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REVIEW ARTICLE

Puzzling role of genetic risk factors in human longevity: "risk alleles" as pro-longevity variants

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Abstract Complex diseases are major contributors to human mortality in old age. Paradoxically, many genetic variants that have been associated with increased risks of such diseases are found in genomes of long-lived people, and do not seem to compromise longevity. Here we argue that trade-off-like and conditional effects of genes can play central role in this phenomenon and in determining longevity. Such effects may occur as result of: (i) antagonistic influence of gene on the development of different health disorders; (ii) change in the effect of gene on vulnerability to death with age (especially, from "bad" to "good"); (iii) gene–gene interaction; and (iv) gene–environment interaction, among other factors. A review of current knowledge provides many examples of genetic factors that may increase the risk of one disease but reduce chances of developing another serious health condition, or improve survival from it. Factors that may increase risk of a major disease but attenuate manifestation of physical senescence are also discussed. Overall, available evidence suggests that the influence of a genetic variant on longevity may be negative, neutral or positive, depending on a delicate balance of the detrimental and beneficial effects of such variant on multiple health and aging related traits. This balance may change with age, internal and external environments, and depend on genetic surrounding. We conclude that trade-off-like and conditional genetic effects are very common and may result in situations when a disease "risk allele" can also be a pro-longevity variant, depending on context. We emphasize importance of considering such effects in both aging research and disease prevention.

Keywords Genetic risk factors · Trade-offs · Longevity · Aging · Physical senescence · Age-specific influence · Conditional effects · Epistasis · Gene–environment interaction · Complex disease

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Introduction

Common complex diseases, such as cancer, cardiovascular diseases (CVD), diabetes, Alzheimer's disease (AD), and some other, are major contributors to mortality in old age. One might expect that genetic factors which increase risks of such diseases would negatively affect lifespan and be less common among

long-lived people as compared to younger aged controls. A number of studies provided evidence in support of this expectation (Bonafe et al. 2002) (Benes et al. 2001; Cirulli et al. 2011; De Benedictis et al. 2001; Lescai et al. 2009; Nebel et al. 2011; Park et al. 2009, 2010; Ruiz et al. 2011). For example, it was found that the 192 QQ genotype of the PON1 (Paraoxonase 1) gene, which has been linked to a higher risk of cardiovascular events (Bhattacharyya et al. 2008), is under-represented among long-living Italians (Bonafe et al. 2002) (Lescai et al. 2009). Another study suggested that centenarians may carry fewer numbers of potentially deleterious alleles, such as rare variants of non-synonymous SNPs (Cirulli et al. 2011).

However, results of many other studies conducted over last two decades, including by authors of this paper, suggest that the presence of so called genetic "risk factors" for major diseases in individual genomes does not always compromise longevity, and that the share of such variants among centenarians is sometimes similar to that in a younger population (Galinsky et al. 1997; Mannucci et al. 1997; Schachter et al. 1994) (Bergman et al. 2007; Bladbjerg et al. 1999; Bonafe et al. 1999; Brattstrom et al. 1998; De Benedictis and Franceschi 1998; Holstege et al. 2011; Pepe et al. 1998; Yashin et al. 1999, 2001) (Beekman et al. 2010) (Freudenberg-Hua et al. 2014; Mooijaart et al. 2011; Sebastiani et al. 2011; Shi et al. 2012). For example, (Shi et al. 2012) found that of the ten most significant late-onset AD susceptibility genes that had been identified through several large genome wide association studies (GWAS), nine did not affect human lifespan, with the exception of APOE. Another recent study reported that many clinically relevant variants for cancer and other diseases, including those linked to autosomal dominant forms of pathology, are present in genomes of centenarians, suggesting that these variants are compatible with exceptional longevity (Freudenberg-Hua et al. 2014).

There may be different explanations for this phenomenon, including non-biological ones, such as flawed study design, differences in statistical approaches, publication bias, etc. There may also be real biological reasons. In this paper, we argue that trade-off-like and conditional effects of genes on phenotypes of health and aging may play a central role in the seemingly paradoxical behavior of the genetic "risk factors". We discuss several biological mechanisms of such effects, including: (i) antagonistic influences of genes on different health disorders; (ii) antagonistic effects of genes on vulnerability to death at different ages; (iii) gene–gene interaction (epistasis); and (iv) gene–environment interaction (G × E), among other factors (Fig. 1).

Trade-off-like influence of genes on different health traits

Here we discuss the situation, in which a genetic variant may antagonistically influence two or more health phenotypes. For instance, it may increase risk of one disease, while reduce risk of another health condition, or improve survival from it. In case the beneficial effect overweighs the detrimental one, the net influence of such variant on survival may be overall beneficial and compatible with longevity.

A number of studies provided evidence of epidemiological trade-offs among major complex diseases as well as suggested their underlying biological mechanisms and potential impact on longevity (Ukraintseva et al. 2010; Yashin et al. 1999, 2001, 2009) (Akushevich et al. 2013). In particular, it was consistently demonstrated that individuals with AD may have lower risk of/mortality from cancer (Driver et al. 2012; Roe et al. 2010; Tabares-Seisdedos et al. 2011; Tabares-Seisdedos and Rubenstein 2013; Ukraintseva et al. 2010; Yashin et al. 2009) (Akushevich et al. 2013). Results of genetic association studies indicate that some genes may have opposing effects on the development of cancer and AD which could contribute to the epidemiological trade-offs.

For example, one of the most extensively studied genetic risk factors for AD, the APOE e4 allele, was also found to be protective against cancer, as well as some other conditions, such as renal disease, liver damage and disability (Finch and Morgan 2007; Kulminski et al. 2011)(Hendrie et al. 2014; Kulminski et al. 2008). The trade-off-like influence of APOE on different health traits may partly explain why some studies could not find a significant association of the APOE polymorphism with longevity (Bader et al. 1998; Galinsky et al. 1997) (Kulminski et al. 2011). The effects of APOE can be modulated by age, sex, ethnicity and other factors, which will be discussed later.

