have an important role in ageing, such as obesity, blood pressure and cholesterol levels, could alter genetic predictions.

Genetic studies of human ageing are currently limited to the study of proxy measures of biological ageing. For many variants implicated in genetic association studies, exact effect mechanisms are unproven, and the general assumption that effects are mediated through the nearest gene is not always true[153]. The effects of some of the multi-trait loci highlighted may be through separate variants and/or different pathways. Much work is needed to establish the biological mechanisms influenced by GWAS-identified variants, including in loci that affect multiple traits.

In the coming years, much more will be learned about human ageing, hopefully with better phenotyping of the biological hallmarks of ageing. Larger sample sizes as well as DNA sequencing and linked studies of proteomics, gene expression and epigenetics will capture more of the genetic variation between individuals, and will help identify the mechanisms of effect of these genetic variations. Thus far, most of the evidence is from European ancestry groups, and studies of others — especially African ancestry groups, who have greater genetic

heterogeneity — are likely to extend findings[154]. It seems probable that much more evidence of ageing pathways will be found, including novel pathways that might provide intervention targets or offer new prevention opportunities. There remains ample scope for using inherited variants to understand human ageing mechanisms. Overall, human genetics is likely to continue to play a major role in our growing insights into how we age and in identifying ways in which we might slow ageing, and thus help more people to age well.

References

1. Partridge, L. & Mangel, M. Messages from mortality: The evolution of death rates in the old. *Trends Ecol. Evol.* **14**, 438–442 (1999).
2. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M. & Kroemer, G. The Hallmarks of Aging. *Cell* **153**, 1194–1217 (2013).

This paper reviews the evidence for nine key mechanisms that are characteristic of mammalian ageing.

3. Partridge, L., Deelen, J. & Slagboom, P. E. Facing up to the global challenges of ageing. *Nature* **561**, 45–56 (2018).
4. Kennedy, B. K. *et al.* Geroscience: Linking Aging to Chronic Disease. *Cell* **159**, 709–713 (2014).

This paper provides an overview of geroscience, which argues that many chronic diseases share underlying ageing mechanisms which should be targeted to improve overall health in later life.

5. Tam, V. *et al.* Benefits and limitations of genome- wide association studies. *Nat. Rev. Genet.* (2019). doi:10.1038/s41576-019-0127-1
6. Nelson, M. R. *et al.* The support of human genetic evidence for approved drug indications. *Nat. Genet.* **47**, 856–860 (2015).

This study found that development of drugs supported by genetic evidence of mechanism could double the success rate.

7. Declerck, K. & Vanden Berghe, W. Back to the future: Epigenetic clock plasticity towards healthy aging. *Mech. Ageing Dev.* **174**, 18–29 (2018).
8. Harries, L. W. *et al.* Human aging is characterized by focused changes in gene expression and deregulation of alternative splicing. *Aging Cell* **10**, 868–78 (2011).
9. Carnes, B. A. What is lifespan regulation and why does it exist? *Biogerontology* **12**, 367–374 (2011).
10. Sebastiani, P. & Perls, T. T. The genetics of extreme longevity: Lessons from the New England centenarian study. *Front. Genet.* **3**, 277 (2012).
11. Evert, J., Lawler, E., Bogan, H. & Perls, T. Morbidity profiles of centenarians: survivors, delayers, and escapers. *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* **58**, 232 (2003).
12. Sebastiani, P. *et al.* Four Genome-Wide Association Studies Identify New Extreme Longevity Variants. *J Gerontol A Biol Sci Med Sci* **72**, 1453–1464 (2017).
13. van den Berg, N. *et al.* Longevity defined as top 10% survivors and beyond is transmitted as a quantitative genetic trait. *Nat. Commun.* **10**, (2019).
14. Zenin, A. *et al.* Identification of 12 genetic loci associated with human healthspan. *Commun. Biol.* **2**, 300889 (2019).
15. Levine, M. E. Modeling the rate of senescence: Can estimated biological age predict mortality more accurately than chronological age? *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* **68**, 667–674 (2013).
16. Liu, Z. *et al.* A new aging measure captures morbidity and mortality risk across diverse subpopulations from NHANES IV: A cohort study. *PLoS Med.* **15**, e1002718 (2018).
17. Matteini, A. M. *et al.* GWAS analysis of handgrip and lower body strength in older adults in the CHARGE consortium. *Aging Cell* **15**, 792–800 (2016).
18. Gow, A. J. *et al.* Stability and change in intelligence from age 11 to ages

70, 79, and 87: the Lothian Birth Cohorts of 1921 and 1936. *Psychol. Aging* **26**, 232–40 (2011).

19. Ben-Avraham, D. *et al.* The complex genetics of gait speed: genome-wide meta-analysis approach. *Aging (Albany. NY).* **9**, 209–246 (2017).
20. Fried, L. P. *et al.* Frailty in Older Adults: Evidence for a Phenotype. *Journals Gerontol. Ser. A Biol. Sci. Med. Sci.* **56**, M146–M157 (2001).
21. Tenesa, A. & Haley, C. S. The heritability of human disease: Estimation, uses and abuses. *Nat. Rev. Genet.* **14**, 139–149 (2013).
22. Herskind, A. M. *et al.* The heritability of human longevity: A population-based study of 2872 Danish twin pairs born 1870–1900. *Hum. Genet.* **97**, 319–323 (1996).
23. Kaplanis, J. *et al.* Quantitative analysis of population-scale family trees with millions of relatives. *Science (80-.).* **175**, 171–175 (2018).
24. Ruby, J. G. *et al.* Estimates of the Heritability of Human Longevity Are Substantially Inflated due to Assortative Mating. (2018). doi:10.1534/genetics.118.301613
25. Skousgaard, S. G. *et al.* Probability and heritability estimates on primary osteoarthritis of the hip leading to total hip arthroplasty: A nationwide population based follow-up study in Danish twins. *Arthritis Res. Ther.* **17**, (2015).
26. Willemsen, G. *et al.* The Concordance and Heritability of Type 2 Diabetes in 34,166 Twin Pairs From International Twin Registers: The Discordant Twin (DISCOTWIN) Consortium. *Twin Res. Hum. Genet.* **18**, 762–771 (2015).
27. Gatz, M. *et al.* Role of genes and environments for explaining Alzheimer disease. *Arch. Gen. Psychiatry* **63**, 168–174 (2006).
28. Zdravkovic, S. *et al.* Heritability of death from coronary heart disease: a 36-year follow-up of 20 966 Swedish twins. *J. Intern. Med.* **252**, 247–54 (2002).
29. Tachmazidou, I. *et al.* Identification of new therapeutic targets for osteoarthritis through genome-wide analyses of UK Biobank data. *Nat.*

Genet. **51**, 230–236 (2019).

