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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. 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.

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 at the molecular and cellular levels, known as biological “hallmarks” of ageing[2], through to declining physiological homeostasis at the organism level as well as lessening abilities to perform everyday physical and cognitive tasks. Ageing also increases the susceptibility to many common diseases, with death rates rising 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 Alzheimer disease, chronic kidney disease, coronary artery disease (CAD), osteoarthritis, stroke, type 2 diabetes mellitus (T2DM) and common

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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, the rates of decline vary enormously. Whereas some people die of age-related disease in their 60s, 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 limited and conventional observational studies are often distorted by confounding factors such as smoking or obesity. However, over the past decade, results of `genome-wide association studies` (GWAS)[5] for many phenotypes relevant to ageing have started to emerge. Inherited (that is, germline) variant associations are minimally affected by confounding and can provide unique biological insights to clarify whether observations in laboratory animals apply to humans. Furthermore, 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]. Indeed, even genes harbouring variants with small effect sizes can provide successful drug targets[5]. Therefore, pinpointing the genetic variation that influences human ageing could help identify suitable targets for anti-ageing interventions in humans.

Genome-wide association studies

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

In this Review, we discuss recent results from the most robust genetic association studies relevant to human ageing, with a focus on ‘multi-trait’ variants, that is, variants that affect several ageing-related phenotypes simultaneously, reflecting the view that correlated changes of ageing have common mechanisms. We describe three key accelerated ageing (progeroid) genetic disorders in humans and review evidence on the accumulation of `somatic mutations` with advancing age, with these two sections providing insights into underlying DNA damage processes that increase cancer risk and may also contribute to functional declines in ageing. Evidence is accumulating for age-related epigenetic[7], gene expression and splicing[8] changes; however, as the causal roles of these changes are uncertain, we do not discuss these topics.

Somatic mutations

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

Heritability of ageing traits

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 and therefore other age-related phenotypes must serve as proxies (BOX 2).

To what extent are these proxy 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[10]. Widely cited heritability estimates for human longevity from twin studies range from 20% to 30%[11], whereas in families with a centenarian, estimates increase to 48% in men and 33% in women[12]. 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[13]. 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%[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.

Common age-related diseases also have substantial heritable components; for example, hip osteoarthritis is estimated to be 68% heritable[15], T2DM heritability is estimated at 61–78%[16], the heritable component of Alzheimer disease is estimated to be 58–79% (depending on the model used)[17], and cardiovascular disease heritability has been estimated at 45–69%[18]. Individual genetic variants that are associated with many ageing phenotypes have now been identified, mostly by GWAS, and the amount of variation in the trait attributed to these specific genetic differences can be estimated. These genotyped variants cumulatively explain 51.9% of the variation in osteoarthritis of the hip[19] and 18% in T2DM[20] but only 8.5% of the variation in parental age at death[21] and 7.1% in Alzheimer disease[22]. 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 a 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[23].

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, specific human genetic variants associated with ageing phenotypes must be determined. Such variants have recently been identified even for traits with modest heritability.

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, yet both approaches include multiple statistical tests. As more variants are compared, it becomes increasingly likely that some will be statistically significant merely 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 a genome-wide statistical significance[24] of $P < 5 \times 10^{-8}$), especially those with independent replication.

Parental lifespan

The most robust identifications of lifespan-related variants currently come from recent, very large cohorts such as the UK Biobank[25], 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, analysis of data from the University of Michigan Health and Retirement Study, a longitudinal study of approximately 20,000 participants aged 51–61 years at baseline who were followed up for 18 years, found that all-cause mortality consistently declined by 19% for each decade that participants' mothers had survived beyond 65 years of age (14% per decade for fathers)[26]. Additionally, study participants had progressively lower incidences of cardiovascular disease and cancers[26] as well as reduced rates of cognitive decline[27], with increasing parental survival. A study of 186,151 non-adopted UK Biobank participants followed up 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 (HR 0.84, 95% CI 0.79–0.89) and 17% for fathers' survival (HR 0.83, 95% CI 0.78–0.89). Cause-specific mortality declined with advancing parental ages, especially for coronary heart disease (20% per decade with decades of mothers' age ≥70 years: HR 0.80, 95% CI 0.68–0.95; and 21% for fathers' age: HR 0.79, 95% CI 0.63–0.98), but declines in cancer mortality (HR 0.92, 95% CI 0.90–0.95) were also present[28].

Several GWAS have been reported for parental age at death (or attained age thus far) either in the UK Biobank cohort alone[21,29,30] or in meta-analyses combining UK Biobank data with data from other cohorts; the LifeGen consortium included data on approximately 160,000 study participants from 25 cohorts in addition to UK Biobank data[31], and a separate analysis included pedigree data from AncestryDNA[32] on 300,000 individuals for a meta-analyses with UK Biobank data. The ages at death of the parents (or current age if still alive) studied in the LifeGen analysis[31] varied from 40 to 107 years, whereas the AncestryDNA[32] 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 the other study. Many of the implicated variants have been linked previously to cardiometabolic conditions (mostly myocardial infarction and T2DM), with some linked to Alzheimer disease, autoimmunity and cancer risk[31], thus reflecting the more common causes of death in older people.

Gene–environment interactions were evident for some variants. For example, the variant *rs1051730* lies in an exon of *CHRNA3*, which encodes a nicotinic acetylcholine receptor subunit, and the lifespan-reducing allele was correlated with *rs8042849*, which increases susceptibility to nicotine dependence[33] and likely reduces lifespan by increasing smoking exposure. Interestingly, this association was stronger for fathers' age at death than mothers' age at death, possibly owing to gender differences in smoking in the parental generation[21]. 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[31]. 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[34].

In a UK Biobank GWAS, sub-analysis of the participants' genotypes in the top 10% of parental survival (with survival to ≥90 years in mothers and ≥87 years in fathers) produced results similar to overall lifespan analyses[29]: 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 the top 10% survival in the analysis of parental lifespan. These results were consistent with an analysis of centenarian parents, with similar genotype–lifespan effect sizes[29], although numbers here were small, with only 1,181 participants having at least one centenarian parent, meaning that only the *APOE* locus reached genome-wide significance[29]. Thus, lifespan-associated variants can also be important for longevity, with some variants likely being specific to longevity.