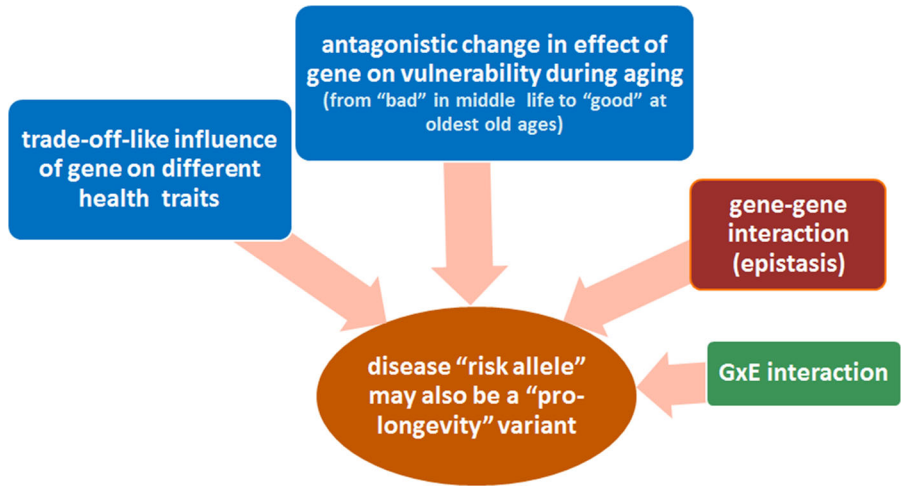

Fig. 1 Trade-off-like and conditional effects of genes on health and aging related traits might explain why genetic "risk factors" for major diseases do not always compromise longevity

Another broadly studied functional polymorphism, C677T ($Ala^{222}Val$) of the MTHFR (Methylenetetrahydrofolate reductase) gene, was also shown to antagonistically influence risks of AD and cancer. The 677T allele corresponds to an enzyme with reduced activity, and homozygous 677TT individuals have higher blood homocysteine levels similar to that observed in low dietary folate intake. The 677T allele or TT genotype showed an inverse association with risks of colorectal cancer (protective effect) and AD (promoting effect) in a number of studies, including meta-analyses (Hua et al. 2011) (Huang et al. 2007) (Peng et al. 2015) (Hubner and Houlston 2007). The antagonistic role of 677TT was also suggested for different types and localizations of colorectal tumors. E.g., the TT genotype was associated with increased risks of proximal colon cancers and decreased risks of distal cancers (Iacopetta et al. 2009; Levine et al. 2010), with the overall effect being protective. As for longevity, the 677TT genotype showed slightly beneficial albeit non-significant effect on all-cause mortality in two large population-based studies (Husemoen et al. 2014; Yang et al. 2012). These results indicate that the risk-promoting and protective effects of the 677TT may offset each other, or the beneficial effect may even prevail in certain environments, which could potentially explain why this "risk genotype" for AD is often found in similar frequencies in the elderly and young people or enriched among the long-lived individuals in some study populations (Galinsky et al. 1997) (Chen et al. 2014b).

It is important to note that G × E may significantly modify the relationship between genetic polymorphism and health outcomes. For example, the protective effect of the MTHFR 677TT genotype on colorectal tumors can be strengthened in individuals with high dietary folate and low alcohol consumption, while low intakes of folate, methionine, vitamins B12 and B6, and high alcohol consumption (which depletes 5-methyltetrahydrofolate) may actually increase the risk of colon cancer in those with 677TT genotype (Chen et al. 1996; Iacopetta et al. 2009; Ma et al. 1997; Slattery et al. 1999; Ulrich et al. 1999). This indicates the potential of lifestyle interventions to reduce the disease risk attributed to genetic background. The G × E impact on longevity will be further discussed in a separate section below.

Many other genes currently known as disease "risk factors" were found to be protective against some serious health problems. For example, ACE (angiotensin I converting enzyme) causes blood vessels to narrow sending the blood pressure up, and the I/D polymorphism of the ACE is thought to influence this blood pressure regulation. The D allele corresponding to a higher level of serum ACE was linked to hypertension and more consistently to myocardial infarction (MI) (Rigat et al. 1990) (Cambien et al. 1992) (Higaki et al. 2000) (Chen et al. 2013). At the same time, a diminished risk of

AD in DD genotype carriers was reported in several studies (Wang et al. 2006) (Alvarez et al. 1999) (Lehmann et al. 2005). Overall, available evidence indicates that the ACE I/D polymorphism may influence multiple health traits, sometimes in opposite directions, also depending on age and interactions with other genes, such as APOE (Wang et al. 2006). In case the deleterious and beneficial effects of ACE variants offset each other, or the beneficial effect prevails, the frequencies of ACE D allele (genetic risk factor for MI) may be similar or even higher in centenarians compared to younger controls, which is often observed in real data (Garatachea et al. 2013; Zajc Petranovic et al. 2012; Faure-Delanef et al. 1998).

Another established risk factor for CVD, lipoprotein (a) [Lp(a)], also shows a trade-off-like influence on major human diseases. Its elevated plasma levels are considered to be an independent risk factor for premature CHD, stroke and peripheral artery disease (Dahlen 1994; Enkhmaa et al. 2011; Erqou et al. 2009). Several LPA [lipoprotein, Lp(a)] genotypes, which result in elevated Lp(a) levels, were shown to increase the risk of CVD (Clarke et al. 2009). However, some of these genotypes were also found to be protective against cancer and other *non-CVD* disorders (Hsieh Wu 2011; Sawabe et al. 2012). This indicates that the impact of the "risk genotypes" for CVD on *all-cause mortality* and longevity may not necessarily be detrimental. This possibility is supported by research on associations of Lp(a) blood levels with longevity and various health disorders. An earlier study reported that mean Lp(a) levels are about the same in centenarians and younger controls; moreover, a quarter of healthy centenarians had the Lp(a) levels that might put them at risk for atherosclerosis (Baggio et al. 1998). The authors concluded that either Lp(a) level is not a risk factor for CVD in the very old, or it is offset by unknown protective factors. In a more recent longitudinal study of the Italian elderly (65–84 years of age), no significant association of Lp(a) serum levels with all-cause mortality was found (Solfrizzi et al. 2009). A meta-analysis of 36 prospective studies, with 126,634 participants in total, revealed that the high Lp(a) concentrations could indeed be considered a risk factor for CVD but not for *non-vascular* deaths including cancer deaths (Erqou et al. 2009). The trade-off-like influence of the Lp(a) on CVD and non-CVD related disorders might in part explain the lack of association of the Lp(a) levels with all-cause mortality.