30. Mahajan, A. *et al.* Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat. Genet.* (2018). doi:10.1038/s41588-018-0241-6
31. Pilling, L. C. *et al.* Human longevity is influenced by many genetic variants: evidence from 75,000 UK Biobank participants. *Aging (Albany. NY).* **8**, 1–24 (2016).
32. Jansen, I. E. *et al.* Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat. Genet.* 258533 (2019). doi:10.1038/s41588-018-0311-9
33. Vinkhuyzen, A. A. E., Wray, N. R., Yang, J., Goddard, M. E. & Visscher, P. M. Estimation and partition of heritability in human populations using whole-genome analysis methods. *Annu. Rev. Genet.* **47**, 75–95 (2013).
34. Barsh, G. S., Copenhaver, G. P., Gibson, G. & Williams, S. M. Guidelines for Genome-Wide Association Studies. *PLoS Genet.* **8**, e1002812 (2012).
35. Bycroft, C. *et al.* The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203–209 (2018).
36. Dutta, A. *et al.* Longer lived parents: Protective associations with cancer incidence and overall mortality. *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* **68**, 1409–1418 (2013).
37. Dutta, A. *et al.* Aging children of long-lived parents experience slower cognitive decline. *Alzheimer's Dement.* **10**, S315–S322 (2014).
38. Atkins, J. L. *et al.* Longer-Lived Parents and Cardiovascular Outcomes: 8-Year Follow-Up In 186,000 U.K. Biobank Participants. *J. Am. Coll. Cardiol.* **68**, 874–5 (2016).
39. Pilling, L. C. *et al.* Human longevity: 25 genetic loci associated in 389,166 UK biobank participants. *Aging (Albany. NY).* **9**, 2504–2520 (2017).
40. Joshi, P. K. *et al.* Genome-wide meta-analysis associates HLA-DQA1/DRB1 and LPA and lifestyle factors with human longevity. *Nat. Commun.* **8**, 910 (2017).
41. RHJ Timmers, P. *et al.* Genomics of 1 million parent lifespans implicates

novel pathways and common diseases and distinguishes survival chances. 1–40 (2019). doi:10.7554/eLife.39856.001

This LifeGen study is a GWAS meta-analysis of parents lifespan using UK Biobank plus 25 independent cohorts, and including data on 1 million parents' lifespans.

42. Wright, K. M. *et al.* A Prospective Analysis of Genetic Variants Associated with Human Lifespan. *G3 (Bethesda).* **9**, 2863–2878 (2019).
43. Keskitalo, K. *et al.* Association of serum cotinine level with a cluster of three nicotinic acetylcholine receptor genes (CHRNA3/CHRNA5/CHRNB4) on chromosome 15. *Hum. Mol. Genet.* **18**, 4007–12 (2009).
44. Timpson, N. J., Greenwood, C. M. T. T., Soranzo, N., Lawson, D. J. & Richards, J. B. Genetic architecture: The shape of the genetic contribution to human traits and disease. *Nat. Rev. Genet.* **19**, 110–124 (2018).
45. Deelen, J. *et al.* Genome-wide association study identifies a single major locus contributing to survival into old age; the APOE locus revisited. *Aging Cell* **10**, 686–698 (2011).
46. Deelen, J. *et al.* Genome-wide association meta-analysis of human longevity identifies a novel locus conferring survival beyond 90 years of age. *Hum. Mol. Genet.* **23**, 4420–32 (2014).
47. Broer, L. *et al.* GWAS of Longevity in CHARGE Consortium Confirms APOE and FOXO3 Candidacy. *J. Gerontol. A. Biol. Sci. Med. Sci.* 1–9 (2014). doi:10.1093/gerona/glu166
48. Deelen, J. *et al.* A meta-analysis of genome-wide association studies identifies novel longevity genes. *Nat. Commun.* (2019). doi:10.1038/s41467-019-11558-2

This is the largest GWAS directly studying long-lived participants (aged ≥90 years) compared to shorter-lived (<65) controls to date.

49. Nikpay, M. *et al.* A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat. Genet.* **47**, 1121–1130 (2015).
50. Belloy, M. E., Napolioni, V. & Greicius, M. D. A Quarter Century of APOE and Alzheimer's Disease: Progress to Date and the Path Forward. *Neuron* **101**, 820–838 (2019).
51. Sebastiani, P. *et al.* APOE Alleles and extreme human longevity. *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* **74**, 44–51 (2019).
52. Kichaev, G. *et al.* Leveraging Polygenic Functional Enrichment to Improve GWAS Power. *Am. J. Hum. Genet.* **104**, 65–75 (2019).
53. Buniello, A. *et al.* The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. *Nucleic Acids Res.* **47**, D1005–D1012 (2019).
54. Yashin, A. I. *et al.* Genetics of human longevity from incomplete data: New findings from the long life family study. *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* **73**, 1472–1481 (2018).
55. Martins, R., Lithgow, G. J. & Link, W. Long live FOXO: Unraveling the role of FOXO proteins in aging and longevity. *Aging Cell* **15**, 196–207 (2016).
56. Bae, H. *et al.* Effects of FOXO3 Polymorphisms on Survival to Extreme Longevity in Four Centenarian Studies. *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* **73**, 1439–1447 (2018).
57. Revelas, M. *et al.* Review and meta-analysis of genetic polymorphisms associated with exceptional human longevity. *Mechanisms of Ageing and Development* **175**, 24–34 (2018).
58. Giuliani, C., Garagnani, P. & Franceschi, C. Genetics of Human Longevity Within an Eco-Evolutionary Nature-Nurture Framework. *Circ. Res.* **123**, 745–772 (2018).
59. Day, F. R. *et al.* Large-scale genomic analyses link reproductive aging to hypothalamic signaling, breast cancer susceptibility and BRCA1-mediated DNA repair. *Nat. Genet.* **47**, (2015).
60. Ruth, K. & Murray, A. Lessons from Genome-Wide Association Studies in

Reproductive Medicine: Menopause. *Semin. Reprod. Med.* **34**, 215–223 (2016).