Genetic associations with longevity.—GWAS have also directly compared long-lived individuals (aged ≥90 years) to younger control individuals (aged <65 years, although definitions vary[35–38], as recently reviewed elsewhere[3]). The most recent meta-analysis included 11,262 participants who lived beyond the 90th percentile[38]. The most robust findings have been for the *APOE* haplotypes, with *ε4* being less common in long-lived participants and *APOE ε2* more common (versus the *ε3* haplotype). The two *APOE* haplotypes have similarly inverse associations with Alzheimer disease[22] and cardiovascular disease[39]. 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[40], 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, whereas the *ε2/ε2* or *ε2/ε3* haplotypes were associated with modestly decreased mortality within the longest-lived 1% of survivors[41]. The recent meta-analysis of longevity GWAS[38] identified a new locus, *GPR78*; variants in this locus associated with longevity were not previously linked in GWAS with other traits, but the gene, which encodes G protein-coupled receptor 78, has been implicated in traits such as lung function[42] in the GWAS Catalog[43].

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[44]. A GWAS in 583 families of the Long Life Family

Study cohort (covering long-lived individuals and offspring, which unusually also included predicted longevities) confirmed associations at the *APOE* locus and also identified a variant (*rs1927465*) between the genes *MYOF* (which encodes myoferlin) and *CYP26A1* (which encodes cytochrome P450 family 26 subfamily A member 1) at genome-wide significance[45]. At the time of writing, *rs1927465* has not been reported in the GWAS Catalog for other phenotypes.

A much studied set of extreme longevity-associated variants has 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[46]. In the longest-lived 1% of survivors, 17 *FOXO3A* variants were more common than in controls (n = 2,072 aged ≥96 years versus <96 years); the strongest association was found for the variant *rs4946935* (OR 1.20 for extreme longevity, $P = 3.2 \times 10^{-5}$)[47]. However, none of these 17 variants affected death rates for the younger 99% of lifespans, which is consistent with no *FOXO3A* variants reaching genome-wide significance in the large parental lifespan GWAS discussed above[29,31].

The evidence on mostly candidate gene variants has also been reviewed, comparing groups aged ≥85 years, including centenarians, versus those aged <85 years, with most aged <60 years[48]. Overall, seven variants claimed to be associated with longevity were 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[49], providing a possible explanation for the limited replication of variants linked to exceptional longevity. Another explanation might be the fairly 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 seems essential (that is, not all long-lived people harbour them) and none seems 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[44] likely affected by large numbers of small effect variants.

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[50], 56 variants were identified, with approximately two-thirds of loci implicated in the DNA damage response (DDR)[51]. As discussed below, unrepaired DNA damage might be a major driver of overall ageing. Moreover, some of the menopause-associated variants have effects on the hypothalamic– pituitary axis, which controls many hormone levels. A `polygenic risk score` for each individual in a study population can be calculated by summing the number of risk-increasing alleles (weighted by published effect size) that each participants carries. However, a genetic risk score for age at menopause was not associated with parental lifespan in the UK Biobank[21]. Menopause-associated variants may therefore have limited effects on human ageing more generally.

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) that the person carries. A polygenic score is computed by summing scores from a large number, potentially all, of the variants in the genome.

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[52]. A GWAS of the full range of strength (measured as grip strength) 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[53]. A targeted study of the human leukocyte antigen (HLA)-mediated autoimmunity-associated region reported associations with low muscle strength in those aged 60–70 years[54] without autoimmune disease, but whether low muscle strength in older people is driven by the same variants is unclear.

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, some of which are treatable if caught early[55]. 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[56]. 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 with polygenic risk scores for CAD, educational attainment and other traits[57]. Another study in 1,176 men aged in their 50s[58] 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[59].

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 that influence age-related macular degeneration[60], the most common cause of blindness in the western world. Two large-effect loci were found: one mapped to *CFH*, which encodes complement factor H in the complement inflammation cascade, and one to *ARMS2* (also known as *HTRA1*), which is involved in extracellular matrix turnover. Both variants were associated with more than 2.5-fold differences in age-related macular degeneration risk in a recent large study[61]. 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].

Genetic variation across common diseases

Composite measures of healthspan

The duration of the period of life free from disease and functional limitations (that is, 'healthspan'[62]) is an important measure of the physical health aspects of ageing well and was recently studied in UK Biobank participants aged 37–73 years[62]. All available age-associated diagnoses were included and a notable variant found to be associated with healthspan had previously been implicated in skin cancers[63]. As skin cancer represents the most common cancer type[64], the prominence of skin cancer variants in the results of this composite healthspan measure is unsurprising. However, skin cancer risk is correlated to high levels of sun exposure[65], which is a highly variable behavioural exposure, especially in older people. Thus, composite measures may highlight common exposures rather than necessarily identifying shared ageing mechanisms.

Multi-trait variants associated with disease

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. 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, such as lung cancer and chronic obstructive pulmonary disease, the risks of which are strongly related to smoking. Based on data from the GWAS Catalog, 961 genome-wide significant variant associations have been reported for common age-related conditions to date (Supplementary Tables 1 and 2). 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.

Genetic correlation between multiple traits.—One approach to explore shared genetic effects is to estimate genetic correlation — the degree of genetic overlap between pairs of traits — using GWAS results[66,67] (FIG. 1; Supplementary Table 3). This method uses `linkage disequilibrium` (LD) 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[66]. Analyses of previously published data show that CAD, osteoarthritis, T2DM and stroke GWAS results correlate negatively with parental longevity, with 40–60% overlap (Supplementary Table 3), 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 variants shared across diseases of ageing are important, albeit not for all phenotypes.

Linkage disequilibrium

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

Associations with polygenic risk scores.—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[21]. Additionally, a 7-month shortening in parental lifespan per unit of genetically determined increasing body mass index (BMI) has been reported[30]. This adverse effect of increased BMI contrasts with claims that being obese or overweight is beneficial in older people[68] but is consistent with the success of calorie restriction in lengthening survival in animal models (BOX 1). Furthermore, high numbers of senescent cells accumulate in adipose tissue with age, especially around internal organs[69,70].