Some studies also suggested that genetic variants that increase risks of autoimmune disorders may not necessarily adversely affect survival, or may even improve it, in case these variants also protect against some other serious health conditions (such as cancer or tuberculosis). For example, G allele of the +49 A/G polymorphism in the CTLA-4 (cytotoxic T lymphocyte antigen-4) gene playing a role in immunosuppression corresponds to a lower CTLA-4 expression and a higher T cell activation in response to stimuli. The G allele has been associated with increased risks of autoimmune conditions and decreased risk of overall cancer in a number of studies (Wang et al. 2015; Brozzetti et al. 2010; Ghaderi 2011; Hu et al. 2010). A trade-off-like association was also found for the tumor necrosis factor-α gene polymorphism with autoimmune disorders (such as lupus and rheumatoid arthritis) and tuberculosis (Correa et al. 2005). The higher risk of the autoimmune disorders could be a natural side effect of the enhanced immune resistance to potentially fatal conditions (tuberculosis and cancer).

Our group recently reported prominent trade-off-like effects of single nucleotide polymorphisms (SNPs) in the NRDE2 and ECHS1 genes on risks of cancer and CVD in Framingham Heart Study participants (Yashin et al. 2015). Male carriers of genotypes associated with better overall survival after age 80 had a lower risk of CVD but a higher risk of cancer at the same ages. The protective effect on CVD apparently outweighed the cancer promoting effect, so that the overall impact of these genotypes on survival after age 80 was beneficial. This study demonstrates that a pro-longevity genotype can also be a risk factor for some major disease (here cancer). This implies that strategies of increasing human longevity through increasing healthy lifespan should be personalized and consider potential trade-offs.

Studies of non-genetic risk factors for major disorders support the idea that the antagonistic influence of the same factor on different health traits can be a common occurrence and contribute to longevity. For example, a high blood cholesterol and total/HDL cholesterol ratio are considered established risk factors for CHD mortality in middle to old age (e.g., Lewington et al. 2008). In a study of about 150,000 men and women aged 20–95 years, the high blood

cholesterol levels (>248 mg/dl) did predict death from CHD (Ulmer et al. 2004). This study, however, also found that low (<187 mg/dl) rather than high cholesterol was significantly associated with *all-cause* mortality after the age 50. In research focusing on the oldest-old (85+) individuals, the lower total cholesterol (<5.5 mmol/l), as well as its larger annual decline, were associated with increased all-cause mortality, while the higher total cholesterol (≥6.5 mmol/l) was associated with longevity, owing to a lower mortality from cancer, respiratory diseases and infections (Petersen et al. 2010; van Vliet et al. 2010; Weverling-Rijnsburger et al. 1997). These results indicate that the lower cholesterol levels, being indeed protective against CHD, may not be so beneficial in relation to other common disorders and total survival, especially in the very old.

Also worth mentioning is an evidence of trade-offs between risk and survival for the same disease. For example, women subjected to hormone replacement therapy had an almost two-fold reduction in the risk of colon cancer, while similarly increased risk of dying from this same cancer in case they got it (Hartz et al. 2012; Taylor and Manson 2011). Such results indicate that it is essential to evaluate the influence of candidate genetic risk factors not only on the risk of a targeted disorder, but also on survival from it, since some risk factors for disease incidence may also influence case-fatality rates.

A general biological mechanism of genetic trade-offs is likely related to differential roles the same biological process may play in the development of various health problems. For instance, suppressed apoptosis is one of the established hallmarks of cancer (Hanahan and Weinberg 2011). It may help transformed cells to escape programmed death and thus facilitate cancer development, while increased apoptotic activity may be cancer protective. On the other hand, the increased apoptosis is a typical feature of AD, which contributes to excessive loss of brain cells in this disorder (Lee et al. 2012). If so, then genetic variants that manifest themselves in a chronically upregulated apoptosis in tissue may potentially be both cancer protective and AD promoting (discussed in Ukraintseva et al. 2010). Better understanding of underlying biological mechanisms of the genetic trade-offs, as well as specific conditions needed for their manifestation, is essential for both getting insights into the relationships between age-associated health decline and longevity, and for the development of efficient personalized prevention and treatments.

Antagonistic change in effect of gene on vulnerability to death with age: from "bad" in middle life to "good" at oldest old ages

Genes may change their impact on vulnerability to death during one's life. Here we will focus on the situation when a genetic variant can be associated with a higher vulnerability to death in middle life but may then become neutral or relatively beneficial at advanced ages (De Benedictis et al. 1998; De Benedictis and Franceschi 2006; Ukraintseva 2005; Yashin et al. 1999, 2001). The manifestation of such a variant as a risk or pro-longevity factor will thus depend on age. For a variant that changes its effect from risk promoting to protective towards extreme ages, the age-pattern of empirical allele frequency will not just increase or decline with age but rather demonstrate a non-monotonic behavior (Fig. 2). For example, in (Yashin et al. 1999) empirical frequencies of several mtDNA haplogroups followed a U-shape pattern: The frequency decreased over middle age, and then increased in the oldest-old age group, resulting in a relatively high frequency of the initially "harmful" variants among the long-lived individuals. The demographic model for such behavior of the allele frequencies corresponds to the intersection of mortality rates for populations of carriers and non-carriers of the particular allele, meaning that the initially deleterious effect of such allele on total survival can be transformed into a relatively beneficial one later in life (Fig. 2). A recent study provided an example of a SNP in the NRDE2 gene manifesting a survival trade-off: carriers of the homozygous major allele had negative effect on survival at ages before 80, while positive effect afterwards, as compared with the minor allele carriers (Yashin et al. 2015).

One should note that this type of antagonistic change in effect of genotype on vulnerability with age (i.e., from "bad" to "good") is different from the case of the antagonistic pleiotropy typically discussed in connection with the evolutionary hypothesis of aging (e.g., Kirkwood and Rose 1991). The latter addresses the situation, in which a genotype may enhance fitness early in life or during the reproductive period at the cost of increasing risks of major diseases at the post-