61. Cooper, R., Kuh, D. & Hardy, R. Objectively measured physical capability levels and mortality: Systematic review and meta-analysis. *BMJ (Online)* **341**, 639 (2010).
62. Willems, S. M. *et al.* Large-scale GWAS identifies multiple loci for hand grip strength providing biological insights into muscular fitness. *Nat. Commun.* **8**, 16015 (2017).
63. Jones, G. *et al.* Sarcopenia and variation in the Human Leukocyte Antigen complex. *J. Gerontol. A. Biol. Sci. Med. Sci.* (2019). doi:10.1093/gerona/glz042
64. Morley, J. E. *et al.* Brain health: the importance of recognizing cognitive impairment: an IAGG consensus conference. *J. Am. Med. Dir. Assoc.* **16**, 731–9 (2015).
65. Davies, G. *et al.* Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. *Nat. Commun.* **9**, 2098 (2018).
66. Ritchie, S. J. *et al.* Polygenic predictors of age-related decline in cognitive ability. *Mol. Psychiatry* (2019). doi:10.1038/s41380-019-0372-x
67. Logue, M. W. *et al.* Use of an Alzheimer's disease polygenic risk score to identify mild cognitive impairment in adults in their 50s. *Mol. Psychiatry* **24**, 421–430 (2019).
68. Corley, J., Cox, S. R. & Deary, I. J. Healthy cognitive ageing in the Lothian Birth Cohort studies: marginal gains not magic bullet. *Psychol. Med.* **48**, 187–207 (2018).
69. Black, J. R. & Clark, S. J. Age-related macular degeneration: Genome-wide association studies to translation. *Genetics in Medicine* **18**, 283–289 (2016).
70. Fritsche, L. G. *et al.* A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat. Genet.* **48**, 134–143 (2016).

71. Barrett, J. H. *et al.* Genome-wide association study identifies three new melanoma susceptibility loci. *Nat. Genet.* **43**, 1108–13 (2011).
72. Guy, G. P., Machlin, S. R., Ekwueme, D. U. & Yabroff, K. R. Prevalence and Costs of Skin Cancer Treatment in the U.S., 2002−2006 and 2007−2011. *Am. J. Prev. Med.* **48**, 183–187 (2015).
73. American Cancer Society. *Cancer facts and Figuers 2019*. (2019).
74. Bulik-Sullivan, B. *et al.* An atlas of genetic correlations across human diseases and traits. *Nat. Genet.* **47**, 1236–41 (2015).
75. van Rheenen, W., Peyrot, W. J., Schork, A. J., Lee, S. H. & Wray, N. R. Genetic correlations of polygenic disease traits: from theory to practice. *Nat. Rev. Genet.* (2019). doi:10.1038/s41576-019-0137-z

This review defines genetic correlations, summarizes methods, and discusses their interpretation and uses with respect to human health and disease.

76. Dixon, J. B., Egger, G. J., Finkelstein, E. A., Kral, J. G. & Lambert, G. W. 'Obesity paradox' misunderstands the biology of optimal weight throughout the life cycle. *Int. J. Obes.* **39**, 82–84 (2015).
77. Tchkonia, T. *et al.* Fat tissue, aging, and cellular senescence. *Aging Cell* **9**, 667–84 (2010).
78. Xu, M. *et al.* Targeting senescent cells enhances adipogenesis and metabolic function in old age. *Elife* **4**, e12997 (2015).
79. Bowman, K., Thambisetty, M., Kuchel, G. A., Ferrucci, L. & Melzer, D. Obesity and Longer Term Risks of Dementia in 65-74 Year Olds. *Age Ageing* 1–6 (2019). doi:10.1093/ageing/afz002
80. Bowman, K. *et al.* Obesity in Older People With and Without Conditions Associated With Weight Loss : Follow-up of 955 , 000 Primary Care Patients Editor ' s Choice. *J. Gerontol. A. Biol. Sci. Med. Sci.* **72**, 203–209 (2017).
81. Pignolo, R. J. Exceptional Human Longevity. *Mayo Clin. Proc.* **94**, 110–124

(2019).

82. Global Lipids Genetics Consortium *et al.* Discovery and refinement of loci associated with lipid levels. *Nat. Genet.* **45**, 1274–83 (2013).
83. Congrains, A., Kamide, K., Ohishi, M. & Rakugi, H. ANRIL: Molecular mechanisms and implications in human health. *International Journal of Molecular Sciences* **14**, 1278–1292 (2013).
84. Michailidou, K. *et al.* Association analysis identifies 65 new breast cancer risk loci. *Nature* **551**, 92–94 (2017).
85. Schumacher, F. R. *et al.* Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. *Nat. Genet.* **50**, 928–936 (2018).
86. Rahmioglu, N. *et al.* Genetic variants underlying risk of endometriosis: insights from meta-analysis of eight genome-wide association and replication datasets. *Hum. Reprod. Update* **20**, 702–16 (2014).
87. Springelkamp, H. *et al.* Meta-analysis of Genome-Wide Association Studies Identifies Novel Loci Associated With Optic Disc Morphology. *Genet. Epidemiol.* **39**, 207–16 (2015).
88. Astle, W. J. *et al.* The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. *Cell* **167**, 1415-1429.e19 (2016).
89. Baker, D. J. *et al.* Naturally occurring p16 Ink4a-positive cells shorten healthy lifespan. *Nature* **530**, 184–189 (2016).

This study of a transgenic mouse model was the first to show that removal of senescent cells from an adult animal extended lifespan and improved some aspects of health.

90. Tchkonia, T. & Kirkland, J. L. Aging , Cell Senescence , and Chronic Disease Emerging Therapeutic Strategies. *JAMA* **320**, 1321–1323 (2018).

This manuscript provides an overview of cell senescence, links to aging,

and future therapeutics.

91. Schmit, S. L. *et al.* Novel Common Genetic Susceptibility Loci for Colorectal Cancer. *J. Natl. Cancer Inst.* **111**, 146–157 (2019).
92. Xiang, J. F., Yang, L. & Chen, L. L. The long noncoding RNA regulation at the MYC locus. *Current Opinion in Genetics and Development* **33**, 41–48 (2015).
93. Hayflick, L. & Moorhead, P. S. The serial cultivation of human diploid cell strains. *Exp. Cell Res.* **25**, 585–621 (1961).
94. Broer, L. *et al.* Meta-analysis of telomere length in 19,713 subjects reveals high heritability, stronger maternal inheritance and a paternal age effect. *Eur. J. Hum. Genet.* **21**, 1163–1168 (2013).
95. Telomeres Mendelian Randomization Collaboration *et al.* Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases: A Mendelian Randomization Study. *JAMA Oncol.* (2017). doi:10.1001/jamaoncol.2016.5945

This study found that genetic predisposition to longer telomeres increased risk of multiple cancers, but reduced risk for some other diseases including cardiovascular disease.