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 must be fairly healthy to maintain their obesity. Longer-term observational analyses minimizing the effects of diseases that cause weight loss showed that those aged 65–74 years with obesity are at higher risk of dementia[71] and have higher death rates[72]. However, whether avoiding obesity is important to reach centenarian status remains unclear[73].

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 the 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 and CAD as well as with exceptional longevity and parental lifespan. Two other loci (*LPA* and *LDLR)* contain variants that affect blood lipid levels[74] and cardiovascular traits[39]. The disease associations of the remaining nine multi-trait loci are more diverse (FIG. 2), as we discuss below.

The CDKN2A/B and CAS8 loci

The *CDKN2A/B* locus (also known as the 9p21 locus) contains genes that produce the $p16^{ink4a}$, $p14^{arf}$ and $p15^{ink4b}$ tumour suppressor proteins (FIG. 3) and the long non-coding RNA (lncRNA) *CDKN2B-AS1* (also known as *ANRIL*), which regulates *CDKN2A/B* expression[75]. Variants in or near these genes have been associated with multiple diseases, including cardiovascular conditions[39], T2DM[20], cancers[76,77], endometriosis[78], glaucoma and related optic disc traits[79] as well as blood cell count[80] and parental lifespan[31] (see Supplementary Table 6 for further details and references). Cell senescence is often accompanied by expression of $p16^{ink4a}$ (*CDKN2A*), and clearance of *CDKN2A*-expressing

cells in mice attenuated age-related deterioration in the eye, kidney, heart and fat, with no overtly adverse effects[81] (BOX 1). Efforts to develop interventions to remove senescent cells in humans are being actively pursued[82].

Interestingly, the disease-associated variants in the *CDKN2A/B* locus are not in coding areas (FIG. 3; Supplementary Table 6) and there is limited overlap in variants associated with different traits. For example, variants associated with vascular disease, such as *rs944797* (REF.[39]), are not associated with T2DM[20] and vice versa. This locus may therefore be an example of genetic variation influencing the 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[76], prostate[77] and colorectal[83] cancers. A T2DM-associated variant is located nearby (<250 kb) in *CASC11* (REF.[20]). Both *CASC8* and *CASC11* are upstream of *MYC*, an oncogene known to be regulated by lncRNAs[84]. This observation could imply a similar mechanism to that of the lncRNA *CDKN2B-AS1*, whereby genetic variants affect regulation of senescence-related genes via lncRNAs.

Telomere-related genetic variants

Four unique genetic variants mapped to the telomerase gene *TERT* have been associated with breast, colorectal and prostate cancer risk in GWAS[76,77,83]. Telomerase is involved in telomere maintenance, the end fragments of chromosomes that shorten with each cell cycle. Telomere shortening is a major contributor to replicative senescence[85] and therefore a biological hallmark of ageing (BOX 2). In humans, telomere length measured in blood has a strong inherited genetic component, with heritability estimates of 34–82%[86]. GWAS have linked 16 inherited variants to human leukocyte telomere length[87], including variants in the genes encoding telomerase and telomere-protective protein genes (*TERC*, *TERT*, *NAF1*, *OBFC1* and *RTEL1*)[88]. A `Mendelian randomization` 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[87], suggesting a trade-off between risks of cancer and chronic age-related disease. No association was found between the genetic predisposition to longer telomeres and parental longevity[21], which raises the possibility that the positive and negative effects on health 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[89].

Mendelian randomization

A method that uses single-nucleotide polymorphisms associated with an exposure as instruments to probe the causal nature of the relationship between this exposure and an outcome of interest.

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 (REF.[90]). GWAS have implicated the *SH2B3* locus and nearby genes (*ATXN2* and *BRAP*) in many diseases[39,83,91]. The likely causal variant in *SH2B3* associated with shorter parental longevity[29,92] is a missense variant (*rs3184504-T*) predicted to disrupt LNK protein functioning. The T allele is more common in autoimmune and cardiovascular conditions[93] and myeloproliferative cancers[90] as well as breast, colorectal and lung cancers[94] (compared with the 'normal' functioning C allele). By contrast, the C allele of *rs3184504* is more common in the offspring of longer-lived parents (those reaching the longest-lived 10%[29] and 1% of lifespans[95]). A GWAS of human blood protein levels[96] found that the *rs3184504* C allele is associated with reduced levels of vascular cell adhesion protein 1 (VCAM1), which functions in leukocyte recruitment in the cellular immune response and in angiogenesis[96], and influences the development and spread of cancers[97]. Interestingly, the *rs3184504* C allele is also associated with an increased cardiovascular risk[39,91] and yet with a decreased cancer risk[83], 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 1 (IGF1) and energy balance signalling modulator. An *SH2B* loss-of-function mutant was shown to be long-lived under starvation conditions as a result of increased carbohydrate stores[98]. Modifications to the IGF pathway in model organisms, from worms to mice, produce dramatic lifespan extensions akin to those seen in dietary restriction experiments[99,100] (BOX 1). However, whereas the human *SH2B1* and *SH2B2* homologues of *SH2B* are important for IGF1 signalling, *SH2B3* is not an important IGF1 regulator[101]. The *SH2B3* locus is therefore clearly important in human ageing but likely through more specialized mechanisms than those targeted in *SH2B* model organisms of ageing, underlining the need for caution in generalizing from ancestral genes in model organisms to humans.

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[102]. Genetic variants near *HLA-DQA1* are associated with Alzheimer disease[22], lifespan[31], prostate cancer[77] and T2DM[20], and also alter levels of the circulating inflammation marker C-reactive protein[103]. An HLA variant has also been linked to low muscle strength[54], 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 similarly, genetic variants in the *ABO* locus have been associated with T2DM[20], breast cancer[76] and stroke[91] as well as altered levels of the circulating inflammation marker C-reactive protein[103]. ABO antigens, which determine blood group types, are expressed on a wide range of tissues and cell surfaces and are important in infectious disease susceptibility, tumori-genesis and cardiovascular disease[104]. In each study, the O (recessive) blood type was protective later in life (compared with the other blood groups) but also

seemed to increase the risk of haemorrhages at younger ages[104], an apparent example of `antagonistic pleiotropy` (BOX 3).