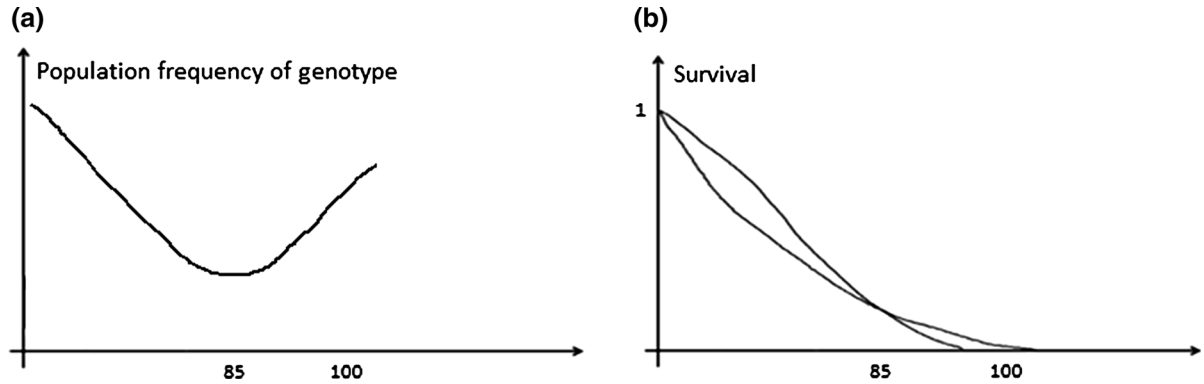

Fig. 2 Simplified illustration of potential consequences of the antagonistic change in effect of genotype on vulnerability to death with age: from increasing the relative vulnerability in middle life to decreasing it at oldest old ages (85+) (not actual data; for empirical examples see references in the text). **a** Population frequency of some "risk" genotypes may change non-monotonically (U-shape-like) with age: first decreasing towards middle-old ages, and then increasing towards extreme ages (e.g., De Benedictis et al. 1998; Yashin et al. 1999; Bergman et al. 2007). **b** Intersection of survival functions for carriers of different genotypes may occur, so that genotype with initially negative effect on survival may have positive effect later in life, at oldest old ages (e.g., Yashin et al. 2001, 2015)

reproductive period. Here we focus on a different situation, in which a gene may change its effect on vulnerability to death from relatively "bad" in middle life to a relatively "good" at oldest old ages (85+), so that this change mostly takes place in the post-reproductive period.

How may a risk factor earlier in life become neutral or beneficial at extreme ages? Several biological mechanisms could contribute to such effect. Yashin and colleagues proposed that genes that promote a higher vulnerability to death in middle life may become less harmful or even beneficial at advanced ages due to aging changes in the internal environment (Ukraintseva 2005; Yashin et al. 1999, 2001). Indeed, aging and ontogeny related transitions in the body (e.g., from growth period to reproductive period to menopause to physical frailty) are accompanied by substantial changes in metabolism, body composition and hormonal profile, which can alter the internal milieu in which genes work. In such a changing environment, genes will not necessarily have the uniform effect on the same phenotype at all ages, and a risk factor for some disease in a middle-aged body may not always be the risk factor in an older body (Robinson et al. 2013; Ukraintseva and Yashin 2001; Yashin et al. 2001). A rise and then a decline of estrogen levels in female body with age, towards menopause, could be an example of a change in internal environment with age, due to ontogeny. The higher estrogen levels at the reproductive period may increase risks of certain cancers, e.g., of female endometrial cancer; however, after menopause there are no longer high estrogen levels in the female body, so this risk factor is no longer present, and the risk of endometrial cancer declines with advancing age accordingly (Ukraintseva et al. 2008; Ukraintseva and Yashin 2003a). Similarly, a genetic risk factor for cancer that acts through the elevation of estrogen levels may cease its cancer promoting effect towards the oldest-old age. Summarizing, one could say that the age-specific effects of genes could be a product of a changing internal G × E with age, and a reason that the risk factor in middle-aged body may not always be the risk factor in an older body.

Another potential mechanism may involve antagonistic influence of a gene on disease and senescence related phenotypes (e.g., Ukraintseva and Yashin 2003b). To better understand how this property may result in changing the impact of a gene on vulnerability to death with age, especially from deleterious to beneficial, consider a hypothetical example. Suppose, there is a gene variant that chronically upregulates production of a growth factor that promotes proliferation and suppresses apoptosis, and through this it may increase the body's susceptibility to cancer. However, due to the same growth promoting and anti-apoptotic properties, this variant may also postpone or attenuate some phenotypes of physical senescence, such as

sarcopenia, muscle atrophy, physical frailty, reduced regenerative ability, slower response to infection and slower healing. Importantly, these (opposing) effects of gene variant on cancer and physical senescence may have a major impact on all-cause mortality predominantly *at different ages*. Indeed, a majority of cancers reach a peak incidence rate at ages before 80; after that cancer risk typically levels off or declines (Akushevich et al. 2012; Ukraintseva et al. 2008; Ukraintseva and Yashin 2003a). As result, cancer is major contributor to mortality at ages before 80, but at the oldest old ages (85+) its relative impact on all-cause mortality diminishes. By contrast, the risks of many senescence-related conditions that may lead to death continue to increase towards the oldest old age, so that their relative contribution to the mortality risk becomes more pronounced than that of cancer at extreme ages. Examples of relevant conditions include poorly healed hip fractures and wounds due to slow regeneration, heart failure due to muscle atrophy, renal failure due to slow metabolism, complications of COPD, flu and pneumonia due to slower immune response, and other. Since mortalities from cancer and from senescence related causes have their peaks at different ages, a genetic variant that favors cancer but attenuates physical senescence may contribute to a higher total mortality risk in middle-old life (when cancer is major contributor to mortality), while to longevity afterwards, when senescence-related causes become leading contributors to the mortality risk (Akushevich et al. 2012; Lloyd-Jones et al. 2002; Neuman et al. 2014; Ruiz et al. 2014; Ukraintseva et al. 2008, 2010; Ukraintseva and Yashin 2003a; Yashin et al. 2001).

Additional examples show that the antagonistic effects of genetic factors on disease and senescence related phenotypes, or on the same phenotype at different ages, could be a common occurrence. An earlier study conducted on the Italian population found a non-monotonic age-trajectory of the frequency of the SS genotype of 3′-APOB-VNTR polymorphism (De Benedictis et al. 1998). That is, the SS frequency in the genotype pool increased from the young group to the middle-aged group and then it declined reaching its minimum value in centenarians. Next, Garasto et al. (2004) studied a correlation between various 3'APOB-VNTR genotypes and blood lipid levels and concluded that the convex trajectory of the SS frequency could be explained by the fact that the S alleles are linked to a lower blood level of LDL-cholesterol, so that the SS genotype may be advantageous in adults by protecting them from CVD. It may, however, be disadvantageous in the very elderly, when the cholesterol level naturally declines, and its excessive lowering, below a critical threshold, could adversely affect tissue regenerative ability and increase mortality associated with a slower regenerative response due to aging (De Benedictis et al. 1998; De Benedictis and Franceschi 2006; Garasto et al. 2004).