96. Codd, V. *et al.* Identification of seven loci affecting mean telomere length and their association with disease. *Nat. Genet.* **45**, 422–427 (2013).
97. Kuo, C.-L., Pilling, L. C., Kuchel, G. A., Ferrucci, L. & Melzer, D. Telomere length and aging-related outcomes in humans: A Mendelian randomization study in 261,000 older participants. *Aging Cell* e13017 (2019). doi:10.1111/acel.13017
98. Maslah, N., Cassinat, B., Verger, E., Kiladjian, J. J. & Velazquez, L. The role of LNK/SH2B3 genetic alterations in myeloproliferative neoplasms and other hematological disorders. *Leukemia* **31**, 1661–1670 (2017).
99. Malik, R. *et al.* Multiancestry genome-wide association study of 520,000

subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat. Genet.* **50**, 524–537 (2018).

100. Fortney, K. *et al.* Genome-Wide Scan Informed by Age-Related Disease Identifies Loci for Exceptional Human Longevity. *PLOS Genet.* **11**, e1005728 (2015).
101. Laroumanie, F., Humphrey, J. D. & Madhur, M. S. LNK deficiency promotes acute aortic dissection and rupture. *JCI Insight* **3**, (2018).
102. Hung, R. J. *et al.* Cross cancer genomic investigation of inflammation pathway for five common cancers: Lung, ovary, prostate, breast, and colorectal cancer. *J. Natl. Cancer Inst.* **107**, djv246 (2015).
103. Kuo, C.-L. *et al.* The Longevity Associated Sh2b3 (LNK) Genetic Variant: Selected Aging Phenotypes in 379,758 Subjects. *J. Gerontol. A. Biol. Sci. Med. Sci.* (2019). doi:10.1093/gerona/glz191
104. Sun, B. B. *et al.* Genomic atlas of the human plasma proteome. *Nature* **558**, 73–79 (2018).
105. Schlesinger, M. & Bendas, G. Vascular cell adhesion molecule-1 (VCAM-1) - An increasing insight into its role in tumorigenicity and metastasis. *Int. J. Cancer* **136**, 2504–2514 (2015).
106. Slack, C. *et al.* Regulation of lifespan, metabolism, and stress responses by the Drosophila SH2B protein, Lnk. *PLoS Genet.* **6**, (2010).
107. Mair, W. & Dillin, A. Aging and survival: the genetics of life span extension by dietary restriction. *Annu. Rev. Biochem.* **77**, 727–54 (2008).
108. Junnila, R. K., List, E. O., Berryman, D. E., Murrey, J. W. & Kopchick, J. J. The GH/IGF-1 axis in ageing and longevity. *Nat. Rev. Endocrinol.* **9**, 366–376 (2013).
109. Desbuquois, B., Carré, N. & Burnol, A. F. Regulation of insulin and type 1 insulin-like growth factor signaling and action by the Grb10/14 and SH2B1/B2 adaptor proteins. *FEBS Journal* **280**, 794–816 (2013).
110. Shiina, T., Hosomichi, K., Inoko, H. & Kulski, J. K. The HLA genomic loci map: Expression, interaction, diversity and disease. *Journal of Human Genetics* **54**, 15–39 (2009).

111. Ligthart, S. *et al.* Genome Analyses of >200,000 Individuals Identify 58 Loci for Chronic Inflammation and Highlight Pathways that Link Inflammation and Complex Disorders. *Am. J. Hum. Genet.* **103**, 691–706 (2018).
112. Franchini, M. & Bonfanti, C. Evolutionary aspects of ABO blood group in humans. *Clin. Chim. Acta* **444**, 66–71 (2015).
113. Jin, T. Current understanding on role of the wnt signaling pathway effector TCF7L2 in glucose homeostasis. *Endocr. Rev.* **37**, 254–277 (2016).
114. Locke, A. E. *et al.* Genetic studies of body mass index yield new insights for obesity biology. *Nature* **518**, 197–206 (2015).
115. Stone, T. W., McPherson, M. & Gail Darlington, L. Obesity and Cancer: Existing and New Hypotheses for a Causal Connection. *EBioMedicine* **30**, 14–28 (2018).
116. Martin, G. M. & Oshima, J. Lessons from human progeroid syndromes. *Nature* **408**, 263–266 (2000).
117. Oshima, J., Sidorova, J. M. & Monnat, R. J. Werner syndrome: Clinical features, pathogenesis and potential therapeutic interventions. *Ageing Res. Rev.* **33**, 105–114 (2017).
118. Pignolo, R. J. *et al.* Defects in telomere maintenance molecules impair osteoblast differentiation and promote osteoporosis. *Aging Cell* **7**, 23–31 (2008).
119. Ahmed, M. S., Ikram, S., Bibi, N. & Mir, A. Hutchinson-Gilford Progeria Syndrome: A Premature Aging Disease. *Mol. Neurobiol.* **55**, 4417–4427 (2018).
120. Nance, M. A. & Berry, S. A. Cockayne syndrome: review of 140 cases. *Am. J. Med. Genet.* **42**, 68–84 (1992).
121. Burla, R., La Torre, M., Merigliano, C., Vernì, F. & Saggio, I. Genomic instability and DNA replication defects in progeroid syndromes. *Nucleus* **9**, 368–379 (2018).
122. Gonzalo, S., Kreienkamp, R. & Askjaer, P. Hutchinson-Gilford Progeria Syndrome: A premature aging disease caused by LMNA gene mutations. *Ageing Res. Rev.* **33**, 18–29 (2017).

123. Scaffidi, P. & Misteli, T. Lamin A-dependent nuclear defects in human aging. *Science* **312**, 1059–63 (2006).
124. Jiang, Y. & Ji, J. Y. Understanding lamin proteins and their roles in aging and cardiovascular diseases. *Life Sci.* **212**, 20–29 (2018).
125. Scheibye-Knudsen, M. *et al.* Cockayne syndrome group A and B proteins converge on transcription-linked resolution of non-B DNA. *Proc. Natl. Acad. Sci. U. S. A.* **113**, 12502–12507 (2016).
126. Lee, J. J. *et al.* Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat. Genet.* **50**, 1112–1121 (2018).
127. Liu, M. *et al.* Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat. Genet.* **51**, 237–244 (2019).
128. Yun, S. & Vincelette, N. D. Update on iron metabolism and molecular perspective of common genetic and acquired disorder, hemochromatosis. *Crit. Rev. Oncol. Hematol.* **95**, 12–25 (2015).
129. Pilling, L. C. *et al.* Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank. *BMJ* **364**, k5222 (2019).
130. Tamosauskaite, J. *et al.* Hereditary Hemochromatosis Associations with Frailty, Sarcopenia and Chronic Pain: Evidence from 200,975 Older UK Biobank Participants. *J. Gerontol. A. Biol. Sci. Med. Sci.* **In press**, (2019).
131. Telenti, A., Perkins, B. A. & Venter, J. C. Dynamics of an Aging Genome. *Cell Metab.* **23**, 949–950 (2016).
132. Zhang, L. & Vijg, J. Somatic Mutagenesis in Mammals and Its Implications for Human Disease and Aging. *Annu. Rev. Genet.* **52**, 397–419 (2018).