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.

Obesity, T2DM and cancer loci

Variants in the *TCF7L2* locus are linked to T2DM[20], breast cancer[76] and colorectal cancer[83]. TCF7L2 is involved in β-cell proliferation and insulin production[105], and variants in this locus are also associated with increased obesity[106], which itself is a driver of T2DM and many cancers[107]. Other multi-trait loci are also linked to T2DM and multiple cancers, including *ZMIZ1* (REFS[20,76,83]), *VEGFA*[20,77] and *FTO*[20,76] (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[69] and the success of caloric restriction in lengthening the lifespan in many laboratory models (BOX 1).

Inferring ageing mechanisms from mutations

The integrity and maintenance of the genome seems to be strongly connected with ageing 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 is associated with phenotypes of ageing and contributes to chronic diseases.

Single-gene disorders of accelerated ageing

Segmental progerias are genetic diseases that exhibit many clinical manifestations similar to those that develop with ageing but that manifest earlier in life[108]. 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 indications on the genetic and biological mechanisms that drive the ageing process.

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[109]. Interestingly, cells from patients with Werner syndrome exhibit a shortened replicative lifespan[110]. 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[111]. Patients with Cockayne syndrome display photosensitivity and developmental failure after 1 year of age, under-represented subcutaneous adipose tissue, premature decline of cognitive function and cardiovascular pathology, leading to a median survival of approximately 12 years[112].

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[113]. 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[109]. More than 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[114]. 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 mechanisms such as DNA double-strand break repair[114]. 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 hetero-chromatin similar to what is often seen in fibroblast nuclei from older persons[115]. Small amounts of progerin accumulate with normal ageing and may contribute to age-related cardiovascular diseases[116]. Finally, Cockayne syndrome is caused by mutations in the *ERCC8* and *ERCC6* genes, respectively, encoding the CSA and CSB proteins, which play central roles in the transcription-coupled nucleotide excision repair that occurs at specific secondary DNA structures[117].

Overall, prototypical progerias suggest that progressive loss of genetic and genomic integrity contributes to the ageing process. So far, data on progerias indicates that mechanisms of DNA repair and maintenance are important for health conservation, but whether they underlie true accelerated ageing syndromes remains uncertain. 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[43] reports that variants in the Werner syndrome-associated *WRN* gene are associated with cognitive function and educational attainment[118], variants in the Hutchinson–Gilford-associated *LMNA* gene are associated with white blood cell counts[42] and height[42], and variants in the Cockayne syndrome-associated *ERCC8* gene affect age at smoking initiation[119]. No variants in *ERCC6* have reached genome-wide significance in studies published in the GWAS Catalog (as of 19 July 2019).

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[120]. The main homozygous *HFE* p.C282Y mutation, which is present in approximately 1 in 150 people of Northern European ancestry, is associated with increased incidence of arthritis, T2DM and liver disease[121], typically after the age of 40 years, as well as low muscle strength and chronic pain in those aged 60–70 years[122]. 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. If so, this disease supports the antagonistic pleiotropy theory of ageing, being a variant selected to enhance reproduction but that has adverse effects later in life (BOX 3). More work is needed to identify other mutations with later life effects[123], including rare mutations.

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[124]. 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` of mutated cells[125]. Stem cells generate new cells for tissue repair or remodelling, and somatic mutations in stem cells therefore 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[126].A study of human B lymphocyte somatic mutations, in both coding and regulatory regions, found <500 mutations per cell in neonates, rising to >3,000 per cell in centenarians[127]. Similar accumulations of somatic mutations with age have been reported for satellite cells in muscle[128]. Moreover, 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[129,130]. There is some evidence that clonal expansion of somatic mutations in haematopoietic stem cells is associated with an increased risk of cardiovascular diseases and leukaemia[131], 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 haematopoietic stem cells did not compromise 10-year survival[132].

Clonal expansion

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

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[133]. 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 hetero-plasmy[134]. Maternally inherited mtDNA variants can cause mitochondrial diseases[135]. Interestingly, inherited mitochondrial diseases are often characterized by progeroid characteristics, such as neurodegenerative and neuromuscular manifestations[136], suggesting that mitochondrial dysfunction contributes 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[137–139]. 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[140]. This accumulation of mtDNA variants may cause many of the phenotypes

of ageing, including metabolic, neurodegenerative and neoplastic diseases[140]. 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 a reduced lifespan and early development of ageing phenotypes[141]. 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[142,143].

Conclusions and future perspectives

Despite still being in the early phases of genetic discovery, available evidence supports an emerging picture of human ageing being driven by a balance of damage and repair processes, influenced by both environmental exposures and genetic variation between people (FIG. 4). Although the hallmark pathways of ageing have been identified mainly in animal models[144], a role for some of these mechanisms is evident in GWAS results: several multi-trait loci, including *CDKN2A/B*, *SH2B3* and *TERT*, as well as inflammation-related 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 (FIG. 4). DNA repair mechanisms have emerged as important for female reproductive ageing as well as being key in progeria syndromes, and evidence is accumulating that unrepaired somatic mutations may be of fundamental importance in human ageing.

In addition to multi-trait loci, many variants that exhibit disease-specific effects are important in how humans age. For example, the vascular disease effects of lipid-altering variants or the cartilage-specific variants involved in osteoarthritis[19] suggest that both ageing mechanisms and disease-specific mechanisms are important in human ageing. Disease-specific genetic and environmental risks help explain the great variability of ages at disease onset 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 an increase of 3–5 years in life expectancy[31]. Although this observation is promising, this variation constitutes only a small proportion of the variation seen in the human lifespan. Additionally, 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[145]. The effects of some of the multi-trait loci highlighted may be through distinct, ‘tagged’ 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[146]. It seems probable that much more evidence of ageing pathways will be found, including novel pathways that could provide intervention targets or offer new prevention opportunities. There remains ample scope for using inherited variants to understand human ageing mechanisms. Overall, human genetics will likely continue to provide growing insights into how we age and play a major role in identifying ways in which we might slow ageing, thus helping more people to age well.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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.