A meta-analysis of published studies found that carriers of the Pro/Pro genotype of TP53, corresponding to a reduced apoptosis in cells, have an increased cancer risk compared to Arg/Arg genotype carriers (van Heemst et al. 2005). The same authors conducted a prospective study of individuals aged 85+ and found that carriers of the Pro/Pro genotype had a significantly increased proportion of cancer deaths. Surprisingly, they also had a significantly increased overall survival (by 41 %), together with decreased proportion of deaths from other causes such as chronic obstructive pulmonary disease (COPD), renal failure, dementia, fractures and senility, which typically accompany physical senescence (van Heemst et al. 2005). That is, the Pro/Pro genotype showed a trade-off-like influence on cancer and senescence related phenotypes. These results indicate that cancer treatment that enhances apoptosis among carriers of the Pro/Pro genotype may promote their survival from cancer but increase risk of death from other aging related disorders.

Elevated levels of plasminogen activator inhibitor-1 (PAI-1) have been linked to CVD and metabolic syndrome (Coffey et al. 2011; Leander et al. 2003). In accord, the 4G4G genotype of the PAI-1 gene, which is associated with a high plasma level of PAI-1, was linked to increased risk of atherothrombosis and MI, as well as to oral cancer, in several studies (Vairaktaris et al. 2006) (Gong et al. 2012) (Vylliotis et al. 2013) (Nikolopoulos et al. 2014). However, the frequency of the PAI-1 4G4G genotype was found to be similar in older (85+) and younger (<65) individuals (Heijmans et al. 1999) (Bladbjerg et al. 1999), or even higher in centenarians compared to younger controls (Mannucci et al. 1997) (Mari et al. 2008). Importantly, in Heijmans et al. (1999), the risk of fatal heart disease was significantly increased in elderly men (85+) carrying the 4G/4G genotype, while the risk of all-cause mortality was not increased at all (RR = 0.9,

95 % CI 0.7–1.1). This indicates that the 4G4G genotype is still a disease risk factor in the very old, but this is compatible with longevity. One potential explanation could be that the 4G/4G genotype may protect older people against another fatal disease or senescence related condition with high impact on the oldest old mortality, so that the deleterious and beneficial effects can offset each other. Results of several studies suggest that this might be the case: increased PAI-1 levels were shown to reduce chances of fatal bleeding and improve wound healing (Iribarren et al. 2008; Iwaki et al. 2011). The latter can be essential for survival at older ages, when the body's resistance to damage deteriorates and recovery slows down. Since medical treatment of the 4G/4G carriers from fatal heart disease may change this delicate balance, one should consider interventions that do not compromise total survival.

Several groups reported changes in the effect of a gene (from deleterious to neutral or beneficial) on the same health trait with increasing age of study participants. For example, Kulminski et al. reported age-dependency of the effect of APOE e4 allele on onset of CVD in the Framingham Study sample (Kulminski et al. 2013). The authors showed that the e4 allele was a risk factor for CVD at ages before 76 years in women, but a rather protective factor at older ages (76+). In a study of the IRF4 (interferon regulatory factor 4) gene polymorphism (Duffy et al. 2010) found that the T allele of the SNP rs12203592 was associated with high melanocytic nevus counts in young adults, but with low counts in older adults. Since a high melanocytic nevus count is considered to be a predictor of melanoma risk, these results suggest that younger people may have higher risk of melanoma than older ones owing to the same allele. Another study showed that a mutation in a gene for haemochromatosis was linked to various diseases in middle age; however, no association with morbidity, all-cause and cause-specific mortality has been found for the same mutation in the oldest-old age group (85+) (van Aken et al. 2002).

Results of many studies also suggest a high prevalence of trade-off-like and age-specific effects of *non-genetic* factors on various health traits. Below are few examples, which provide additional insights into mechanisms of respective genetic effects. A downregulation of IGF-1 has been associated with both cancer protection and cardiovascular risks (Bartke 2012; Conti et al. 2011; Sonntag et al. 2012; Ungvari and Csiszar 2012). The higher levels of IGF-1 were linked to both cancer and an almost twofold reduction in the risk of heart failure in the elderly (Renehan et al. 2004; Vasan et al. 2003), as well as to attenuation of other phenotypes associated with physical senescence, such as frailty, sarcopenia, muscle atrophy, and to better muscle regeneration (Vasan et al. 2003) (Conti et al. 2011; Musaro 2012; Renehan et al. 2004; Vinciguerra et al. 2010; Werner and Bruchim 2012).

A meta-analysis of 36 prospective studies exploring the effect of Lp(a) concentrations on CVD and non-CVD risks showed that the association of high Lp(a) levels with CVD steadily declined with age and remained significant only at ages below 70, but not afterwards (Erqou et al. 2009). This indicates that Lp(a) genetic variants that had been linked to a higher Lp(a) levels (Clarke et al. 2009) may also diminish their effect on CVD in advanced age.

High blood pressure is viewed as a risk factor for renal disease (Hsu et al. 2005); however, it appears to cease being such a risk factor in the oldest-old (van Bemmel et al. 2006). Also, an elevated systolic blood pressure (SBP) in older men (mean age 68 years) was associated with the lowest risk of death from *all causes* combined. The same values of SBP in the same sample were associated with a 15 times increased risk of end stage renal disease (Agarwal 2009). These results indicate that the same risk factor (blood pressure), and possibly genes that regulate its manifestation (such as ACE and other), may be involved in multiple types of trade-offs. For example, the ACE polymorphism may show age-specific influence on one health trait, and also antagonistically influence several other health traits (e.g., Hamelin et al. 2011; Helbecque et al. 2009; Higaki et al. 2000; Konoshita et al. 2001; Lehmann et al. 2005).

Another study found that the cumulative mortality from infections during 10 years of follow-up of oldest-old individuals with higher total cholesterol levels was less than half that of those with normal or lower concentrations (Weverling-Rijnsburger et al. 1997). An increased risk of dying from respiratory disease and infection is major life threat in the senescent state due to deteriorated stress responses and slower recovery (Padgett et al. 1998). An elevated cholesterol may help the body to cope better with such challenges of aging (Ravnskov 2003).

Altogether, the available evidence suggests that an age-dependency of genetic influence on health traits and survival is frequently encountered. Some genes may change their effect on person's vulnerability to death with age from "bad" to neutral to "good", towards extreme ages. Established non-genetic "risk factors", such as high cholesterol and elevated blood pressure, may also become beneficial at oldest old ages, in relation to all-cause mortality. This may seem counterintuitive, but could potentially be explained by opposite effects of genes and their products on development of some disease and senescence related phenotypes. Changes in internal G × E (e.g., due to aging and ontogeny related metabolic transitions in the body) may also contribute to the age-specific effects of genes. Environmental exposures, genetic background, lifestyle, medications and other factors may modulate the age-specific influence of genetic variants on health related phenotypes and on survival. This makes development of efficient personalized medicine a challenging problem (Schork 2015).