This paper reviews the literature on low-abundance somatic DNA mutations in cells, in human and animal tissues and new technology that allows their assessment, with a focus on their possible functional consequences.

133. Risques, R. A. & Kennedy, S. R. Aging and the rise of somatic cancer-associated mutations in normal tissues. *PLOS Genet.* **14**, e1007108 (2018).
134. Blokzijl, F. *et al.* Tissue-specific mutation accumulation in human adult stem cells during life. *Nature* **538**, 260–264 (2016).
135. Zhang, L. *et al.* Single-cell whole-genome sequencing reveals the functional landscape of somatic mutations in B lymphocytes across the human lifespan. *PNAS* (2019). doi:10.1101/535906
136. Franco, I. *et al.* Somatic mutagenesis in satellite cells associates with human skeletal muscle aging. *Nat. Commun.* **9**, 800 (2018).

This study investigated somatic mutations in human B lymphocytes. Results indicate that spontaneous somatic mutations accumulate with age may contribute to both the increased risk for leukemia and the functional decline of B lymphocytes in the elderly.

137. Martincorena, I. *et al.* Somatic mutant clones colonize the human esophagus with age. *Science (80-.).* **3879**, eaau3879 (2018).
138. Yokoyama, A. *et al.* Age-related remodelling of oesophageal epithelia by mutated cancer drivers. *Nature* **565**, 312–317 (2019).
139. Fuster, J. J. & Walsh, K. Somatic Mutations and Clonal Hematopoiesis. *Circ. Res.* **122**, 523–532 (2018).
140. Van Den Akker, E. B. *et al.* Uncompromised 10-year survival of oldest old carrying somatic mutations in DNMT3A and TET2. *Blood* **127**, 1512–1515 (2016).
141. Andrews, R. M. *et al.* Reanalysis and revision of the Cambridge reference sequence for human mitochondrial DNA. *Nat. Genet.* **23**, 147 (1999).
142. Stewart, J. B. & Chinnery, P. F. The dynamics of mitochondrial DNA heteroplasmy: implications for human health and disease. *Nat. Rev. Genet.* **16**, 530–42 (2015).

143. Hutchison, C. A., Newbold, J. E., Potter, S. S. & Edgell, M. H. Maternal inheritance of mammalian mitochondrial DNA. *Nature* **251**, 536–8 (1974).
144. Scheibye-Knudsen, M., Scheibye-Alsing, K., Canugovi, C., Croteau, D. L. & Bohr, V. A. A novel diagnostic tool reveals mitochondrial pathology in human diseases and aging. *Aging (Albany. NY).* **5**, 192–208 (2013).

This paper describes a novel classification algorithm based on qualitative and quantitative characteristics assessing whether a disorder can be characterized as mitochondrial. Using this tool, the authors find that many of the features of normal aging may be linked to mitochondrial dysfunction.

145. Wallace, D. C. *et al.* Sequence analysis of cDNAs for the human and bovine ATP synthase beta subunit: mitochondrial DNA genes sustain seventeen times more mutations. *Curr. Genet.* **12**, 81–90 (1987).
146. Bua, E. *et al.* Mitochondrial DNA-deletion mutations accumulate intracellularly to detrimental levels in aged human skeletal muscle fibers. *Am. J. Hum. Genet.* **79**, 469–80 (2006).
147. Greaves, L. C. *et al.* Clonal expansion of early to mid-life mitochondrial DNA point mutations drives mitochondrial dysfunction during human ageing. *PLoS Genet.* **10**, e1004620 (2014).
148. Picard, M., Wallace, D. C. & Burelle, Y. The rise of mitochondria in medicine. *Mitochondrion* **30**, 105–16 (2016).
149. Trifunovic, A. *et al.* Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature* **429**, 417–23 (2004).

This manuscript describes the phenotype of a homozygous knock-in mice that expresses a proof-reading-deficient version of PolgA, the nucleus-encoded catalytic subunit of mtDNA polymerase. The PolgA mouse accumulates point mutations in mitochondrial DNA much faster than wild-type and shows reduced lifespan and premature

onset of ageing-related phenotypes.

150. Kraytsberg, Y. *et al.* Mitochondrial DNA deletions are abundant and cause functional impairment in aged human substantia nigra neurons. *Nat. Genet.* **38**, 518–20 (2006).
151. Franco-Iborra, S., Vila, M. & Perier, C. Mitochondrial Quality Control in Neurodegenerative Diseases: Focus on Parkinson's Disease and Huntington's Disease. *Front. Neurosci.* **12**, 342 (2018).
152. Ferrucci, L., Levine, M. E., Kuo, P. & Simonsick, E. M. Time and the Metrics of Aging. *Circ. Res.* **123**, 740–744 (2018).
153. Zhu, Z. *et al.* Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet.* **48**, 481–7 (2016).
154. Campbell, M. C. & Tishkoff, S. A. African Genetic Diversity: Implications for Human Demographic History, Modern Human Origins, and Complex Disease Mapping. *Annu. Rev. Genomics Hum. Genet.* **9**, 403–433 (2008).
155. Kenyon, C. J. The genetics of ageing. *Nature* **464**, 504–512 (2010).
156. McKay, J. P., Raizen, D. M., Gottschalk, A., Schafer, W. R. & Avery, L. eat-2 and eat-18 are required for nicotinic neurotransmission in the Caenorhabditis elegans pharynx. *Genetics* **166**, 161–9 (2004).
157. Greer, E. L. & Brunet, A. Different dietary restriction regimens extend lifespan by both independent and overlapping genetic pathways in C. elegans. *Aging Cell* **8**, 113–127 (2009).
158. Gingras, A.-C., Raught, B. & Sonenberg, N. eIF4 Initiation Factors: Effectors of mRNA Recruitment to Ribosomes and Regulators of Translation. *Annu. Rev. Biochem.* **68**, 913–963 (2002).
159. Lakowski, B. & Hekimi, S. Determination of life-span in Caenorhabditis elegans by four clock genes. *Science* **272**, 1010–3 (1996).
160. Liu, X. *et al.* Evolutionary conservation of the clk-1-dependent mechanism of longevity: Loss of mclk1 increases cellular fitness and lifespan in mice. *Genes Dev.* **19**, 2424–2434 (2005).
161. Bansal, A., Zhu, L. J., Yen, K. & Tissenbaum, H. A. Uncoupling lifespan

and healthspan in Caenorhabditis elegans longevity mutants. *Proc. Natl. Acad. Sci. U. S. A.* **112**, E277 (2015).