Targeting nutrient sensing and dietary restriction

Various genetic manipulations can markedly prolong survival in *Caenorhabditis elegans*. Long-lived genetic mutants 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 (IGF1) signalling and upregulation of autophagy[147]; *eat-2* codes for a defective nicotinic acetylcholine receptor, causing impaired pharyngeal pumping and a genetic form of caloric restriction[148,149]; knockdown of *ife-2* increases lifespan by downregulating protein translation[150]; and knockdown of the clock gene *clk-1* affects longevity by impairing mitochondrial electron transport chain activity, thereby reducing oxidative stress[151,152]. However, only the modulation of insulin–IGF1 (via daf-2) shows an increased healthspan and, in all four long-lived mutants, the period of frailty is disproportionally extended compared with lifespan[153].

Restricting calorie intake while maintaining necessary micronutrient intakes produces lean animals and improves functioning and lengthens life in many but not all mouse strains[154]. Dietary restriction increases longevity by modulating the expression of growth factors, such as IGF1, and affecting the mammalian target of rapamycin (mTOR) and ribosomal protein S6 kinase (S6K) signalling pathway[155]. The effectiveness of dietary restriction in promoting healthspan and lifespan seems to be evolutionarily conserved in yeast, worms, flies and some mouse strains[154]. 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[156]. Nevertheless, whether such positive effects of metabolic controls are strong enough to affect longevity remains unclear.

Caloric restriction in healthy, non-obese humans has beneficial effects on multiple cardiometabolic risk factors, might prevent decline of memory and is associated with the slowing down of a proxy biomarker of biological ageing[157–159], 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[160,161].

Targeting mTOR

The mTor signalling pathway, a central regulator of cell metabolism, growth, proliferation and survival[162], 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[163]. A human

trial of a low-dose rapamycin analogue reported enhanced immune function and a reduction in infections but the potential effect on longevity in humans is unknown[164]. The effects of rapamycin include increasing autophagy, which may counteract immune senescence by affecting energy metabolism and organelle recycling as well as the fate and function of immune cells[165].

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[82]. A targeted removal of senescent cells expressing $p16^{ink4a}$ resulted in the reversal of several features of ageing in mouse models[81]. 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[166].

Box 2 |

Proxy phenotypes of ageing

Lifespan

Lifespan, the time from birth to death, is an often-measured ageing proxy. Longevity (used here to mean relatively long lifespans, combining a variety of specific definitions) is a particularly popular ageing measure, as some long-lived people, especially centenarians, experience delayed onset of age-related diseases, with compression of morbidity into a smaller proportion of their lifespans[12]. For example, in one study of centenarians, 32% of men and 15% of women had no age-associated diagnoses at age 100 years[167]. Longevity has been defined in terms of arbitrary age cut-off points (for example, ≥85 years or centenarians) or by, for example, the longest 10% or 1% of lifespans within a specified cohort[168]. Some studies have focused on exceptional longevity in the context of long-lived families, as there is evidence of increased heritability of longevity in this context[44].

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[62] can be made from the duration of life spent without major age-associated conditions, including dementia, myocardial infarction, stroke and type 2 diabetes mellitus. 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, and kidney and liver function[169,170] — can be combined into indices that predict later clinical outcomes in ageing and can serve as proxy ageing phenotypes. Various physiological characteristics that decline with age are measurable, for example, muscle strength[171], cognitive function[172] and gait speed[173]. Measures of disability and frailty — the age-associated increase in vulnerability to stresses and adverse outcomes[174] — have also been developed.

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 DNA damage pathways related to UV light exposure. 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.

Box 3 |

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 of which 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]. Additionally, 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 variations 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 lifespan across species[183]. This theory is also consistent with the current consensus that ageing results from the accumulation of unrepaired cellular and molecular damage[2,183]. 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.