Epistasis and mortality selection

Genetic interactions may influence susceptibility to death and generate a mortality selection process that can change the genetic structure of heterogeneous population cohorts with age. This process may help keep "risk alleles" in the genomes of long-lived people. As discussed above, the population frequency of some "risk alleles/genotypes" may change U-shape-like with age: decrease from middle to old age, and then increase towards extreme ages (Bergman et al. 2007; De Benedictis et al. 1998; Yashin et al. 1999). There may be several reasons for this behavior. Some of them were discussed above, such as change in effect of gene on a person's vulnerability during aging (from "bad" in middle life to "good" at advanced ages) due to ontogeny and senescence related changes in internal G × E, or due to the opposite influence of gene on some disease and senescence related phenotypes. Another mechanism may involve epistasis.

The term *epistasis* broadly refers to gene–gene interaction, such as when an allele of one gene modifies the phenotypic effect of another allele at another locus (e.g., (Cordell 2002). Most relevant to the topic of this paper are epistatic interactions that can change the effect of an allele on phenotype from deleterious to beneficial upon the presence of another allele in another locus. There are several types of epistatic effects and not all of them may result in increasing the fraction of "risk alleles" among the oldest old. Also, not all of them may involve "pro-longevity" alleles as modifying gene variants. To better illustrate this, we outline several situations in which epistasis may differentially impact the age-dynamics of allelic frequencies:

(i) Assume that a certain "risk allele" in one gene interacts with another allele in another locus, and this interaction neutralizes the deleterious effect of the risk allele on disease risk or survival. Since only some carriers of the risk allele will also have the "neutralizing" allele in their genomes, while other will not, the proportion of individuals who do not carry the neutralizing allele will decline with age. The proportion of carriers of both alleles, however, is *not* expected to increase if epistasis just eliminates the deleterious property of the risk allele. The proportion of the carriers of the risk allele will decline tending to approach a constant level with increasing age.

(ii) In case the neutralizing allele also favors longevity and keeps this property in combination with the risk allele of the other gene, the proportion of the risk allele will tend to increase with advancing age. This may contribute to situations in which potentially deleterious alleles are found among long-lived individuals in similar or sometimes even higher proportions as in younger controls (Bladbjerg et al. 1999; Beekman et al. 2010; Freudenberg-Hua et al. 2014).

(iii) The epistatic interaction between the risk allele and the modifying allele in another locus may change the impact of the risk allele on vulnerability from deleterious to beneficial. In this case the proportion of individuals carrying the risk allele may increase with age so that the frequency of the original risk allele may be higher among the oldest-old compared to the middle-aged individuals. Note that in this scenario the modifying allele may not necessarily belong to the group of "longevity" alleles, although this could

happen. Other individuals who carry the risk allele in one locus and do not carry the advantageous modifying allele in the other locus will tend to die out earlier and be wiped out of the cohort.

(iv) In addition to the type of epistasis in which a "good" allele in one locus may alleviate the effect of a "bad" allele in another gene or even make such an allele protective, there may also exist a positive antagonistic epistasis, in which two *deleterious* alleles (each separately having a detrimental effect on phenotype) may become less deleterious, neutral, or even beneficial when acting together. This type of epistasis may also contribute to a presence of "risk" alleles in genomes of long-lived people.

Research on the role of epistasis in determining human longevity has been rather limited in the past; however evidence of a significant impact of genetic interactions on health and survival is quickly growing in both human and animal studies (Tan et al. 2002; Gregersen et al. 2006; He et al. 2010; Moore 2003; Yamamoto et al. 2009; Trindade et al. 2009; Snitkin and Segre 2011; Niemi et al. 2005; Napolioni et al. 2011a, b; Jazwinski et al. 2010; Tan et al. 2013). Below are several examples of studies suggesting that "risk" variants may become less damaging, neutral or even beneficial in aged humans, as result of gene–gene interaction.

Genetic interactions that significantly contribute to human longevity have been found between SNPs in FOXO1A and FOXO3A genes (Tan et al. 2013). Zeng et al. (2010) reported that the positive effect of FOXO3A and negative effect of FOXO1A on longevity may largely compensate each other if one carries both, though the positive impact of FOXO3A was overall stronger.

It was suggested that individuals with exceptional longevity may carry "risk" alleles for common diseases because the detrimental effects of such alleles may be "buffered" by beneficial pro-longevity alleles in other genes (Bergman et al. 2007). The authors provided examples of the "buffering" pro-longevity genotypes (CETP VV, APOC3 CC), as well as the "buffered" ones (potentially deleterious alleles of KLOTHO and LPA genes). In a more recent paper, the U-shaped frequency curve for the MTP CC genotype (i.e., a lower frequency at ages 55–85, and a higher frequency in those who lived 90+) was explained in terms that the MTP CC is a deleterious genotype which is "buffered" by any of the three "longevity" genotypes of CETP, APOC3, or ADIPOQ (Huffman et al. 2012). In these examples, a pro-longevity variant could "buffer" the negative effect of the risk allele as result of epistasis.

A case of a positive antagonistic epistasis was explored by Mansoori et al. (2012) who found a significant association of the C allele of rs1801131 polymorphism in the MTHFR gene with AD. They also found a significant association of the C allele of another SNP rs1800795 in IL-6 gene with vascular dementia (VaD), where the CC genotype increased the odds of VaD by 2.2-fold. However, the presence of the CC genotype of rs1801131 (in the MTHFR gene) *nullified* the detrimental effect of the CC genotype of rs1800795 (in IL-6 gene) in carriers of the two genotypes (Mansoori et al. 2012). Another study found that deleterious effects of single variants in the ADRB2 and ACE genes on the risk of MI can be altered by interactions between the two genes (Kulminski et al. 2010).

With a rapidly increasing number of relevant studies, the role of epistasis in determining human longevity should soon be supported with a larger pool of direct evidence. Also, an important issue for personalized prevention and developing pro-longevity interventions is to better understand how the epistatic effects on human health and lifespan are modulated by age, gender, and internal and external exposures, including medications.