162. Mitchell, S. J. *et al.* Effects of Sex, Strain, and Energy Intake on Hallmarks of Aging in Mice. *Cell Metab.* **23**, 1093–1112 (2016).
163. Fontana, Luigi; Partridge, Linda; Longo, valter D. Extending Healthy Life Span — From Yeast to Humans. *Science (80-.).* **328**, 321–326 (2010).
164. Mattison, J. A. *et al.* Caloric restriction improves health and survival of rhesus monkeys. *Nat. Commun.* **8**, 1–12 (2017).
165. Kraus, W. E. *et al.* 2 years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicentre, phase 2, randomised controlled trial. *lancet. Diabetes Endocrinol.* **0**, (2019).
166. Belsky, D. W., Huffman, K. M., Pieper, C. F., Shalev, I. & Kraus, W. E. Change in the Rate of Biological Aging in Response to Caloric Restriction: CALERIE Biobank Analysis. *Journals Gerontol. Ser. A* **73**, 4–10 (2018).
167. Leclerc, E. *et al.* The effect of caloric restriction on working memory in healthy non-obese adults. *CNS Spectr.* 1–7 (2019). doi:10.1017/S1092852918001566
168. Madeo, F., Carmona-Gutierrez, D., Hofer, S. J. & Kroemer, G. Caloric Restriction Mimetics against Age-Associated Disease: Targets, Mechanisms, and Therapeutic Potential. *Cell Metab.* **29**, 592–610 (2019).
169. Most, J., Tosti, V., Redman, L. M. & Fontana, L. Calorie restriction in humans: An update. *Ageing Res. Rev.* **39**, 36–45 (2017).
170. Laplante, M. & Sabatini, D. M. mTOR signaling at a glance. *J. Cell Sci.* **122**, 3589–3594 (2009).
171. Harrison, D. E. *et al.* Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* **460**, 392–395 (2009).
172. Mannick, J. B. *et al.* TORC1 inhibition enhances immune function and reduces infections in the elderly. *Sci. Transl. Med.* **10**, eaaq1564 (2018).
173. Dowling, R. J. O., Topisirovic, I., Fonseca, B. D. & Sonenberg, N. Dissecting the role of mTOR: Lessons from mTOR inhibitors. *Biochimica et Biophysica Acta - Proteins and Proteomics* **1804**, 433–439 (2010).

174. Justice, J. N. *et al.* Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. *EBioMedicine* **40**, 554–563 (2019).
175. Butler, P. G., Wanamaker, A. D., Scourse, J. D., Richardson, C. A. & Reynolds, D. J. Variability of marine climate on the North Icelandic Shelf in a 1357-year proxy archive based on growth increments in the bivalve Arctica islandica. *Palaeogeogr. Palaeoclimatol. Palaeoecol.* **373**, 141–151 (2013).
176. Weismann, A., Poulton Sir, E. B., Schönland, S. & Shipley Sir, A. E. (Arthur E. *Essays upon heredity and kindred biological problems*. **v.1**, (Clarendon Press, 1891).
177. Fabian, D. & Flatt, T. The Evolution of Aging. *Nat. Educ. Knowl.* **3**, 9 (2011).
178. Medawar, P. B. An Unsolved Problem of Biology. *Evolution in Health and Disease* 24 (1951). doi:10.1016/S0140-6736(00)99799-X
179. Partridge, L. & Barton, N. H. Optimally, mutation and the evolution of ageing. *Nature* **362**, 305–311 (1993).
180. Williams, G. C. Pleiotropy, Natural Selection, and the Evolution of Senescence. *Evolution (N. Y).* **11**, 398 (2006).
181. Campisi, J. Senescent cells, tumor suppression, and organismal aging: good citizens, bad neighbors. *Cell* **120**, 513–22 (2005).
182. Kirkwood, T. B. L. Evolution of ageing. *Nature* **270**, 301–304 (1977).
183. Pride, H. *et al.* Long-lived species have improved proteostasis compared to phylogenetically-related shorter-lived species. *Biochem. Biophys. Res. Commun.* **457**, 669–675 (2015).
184. Krzywinski, M. Circos Table Viewer - Circular Visualization of Tabular Data // with Circos - Circular Genome Data Visualization. (2019). Available at: http://mkweb.bcgsc.ca/tableviewer/visualize/. (Accessed: 5th March 2019)
185. Pruim, R. J. *et al.* LocusZoom: regional visualization of genome-wide association scan results. *Bioinformatics* **26**, 2336–7 (2010).
186. Pingault, J. B. *et al.* Using genetic data to strengthen causal inference in observational research. *Nat. Rev. Genet.* **19**, 566–580 (2018).

Acknowledgements

D.M. and L.C.P. are supported by the University of Exeter Medical School and additionally by the University of Connecticut School of Medicine. This work is supported in part by the UK Medical Research Council (grants MR/M023095/1 and MRS009892/1). This work was also supported in part by the Intramural Research Program at the National Institute on Aging.

Competing interests

The authors declare no competing interests.

RELATED LINKS

The CHARGE Consortium http://www.chargeconsortium.com/

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Online Mendelian Inheritance of Man (OMIM) https://www.omim.org

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Box 1. Slowing ageing in laboratory models.

Interventions in laboratory models can delay or reverse specific aspects of ageing. These models provide robust insights into ageing mechanisms, which might be conserved across species.

[b1] Targeting nutrient sensing and dietary restriction

A number of genetic manipulations can markedly prolong survival in *Caenorhabditis elegans.* Long-lived genetic mutans may result from modulation of different, independent biological pathways. For example, *daf-2* affects nutrient sensing through modulation of insulin–insulin-like growth factor 1 (IGF-1) signalling and upregulation of autophagy [155]; *eat-2* codes for a defective nicotinic acetylcholine receptor causing impaired pharyngeal pumping and a genetic form of caloric restriction [156,157]; knockdown of *ife-2* increases lifespan by downregulating protein translation [158]; and knockdown of the clock gene *clk-1* affects longevity by impairing mitochondrial electron transport chain activity, therefore reducing oxidative stress [159,160]. However, only the modulation of insulin–IGF-1 (via daf-2) shows increased health span, and in all four long-lived mutants the period of frailty is disproportionally extended compared to lifespan[161].