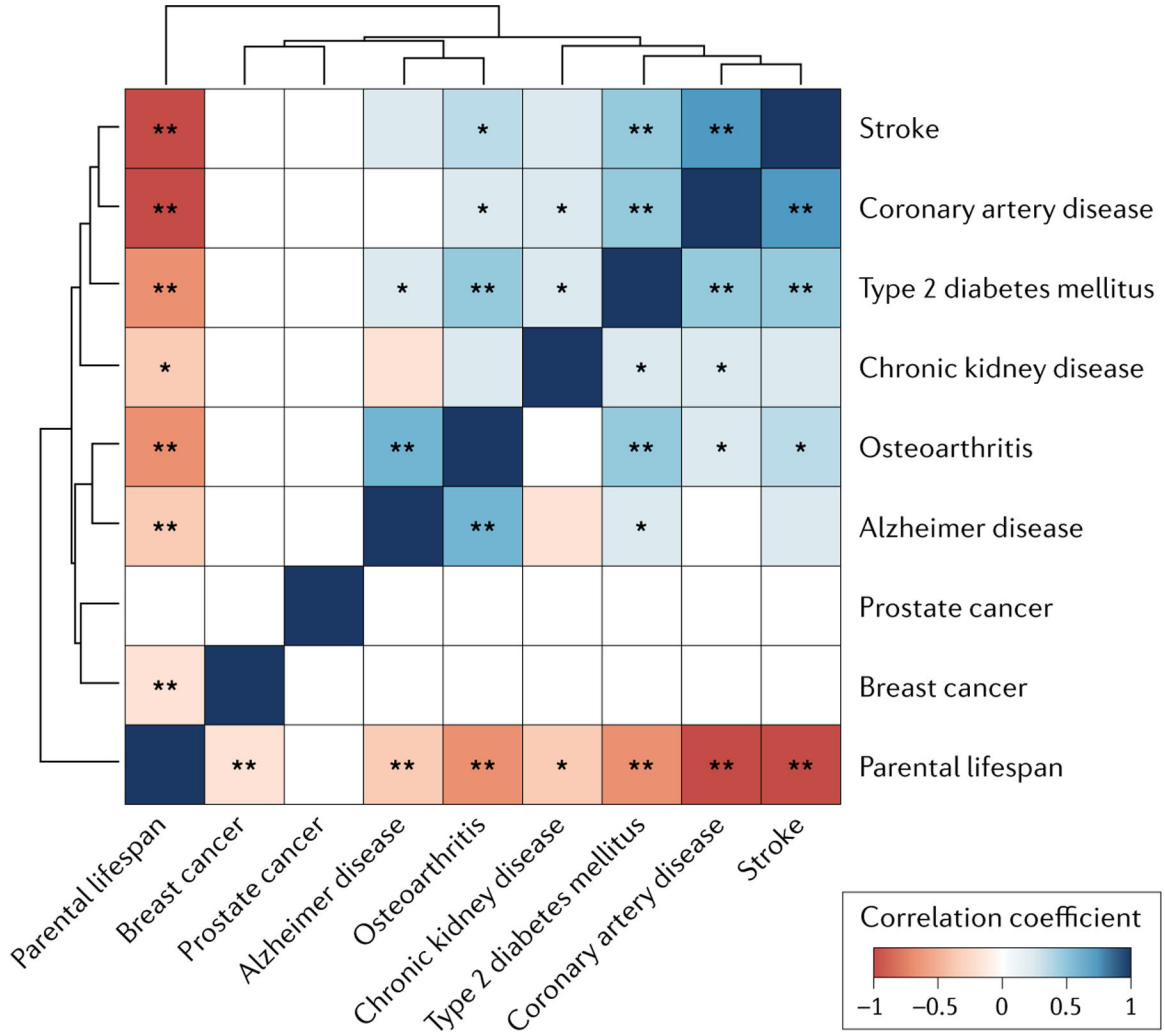

Fig. 1 |. Genetic overlap between age-related chronic diseases and parental longevity , based on correlations between whole-genome association results.

Genetic correlations are from linkage disequilibrium score regression methods using available genome-wide association study summary statistics[20,22,31,39,76,77,83,91,184,185]. 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). The diseases and parental lifespans are ordered by similarity in patterns of genetic correlations using hierarchical clustering (see Supplementary Table 3 for details).

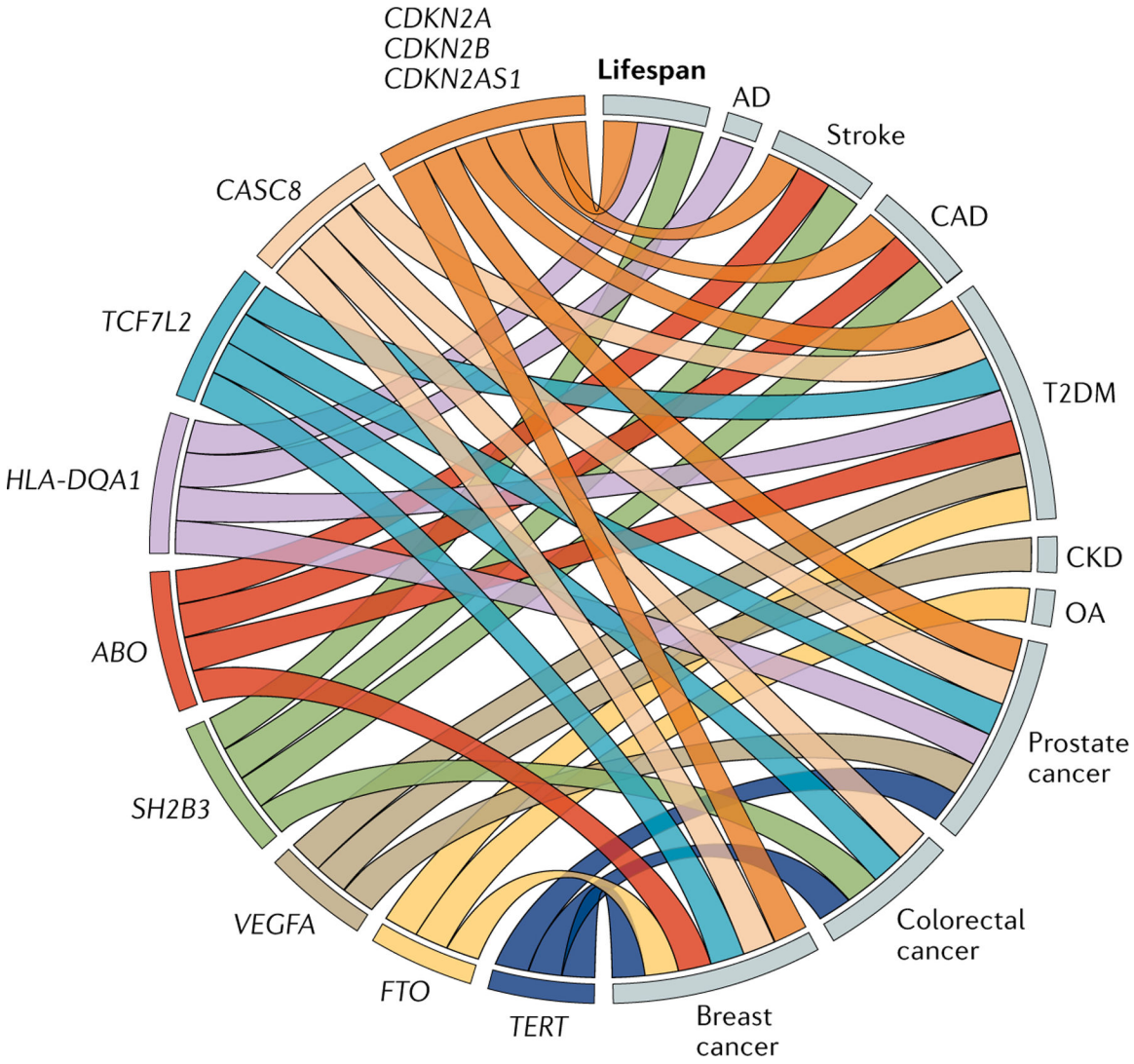

Fig. 2 |. Selected loci with correlated variants associated with three or more age-related diseases or lifespan.