Gene-environment interaction and other factors

The G × E determines the "norm of reaction"—the range of phenotypic manifestation of a genotype across the possible range of environments. Some genotypes may significantly vary in their phenotypic manifestation between different environments, and the same genetic variant may sometimes behave as "risk allele" in one environment and as neutral or protective factor in another. Figure 3 illustrates this with a hypothetical example of the change in G × E over time. In this figure, the effect of genotype on phenotype (e.g., disease risk) is different in different period-specific environments, and it may change over

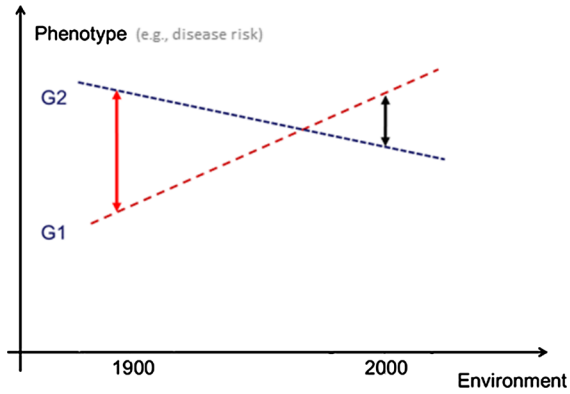

Fig. 3 A hypothetical example of the change in G × E interaction over time. The G × E determines the "norm of reaction"—the range of possible phenotypic manifestations of a genotype across different environments. It can contribute to situations in which the genotype behaves as a risk factor for a disease in one environment, but as neutral or protective factor in another environment

time from beneficial (lowering the risk) to detrimental (increasing the risk), and vice versa. Similarly, the effect of genotype on phenotype may change over place (due to population-specific environments), gender (due to differences in both GxG and G × E interactions between males and females) and age (due to changes in both internal and external environments occurring during aging). The G × E interaction is an important factor contributing to a highly conditional character of genetic influence on longevity and to a lack of replication in genetic association studies. Indeed, if a genetic variant increases risk of some major disease in certain environment today, this environment may be different from that experienced by the long-lived people in the past, so that this variant may not necessary pose the same risk to its long-lived carriers over the course of their lives.

Probably most "extreme" examples illustrating the high importance of the G × E in determining lifespan come from Mendelian disorders. For example, phenylketonuria (PKU) is a well-known autosomal recessive genetic disorder characterized by a mutation in the PAH gene encoding the enzyme phenylalanine hydroxylase. The PKU can lead to severe intellectual disability and other serious medical problems when affected children are allowed to eat common food. However, when treated with a strict phenylalanine-restricted diet, PKU patients can have a normal lifespan with normal mental development (van Spronsen 2010). That is, the effect of this Mendelian mutation can be nullified by a G × E due to dietary change. This reminds that even genetic mutations with high penetrance and potentially dramatic impact on health may significantly vary in their expressivity and therefore in the effect on lifespan upon presence or absence of certain environmental factors.

In previous sections we mentioned the role of internal G × E in age-specific influence of genes on vulnerability to death, among other factors. Here we emphasize the role of the G × E in population-, exposure-, sex-, and generation- specific effects of genes. Such effects can be of mixed origin, and involve both genetic and non-genetic causes, such as differences in study design, statistical approaches and population structure, but they can also be due to G × E. Since G × E is a broadly observed phenomenon in genetic association studies, with thousands of relevant publications, here we will provide only few representative examples suggesting that G × E can be major contributor to a highly conditional character of genetic influence on health and lifespan.

Interactions between genes and life style exposures such as smoking and diet may significantly modify the health effects of genetic polymorphisms that have been implicated in longevity. It was shown, for example, that the impact of the APOE e4 allele on dementia can be modified by exposure to tobacco smoking in a rather non-expected way. Smokers were at relatively decreased risk of cognitive deterioration in e4 carriers, but the risk was increased in non-carriers (Dufouil et al. 2000). In a large sample of a Mediterranean population followed up over a 10-year period, saturated fat intake substantially modified the effect of the APOE polymorphism on CHD risk. When saturated fat provided less than 10 % of energy, no significant association between the APOE polymorphism and CHD risk was observed. However, with higher intake, the differences between e2 and e4 carriers became significant and pronounced (Corella et al. 2011). This result stresses a major role of diet in neutralizing the deleterious effects of the "risk" allele on health phenotypes. More recently, a study involving co-authors of this paper showed that the effect of FOXO genotypes on cognitive disability in the Chinese oldest old is strongly modified by regular tea drinking at around age 60 (Zeng et al. 2015).

In addition, the mitochondrial superoxide dismutase 2 (SOD2) gene polymorphism rs4880 (47T>C, Val16Ala) provides a good example of a highly context dependent effect of genetic variation on health and survival. It has been shown to influence multiple health disorders, with frequent trade-offs and outcomes that can be substantially modified by both G × G and G × E. For example, no associations of colorectal, breast and prostate cancer risks and survival with the rs4880 polymorphism were found in several large studies (Blein et al. 2014; Chen et al. 2014a). However, G × E appears to modify the effect of this polymorphism on cancer. The CC (Ala/Ala) genotype may negatively affect survival of breast cancer patients who received cyclophosphamide chemotherapy (Glynn et al. 2009). The higher iron and low vegetable intake in TT (Val/Val) carriers was associated with increased risk of aggressive prostate cancer (Choi et al. 2008). In Greek-Cypriot women, high fish and vegetable intake reduced breast cancer risk in TT genotypes (Kakkoura et al. 2015). As for other diseases, the TT genotype was associated with CHD in females but not males (Jones et al. 2010), and with CHD in hereditary hemochromatosis patients (Valenti et al. 2004), thus suggesting a GxG impact. As for the C allele, a meta-analysis and smaller studies concluded that it has protective effects on risks of diabetes and its complications (Nakanishi et al. 2008; Tian et al. 2011). However, there is also substantial evidence of the negative impact of the C allele on survival of people in critical condition. The C allele was associated with significantly higher frequency of septic shock among critically ill patients (Paludo et al. 2013). This frequency was highest for patients with both the SOD2 47C and glutathione peroxidase 593T allele as compared with other genotype combinations, thus suggesting additional impact of GxG on the rs4880 manifestation (Majolo et al. 2015). The multiple conditional and trade-off-like effects of rs4880 polymorphism on different health traits could be a reason that no consistent influence of this polymorphism on human longevity was found. Specifically, only moderately decreased mortality in individuals with the C allele (HR = 0.91) was reported in a Danish cohort (Soerensen et al. 2009); however no association was detected between the C (or T) variant and longevity in a long-lived sample of the German population (Gentschew et al. 2013).