Restricting calorie intake while maintaining necessary micronutrient intakes produces lean animals and improves functioning and lengthens life in many but not all mouse strains[162]. Dietary restriction increases longevity by modulating the expression of growth factors, such as IGF-1, and affecting the mammalian target of rapamycin (mTOR) and ribosomal protein S6 kinase (S6K) signalling pathway[163]. The effectiveness of dietary restriction in promoting health span and life span seems to be evolutionally conserved in yeast, worms, flies and some mouse strains[162]. However, in primates, the effect of caloric restriction varied between experiments, with some detectable positive effects on metabolic disease prevention, which may be partially related to the effect of the intervention on body composition[164]. However, whether such positive effects of metabolic controls are strong enough to affect longevity is still in question.

Caloric restriction in healthy, non-obese humans has beneficial effects on multiple cardiometabolic risk factors, might prevent decline of memory and is associated with slowing down of a proxy biomarker of biological ageing[165,166,167], although these findings need confirmation with longer follow-up times. Several nutritional interventions are under development to delay ageing, including different forms of caloric restriction, fasting and calorie restriction mimetics, agents that mimic the beneficial effects of dietary restriction without necessarily restricting calories, thus avoiding detrimental impact[168],[169].

[b2] Targeting mTOR

The mTOR signalling pathway, a central regulator of cell metabolism, growth, proliferation and survival[170], has been extensively implicated in ageing. Rapamycin, a licensed immunosuppressive drug targeting mTOR, extended healthspan and lifespan even in already older mice, in randomized trials in three different studies[171]. A human trial of low-dose rapamycin analogue reported enhanced immune function and a reduction in infections but the potential effect on longevity in humans is unknown[172]. The effects of rapamycin include increasing autophagy, which may counteract immune senescence by affecting energy metabolism, organelle recycling, as well as the fate and function of immune cells [173].

[b3] Targeting senescent cells

A wide range of biological stresses that cause cell damage can lead to cellular senescence, in which cells become unable to replicate, secrete large quantities of cytokines, chemokines, proteases and growth factors, and develop resistance to apoptosis[90]. A targeted removal of senescent cells expressing $p16^{ink4a}$ resulted in the reversal of several features of ageing in mouse models[89]. The development of senolytic molecules that can selectively induce apoptosis of senescent cells is an active area of investigation, with a ‘first in man’ clinical trial in idiopathic pulmonary fibrosis recently reporting efficacy and safety[174].

Box 2. Evolutionary theories of ageing

Lifespans of different animal species vary enormously, from less than 1 day in mayflies to more than 400 years in ocean quahog clams[175], and this variation must ultimately arise from evolved differing abilities to adapt to the surrounding environment and respond to stress, both abilities that are likely genetically encoded.

The early theory of *group selection* argued that ageing is a genetically encoded adaptive trait that increases mortality in individuals with declining reproductive potential, thereby freeing up resources for the younger generation to reproduce[176]. This theory was soon abandoned by the original author because of evidence that natural selection is most effective at the individual level even when it may conflict with the interests of the species[177]. Also, no organism-level 'programmed death gene' has been found. Currently, the most widely accepted theories of ageing are the mutation accumulation theory, the antagonistic pleiotropy theory and the disposable soma theory.

The *mutation accumulation theory* proposes that organisms accumulate damaging germline mutations that are expressed only in the post-reproductive period of life, as these mutations would not be eliminated by earlier selective pressures[178]. This theory interprets differences in lifespan between different mammal species as related to differences in age of sexual maturity. Huntington disease provides a prominent example. However, the rapid post-reproduction increase in death rates that would be expected according to this theory has not been detected in humans or in animal species[179].

The *antagonistic pleiotropy theory* argues that some mutations selected because they are beneficial to early fitness become harmful late in life, causing ageing[180]. Cell senescence pathways may provide examples of antagonistic pleiotropy: programmed senescence occurs during normal mammalian development, protects against cancer and promotes wound healing at younger ages but contributes to degenerative chronic disease at older ages[181].

The *disposable soma* theory states that given the availability of limited resources, ageing arises from evolutionary trade-offs between growth and reproduction on the

one hand and repair mechanisms on the other[182]. This theory is consistent with evidence that long-lived species such as humans evolved by developing more sophisticated and effective, albeit not unlimited, repair mechanisms. For example, comparative studies have found that the capacity to recycle deteriorated macromolecules and organelles by autophagy correlates with life-span across species[183]. This theory is also consistent with the current consensus that ageing results from the accumulation of unrepaired cellular and molecular damage[1832]. Human resilience mechanisms were likely selected to be robust enough to match the high environmental pressures that drove human evolution. The very recent dramatic decline of environmental pressures has extended survival beyond the previous resilience 'warranty period'. Contemporary environments allow lengthy survival after the reproductive period, with an eventual increasing predominance of damage over repair.

Figure 1. Genetic overlap between age-related chronic diseases and parental longevity, based on correlations between whole-genome association results.

Genetic correlations are from linkage disequilibrium (LD) score regression methods using available genome-wide association study (GWAS) summary statistics. Statistically significant correlations are indicated with an asterisk (single for nominal $P<0.05$ significance, double indicates significant after Bonferroni correction for 36 tests in this analysis). Ordered by similarity using hierarchical clustering (Supplementary table 3 for details).

Figure 2. Selected loci with correlated variants associated with three or more age-related diseases or lifespan.

Nine loci identified as hotspots for at least three major age-related diseases or lifespan in genome-wide association study (GWAS) that included multiple correlated ($R^2>0.6$) genetic variants (see Supplementary tables 4 and 5 for details). The lipid-related variants *LPA*, *LDLR* and *APOE* were excluded for simplicity. Genes are shown on the left, with each 'link' to a disease on the right indicating a

GWAS-identified signal. Lifespan refer to parental lifespan. AD, Alzheimer disease; CAD, coronary artery disease; CKD, chronic kidney disease; OA, osteoarthritis. Circos table viewer was used for visualization[184].

Figure 3. Disease-associated genetic variants in the 9p21.3 locus, by effect size of association with parents' lifespan.