Nine loci were identified as hot spots for at least three major age-related diseases or lifespan in genome-wide association studies (GWAS) that included multiple correlated (R^2 > 0.6) genetic variants[20,22,31,39,76,77,83,91,184,185] (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 refers to parental lifespan. Circos Table Viewer[186] was used for visualization. AD, Alzheimer disease; CAD, coronary artery disease; CKD, chronic kidney disease; OA , osteoarthritis; T2DM, type 2 diabetes mellitus.

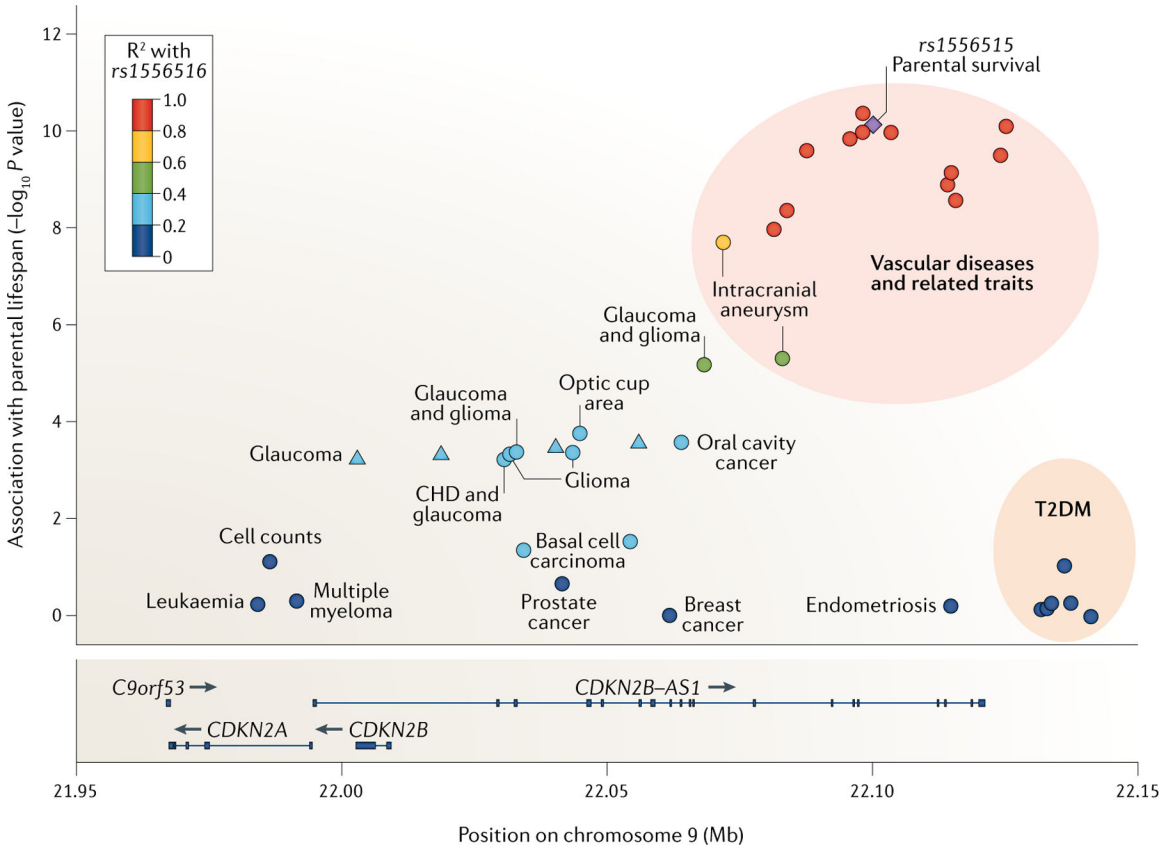

Fig. 3 |. Disease-associated genetic variants in the 9p21.3 locus by effect size of association with parental lifespan.

LocusZoom[187] plot of known disease-associated variants in the 9p21.3 locus, which harbours the genes *CDKN2A* (encodes $p16^{ink4a}$), *CDKN2B* (encodes $p15^{ink4b}$) and *CDKN2B-AS1* (encodes the long non-coding RNA *ANRIL*). Genetic variants are labelled with the traits they are reported to be associated with in published genome-wide association studies (GWAS) (see Supplementary Table 6 for details). The *y*-axis shows the association ($-\log_{10}$ *P* value) with parental lifespan from the 2019 UK Biobank and LifeGen cohort GWAS meta-analysis[31]. The variant in purple (*rs1556516*) is the lead signal at this locus from the parental lifespan analysis. The other variants are coloured according to their correlation with *rs1556516* in 1000 Genomes European ancestry data (v. Nov 2014). CHD, coronary heart disease; T2DM, type 2 diabetes mellitus.