Gender-specific effects of genes on disease risks are also very common. For example, an earlier research in the Framingham Study Offspring cohort reported an association of the APOE e4 with the age-adjusted prevalence of heart disease, which had a more pronounced effect in women (Wilson et al. 1994). A more recent study in the same cohort confirmed that the APOE e4 is a risk factor for CVD primarily in women, and also found that it can be protective against cancer primarily in men (Kulminski et al. 2013). A genetic variation in an anti-inflammatory IL-10 cytokine was shown to be associated with longevity only in male but not in female centenarians (Lio et al. 2002). Such gender effects could be due to both GxG and G × E differences between men and women. A genetic variant that negatively influences survival only in men could still be prevalent among the long-lived people because the majority of centenarians are women.

Broadly observed population-specific effects of genes also suggest the role of G × E in modifying the influence of genetic "risk factors" on health traits. In studies of Italian centenarians and other long-living people from different European regions, the association of polymorphism in IL-6 with longevity was markedly population-specific (Pes et al. 2004) (Di Bona et al. 2009). As mentioned above, elevated Lp(a) blood levels have been linked to a higher risk of CVD in many studies. Respectively, the LPA gene polymorphisms that increase the Lp(a) levels were thought to increase CVD risk as well. However, this was not the case for at least some populations (Enkhmaa et al. 2011; Qi et al. 2012). This indicates that the LPA variants may be genetic "risk factors" for CVD only in certain environments. These results may also indicate that the association between Lp(a) level and CVD could be because of confounding, or inverse causation. Estimates of direct associations of the LPA variants with disease risk are needed to evaluate the causality of the genetic influence. The 4G4G genotype of PAI-1 (Plasminogen activator inhibitor-1), may serve as another example of the population/study specific influence of genotype on health outcomes that can vary from deleterious to neutral to beneficial in relation to the same health trait across different populations. While the 4G4G genotype was found to be protective against stroke in some populations, it was also found to have no effect or even increase the risk of stroke in other populations (Hoekstra et al. 2003; van Goor et al. 2005; Wiklund et al. 2005). Understanding factors and mechanisms responsible for the differences

in impact of the 4G4G genotype on stroke occurrence in different populations may provide useful insights into efficient personalized preventive strategies for carriers of and non-carriers of this genotype.

Generation-specific effects of genes may create a situation in which a genetic variant that increases risk of some disease in parents may become neutral or beneficial in relation to the same disease (or survival) in offspring. One of few studies on intergenerational trade-offs between health and survival traits found that the offspring of mothers with AD have increased longevity compared to the offspring of mothers without AD (Silverman et al. 2008). Period-specific G × E could contribute to these effects.

In sum, an important message from the studies discussed in this section is that the influence of genotype on health traits and longevity is often conditional and cannot be described in simple terms such as "harmful" or "beneficial". The allele showing a deleterious effect in one environment will not necessarily demonstrate this same property in other environment. The G × E could contribute to a typically poor replication of results of genetic association studies. "Longevity genes" that might help someone to become a centenarian in the past may not necessarily help to achieve extreme longevity nowadays. Long-lived people from different populations were exposed to distinct environments in their lives, so they may have different sets of genes associated with their longevity.

Concluding remarks

Genetic "risks factors" for major diseases are often found in genomes of long-lived people and do not seem to compromise longevity. The review of current evidence performed in this paper suggests that the trade-off-like and conditional effects of genes on phenotypes of health and aging could play central role in this phenomenon and in determining longevity. Such effects are common and may result in situations in which the same genetic variant can be both a disease risk factor and a pro-longevity variant.

The effect of a particular gene on a person's vulnerability to death at a given age is an aggregated outcome of increased and decreased risks of/mortalities from various conditions that are influenced by that gene in the presence of other genetic factors and the person's history of internal and external exposures. When a gene variant increases risk of certain disease, this fact itself does not guarantee that the same variant will negatively affect total survival chances of an individual because it may, in principle, be protective against some other major health disorder or senescence related phenotype. The effect of a genetic "risk factor" on a person's survival and longevity may thus be negative, neutral or positive, depending on the interplay of its detrimental and beneficial effects on multiple health and aging traits, and it can be modulated by age, internal and external environments, genetic surrounding, and other factors. If the protective effect prevails, then the frequency of such a variant may be higher in the long-lived people.

Investigating the trade-off like and conditional effects of genes is critically important both for understanding the relationships between aging, health decline and longevity and for facilitating progress in personalized prevention and treatment. Such effects have to be taken into account to develop efficient methods of personalized medicine (Schork 2015). For instance, the existence of a trade-off between cancer and AD implies that some factors that promote development of AD may potentially be protective against cancer, and that measures aiming to prevent AD may increase cancer risk in some individuals. This and similar possibilities should be considered by health policy makers, who develop both personalized and population-wide preventive strategies. In addition to reducing the risks of separate diseases, an important focus of prevention could be a reduction of all-cause mortality risk in individuals.

The highly conditional character of genetic influence on longevity is likely to also contribute to the weakness of genetic signals, and the lack of replication in genetic association studies. Different sets of genes may be activated in response to different age- and population-specific environments and exposures, so that the same health or survival outcome will not necessarily be associated with the same set of genes in the different populations or age groups.

The relationships discussed in this paper have an additional important implication for further studies of the roles of genetic factors in human health and lifespan. In particular, they indicate that an increase in sample size of study subjects, traditionally recommended in cases of the low significance, small effect sizes, and a lack of replication in GWAS, may not

always be a good strategy (e.g., Kulminski et al. 2015). Indeed, the sample size can be increased by pooling the data from several studies of independent populations. However, some genetic variants may have opposite effects on the trait of interest, e.g., due to differences in histories of environmental exposures, or due to the differences in genetic backgrounds of individuals comprising the populations. Hence, such pooling may not necessarily improve estimates of the genetic association.

Overall, the results of this review suggest that there is probably no such thing as unconditionally 'bad' or 'good' allele of a common genetic polymorphism in regard to its role in human aging, health and lifespan. Our analyses indicate that integration and coordination of studies of (i) pleiotropic, including trade-off-like, influence of genes on phenotypes of health and senescence, (ii) age-patterns of the genetic effects on individual vulnerability to death, (iii) gene–gene, and (iv) G × Es effects on lifespan, among other factors, may substantially improve our understanding of the dynamic relationships among genetic and non-genetic regulators of aging, health and longevity in humans.

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