LocusZoom[185] plot of known disease-associated variants in the 9p21.3 locus, containing genes *CDKN2A* ($p16^{ink4a}$), *CDKN2B* ($p15^{ink4b}$) and *CDKN2B-AS1* (the lncRNA ANRIL). Genetic variants are labelled with the trait(s) they are reported to be associated with in published genome-wide association study (GWAS) (see Supplementary Table 6 for details). The y-axis shows the association ($-\log_{10}$ p-value) with parental lifespan from the 2019 LifeGen GWAS[41]. The variant in purple (rs1556516) is the lead signal at this locus from the parents' lifespan analysis. The other variants are coloured according to their correlation with rs1556516 in 1000 Genomes European ancestry data (v. Nov 2014).

Figure 4. Diagram of the major influences and mechanisms of human ageing.

The emerging picture from genetic studies of human ageing supports the hypothesis that ageing is driven by the balance of damage and repair processes. There is genetic evidence for the importance of several damage pathways in humans. Damage can be intrinsic, for example, through somatic mutations arising during cell division. Also important are health behavioural risk factors such as smoking and obesity, which are also influenced by gene–environment interactions. The net impact of damage depends on repair and response mechanisms. At the cellular level, complete repair can yield undamaged cells (not shown, to simplify the figure). By contrast, unrepaired damage can lead to cell death (apoptosis), preventing cancers but leading to depletion of stem cells and loss of regenerative capacity. Cells with somatic oncogene mutations can survive and replicate, sometime producing cancers. Alternatively, damaged cells can enter senescent states and produce a secretory senescence phenotype (SASP), resulting in inflammation and reduced repair that contributes to degenerative diseases[90].

These mechanisms can result in reduced repair and increasing incidence of chronic diseases of ageing but with decreased cancer risks, or vice versa. This ageing versus cancer trade-off is evident for several of the loci described, notably in the 9p21 cell cycle- and senescence-related locus, telomere variation and in the *SH2B3* locus.

Table 1. Genetic variants associated with parental lifespan

Study	rsID (effect allele)	Effect[a]	Mapped gene(s)	Gene name	Variant position	Associated disease
Loci significant in both[b]:						
UKB + LifeGen cohorts[41]	rs429358 (T)	1.06	APOE	Apolipoprotein E	missense	Cardiometabolic, dementia
UKB + AncestryDNA[42]	rs10455872 (A)	0.76	LPA	Lipoprotein A	intronic	Cardio-metabolic
	rs8042849 (T)[c]	0.44	CHRNA3/5	Cholinergic receptor nicotinic alpha 3/5 subunit	intronic	Smoking-related
	rs142158911 (A)	0.36	LDLR	Low density lipoprotein receptor	intergenic	Cardio-metabolic
	rs11065979 (C)[d]	0.28	SH2B3 .. ATXN2	SH2B adaptor protein 3 .. Ataxin 2	intergenic	Cardio-metabolic, cancers, autoimmunity[h]
	rs1556516 (G)	0.25	CDKN2B-AS1	CDKN2B antisense RNA 1	intronic	Cardio-metabolic, cancers[h]
Loci significant in only:						
UKB + LifeGen cohorts	rs34967069 (T)	0.56	HLA-DQA1	Major histocompatibility complex, class II, DQ alpha 1	intergenic	Autoimmune
	rs1230666 (G)	0.32	MAGI3	Membrane associated guanylate kinase, WW and PDZ domain containing 3	intronic	Autoimmune
	rs12924886 (A)	0.28	HP	Haptoglobin	intergenic	Cardio-metabolic
	rs1275922 (G)	0.26	KCNK3	Potassium two pore domain channel subfamily K member 3	intronic	Cardio-metabolic
	rs6224 (G)[e]	0.25	FURIN/FES	Furin, paired basic amino acid cleaving enzyme	intronic	Cardio-metabolic
	rs61348208 (T)	0.23	HTT	Huntingtin	intronic	
Loci significant in only:						
UKB + AncestryDNA	rs7844965 (G)[f]	0.25	EPHX2	Epoxide Hydrolase 2	intronic	
	rs4774495 (G)[f]	0.23	SEMA6D	Semaphorin 6D	intronic	
	rs599839 (G)[f]	0.21	CELSR2 .. PSRC1	Cadherin EGF LAG Seven-Pass G-Type Receptor 2 .. Proline And Serine Rich Coiled-Coil 1	intergenic	Cardio-metabolic
	rs3131621 (G)[f]	0.20	MICA .. MICB	MHC Class I Polypeptide-Related Sequence A .. B	intergenic	
	rs15285 (G)[f]	0.18	LPL	Lipoprotein Lipase	3' UTR	Cardio-metabolic
	rs9872864 (G)[g]	0.14	IP6K1	Inositol Hexakisphosphate Kinase 1	intronic	

a) Effect = years added to lifespan of parents (from LifeGen analysis[41]).
b) "rsID (effect allele)" and "Effect" information from LifeGen analysis[41]. The AncestryDNA analysis may have reported a different lead SNP for the same locus.
c) HYKK neighbouring gene to CHRNA3 and CHRNA5.
d) variant located between ATXN2 and BRAP, but is correlated (R2>0.8) with missense variant in SH2B3.
e) located in the intron of gene FURIN.
f) Significantly associated with father's lifespan, not mother's
g) Significantly associated with mother's lifespan, not father's
h) not exhaustive list.

Glossary

Genome-wide association study

(GWAS) A study that involves genotyping large numbers of participants to identify statistical associations between genetic variants and traits of interest.

Somatic mutations

Changes to the genetic code arising from errors during DNA damage repair, DNA replication, or mitosis, occurring in somatic (non-germline) tissues[132].

Healthspan

The period of life free from disease and functional limitations[14].

Heritability

The proportion of variance in a phenotype that can be attributed to genetic differences among individuals in a given population. Narrow-sense heritability estimates additive genetic effects. Broad-sense heritability includes both additive and dominance effects[186].

Polygenic risk score

Individual-level scores that summarize genetic risk (or protection) for a given phenotype. For each person a score is computed by counting the number of effect alleles (genetic variants) - weighted by their effect – the person carries. A polygenic score is computed by summing scores from a large number, potentially all, of the variants in the genome[186].

Linkage disequilibrium

(LD) Non-random associations between alleles at different loci[186].

Mendelian randomization

A method that uses single nucleotide polymorphisms (SNPs) associated with an exposure as instruments to probe the causal nature of the relationship between this exposure and an outcome of interest[186].

Antagonistic pleiotropy

Theory arguing that some mutations are selected because they are beneficial to early-life fitness but become harmful later in life, thus causing ageing.

Clonal expansions

The production of daughter cells from a single parent cell, all sharing a particular characteristic or trait.