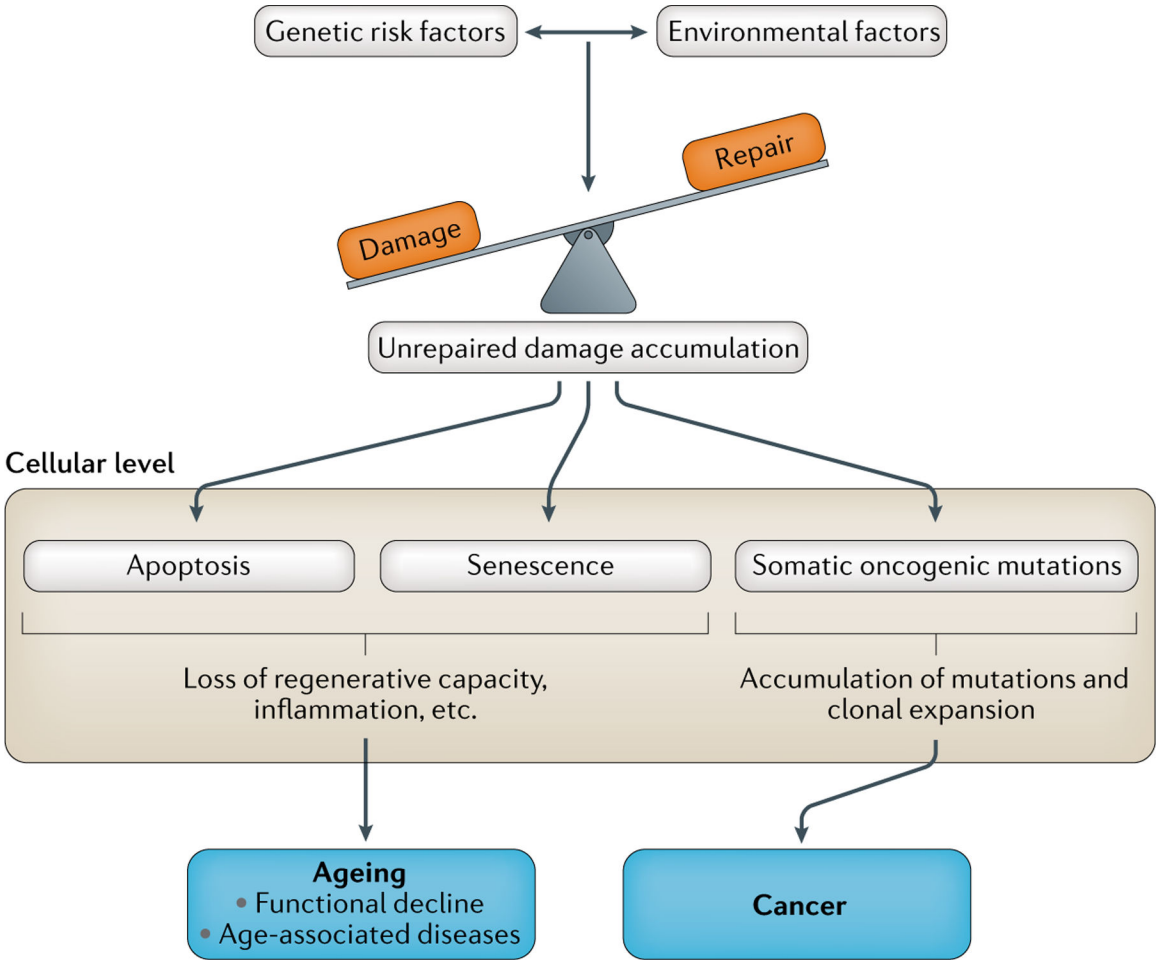

Fig. 4 |. Diagram of the major influences and mechanisms of human ageing.

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 the activity of repair and response mechanisms. At the cellular level, complete repair can yield undamaged cells (not shown). By contrast, unrepaired damage can lead to cell death (apoptosis), preventing cancers but leading to the depletion of stem cells and loss of regenerative capacity.

Cells with somatic oncogene mutations can survive and replicate, sometimes leading to tumour development. Alternatively , damaged cells can enter senescent states and produce a secretory senescence phenotype (SASP), resulting in inflammation and reduced repair that contributes to degenerative diseases5[82]. 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

rsID (effect allele)	Effect[a]	Mapped genes	Gene name	Variant position	Associated disease
Loci significant in both[b] GWAS meta-analyses[31,32]					
rs429358 (T)	1.06	*APOE*	Apolipoprotein E	Missense	Cardiometabolic, dementia
rs10455872 (A)	0.76	*LPA*	Lipoprotein A	Intronic	Cardiometabolic
rs8042849 (T)[c]	0.44	*CHRNA3/5*	Cholinergic receptor nicotinic α3/5 subunit	Intronic	Smoking related
rs142158911 (A)	0.36	*LDLR*	Low-density lipoprotein receptor	Intergenic	Cardiometabolic
rs11065979 (C)[d]	0.28	*SH2B3, ATXN2*	SH2B adaptor protein 3, ataxin 2	Intergenic	Cardiometabolic, cancer, autoimmunity[e]
rs1556516 (G)	0.25	*CDKN2B-AS1*	CDKN2B antisense RNA 1	Intronic	Cardiometabolic, cancer[e]
Loci significant only in the UK Biobank and LifeGen cohorts [31]					
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	Cardiometabolic
rs1275922 (G)	0.26	*KCNK3*	Potassium two pore domain channel subfamily K member 3	Intronic	Cardiometabolic
rs6224 (G)[f]	0.25	*FURIN/FES*	Furin, paired basic amino acid cleaving enzyme	Intronic	Cardiometabolic
rs61348208 (T)	0.23	*HTT*	Huntingtin	Intronic	NR
Loci significant only in the UK Biobank and AncestryDNA cohorts [32]					
rs7844965 (G)[g]	0.25	*EPHX2*	Epoxide hydrolase 2	intronic	NR
rs4774495 (G)[g]	0.23	*SEMA6D*	Semaphorin 6D	intronic	NR
rs599839 (G)[g]	0.21	*CELSR2, PSRC1*	Cadherin EGF LAG seven-pass G-type receptor 2, proline and serine rich coiled-coil 1	intergenic	Cardiometabolic
rs3131621 (G)[g]	0.20	*MICA/B*	MHC class I polypeptide-related sequence A/B	intergenic	NR
rs15285 (G)[g]	0.18	*LPL*	Lipoprotein lipase	3' UTR	Cardiometabolic
rs9872864 (G)[h]	0.14	*IP6K1*	Inositol hexakisphosphate kinase 1	intronic	NR

GWAS, genome-wide association study; NR , none reported; rsID, Reference SNP cluster ID; UTR , untranslated region.

[a]Effect, years added to lifespan of parents (from LifeGen analysis[31]).

[b]rsID (effect allele) and 'Effect' information from LifeGen analysis[31]. The AncestryDNA analysis may have reported a different lead SNP for the same locus.

[c] Intron variant of the *HYKK* gene in the *CHRNA3/5* locus.

[d] Variant located between *ATXN2* and *BRAP* but is correlated ($R^2 > 0.8$) with missense variant in *SH2B3*.

[e] Not exhaustive list.

[f] Located in the intron of gene *FURIN*.

[g] Significantly associated with fathers' lifespan, not mothers'.

[h] Significantly associated with mothers' lifespan, not fathers'.