What evidence is there for the existence of individual genes with antagonistic pleiotropic effects?

Armand M. Leroi, Andrzej Bartke, Giovanna De Benedictis, Claudio Franceschi, Anton Gartner, Eleftherios Ganos, Martin E. Feder, Toomas Kivisild, Sylvia Lee, Nesrin Kartal-Özer, Michael Schumacher, Ewa Sikora, Eline Slagboom, Mark Tatar, Anatoli I. Yashino, Jan Vijg, Bas Zwaan

Department of Biological Sciences, Imperial College London, Silwood Park Campus, Ascot, Berks., SL5-7PY, UK
Department of Physiology and Internal Medicine, Southern Illinois University School of Medicine, 80 N. Rutledge, Room 4389, Springfield, IL 62794, USA
Department of Cell Biology, University of Calabria, Ponte P. Bucci, 4C, 87036 Arcavacata, Rende, Italy
Direzione Scientifico, Instituto INRCA Via Birarelli 8, Ancona, Italy
Max Planck Institute for Biochemistry, Am Klopferspitz, 18a, Martinsried, Germany
National Hellenic Research Foundation (NHRF), 48 Vas Constantinou Ave, Athens, Greece
Department of Organisms Biology and Anatomy, University of Chicago, 1027, E 57th St, Chicago, USA
Estonian Biocenter, Riiia 23, Tartu, Estonia
339 Biotechnology Building, Cornell University, Department of Molecular Biology and Genetics, Ithaca, NY, USA
Mamura University, Faculty of Medicine, Department of Biochemistry, Haydarpaşa, 34668 Istanbul, Turkey
INSERM U488, 80 Rue du Général Leclerc, Kremlin-Bicêtre, France
Nencki Institute of Experimental Biology, Pasteur St, Warsaw, Poland
Section Molecular Epidemiology, Sylvis Laboratory, Leiden University Medical Centre, PO Box 9503, Leiden, Netherlands
Department of Ecology and Evolutionary Biology, Box G-W, Brown University, Providence, USA
Max-Planck Institute for Demographic Research, Dobernaner Strasse 114, Rostock, Germany
University of Texas Health Science Center, Department of Physiology, STCBM Building, Suite 2.200, 15355 Lambda Drive, San Antonio, Texas 78245, USA
Section of Evolutionary Biology, Institute of Biology, Leiden University, Kaiserstraat 63, PO Box 9516, Leiden, Netherlands

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Abstract

Classical evolutionary theory predicts the existence of genes with antagonistic effects on longevity and various components of early-life fitness. Quantitative genetic studies have provided convincing evidence that such genes exist. However, antagonistic pleiotropic effects have rarely been attributed to individual loci. We examine several classes of longevity-assurance genes: those involved in regulation of the gonad; the insulin-like growth factor pathway; free-radical scavenging; heat shock proteins and apoptosis. We find initial evidence that antagonistic pleiotropic effects are pervasive in each of these classes of genes and in various model systems—although most studies lack explicit studies of fitness components. This is particularly true of human studies. Very little is known about the early-life fitness effects of longevity loci. Given the possible medical importance of such effects we urge their future study.

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1. Happy gerontocrats?

Towards the end of his life, Alexander Graham Bell, inventor of the telephone, turned his hand to genetics. He was particularly interested in the genetics of longevity. He
proposed, and began, the compilation of a vast number of longevity records from Washington DC area schools. His idea was to ask children how old their parents and grandparents were and then publish the results along with their names and addresses in a document that he frankly called ‘his human stud-book’. The descendants of long-lived individuals would seek each other out, fall in love, and breed so giving rise to a “race” of exceptionally long-lived people—a true gerontocracy (Leroi, 2003, pp. 304–305).

Bell’s scheme, which was slightly mad, foundered with his death in 1922. But had it worked, what would have been the result? It is certain that his line of gerontocrats would have, sooner or later, come to be long lived—estimates place the heritability of longevity in western populations around 25% (Skytthe et al., 2003). But would selection for increased human longevity have been an unalloyed good?

Evolutionary theory suggests not. In 1957, George Williams proposed the “antagonistic pleiotropy” theory of senescence (Williams, 1957). Briefly, this theory held that ageing was due to the decline of the force of natural selection late in life, and that the fixation of alleles with positive effects upon fitness early in life also had deleterious effects late in life. These later deleterious effects are, in this view, the direct cause of ageing. Williams’s theory remained largely untested until the 1980s and 1990s when several groups of workers showed that lines of fruit-flies selected for late-life reproductive success became long-lived while also experiencing a decline in early-life fitness (fecundity, mating success) relative to lines selected for early-life reproductive success (Rose, 1984; Sgroì and Partridge, 1999). These results have been widely taken as direct evidence for the existence of antagonistic pleiotropic alleles segregating in natural populations. But this early work, which was couched in terms of quantitative genetic effects, did not identify individual loci with antagonistic pleiotropic effects. Even so, the concept of antagonistic pleiotropy has continued to inspire workers in diverse areas of gerontology. Twenty years later we ask: does evidence for such genes exist? Or, if not, what evidence is required? To answer this question we draw on studies of human longevity genes, genetic analysis in model systems and cell biological studies. Each approach has its virtues and limitations, to which we now turn.

2. Elusive antagonistic pleiotropy

Williams’s theory is concerned with the early and late-life fitness effects of alleles in natural populations. As such, the difficulties of identifying alleles with such effects are considerable. Relative fitnesses are always hard to estimate, more so in the wild. Most workers therefore content themselves with measuring fitness components such as early and late-life survival, fecundity and mating success or else measures of physiological performance such as frailty, cardiovascular health, incidence of cancer and the like. The study of human populations, which seem to have wealth of demographic data (and a wealth of longevity-assurance genes), are bedevilled by population stratification (in the case of cross-sectional studies), a lack of fertility data and the sheer length of time required to carry out the longitudinal studies that would truly carry conviction. Indeed, most longitudinal studies of longevity genes begin in mid-life and do not examine early-life fitness components at all. Furthermore, most human studies are association studies and so are always subject to the caveat that apparent pleiotropies (or even the main effect) may be due to linked loci. While it is certainly possible to measure fitness in laboratory populations of model organisms, such studies, if done at all, suffer from two objections: the alleles studied are often not natural polymorphisms but severe loss of function or even null mutants; and plush laboratory environments may obscure allelic effects that would be apparent in the wild (Zwaan, 2003).

A deeper problem is the sheer complexity and subtlety of antagonistic pleiotropic effects, or rather the relationship of gene action to fitness. A given gene may have antagonistic pleiotropic effects by virtue of the way it regulates other genes, or by the way that it is itself regulated over the course of the animal’s lifespan (Fig. 1).

Is it, then, impossible to make a case for the existence of antagonistic pleiotropy? Acknowledging the above caveats, we believe that such a case can be made. A combination of the study of natural polymorphisms in humans, genetic studies in model organisms and detailed cellular studies in vitro have, we suggest, provided persuasive evidence that at least a few molecular pathways exert antagonistic pleiotropic effects on early and late-life fitness. Here we focus on five possible sources of antagonistic pleiotropy: gonadal signals, insulin-like growth factor signals, the control of free-radical production, heat-shock proteins and the control of apoptosis.

3. The gonad speaks

Reproduction is a delicate matter. As anyone who has worked with model organisms knows, it is hard to find a mutation or environmental manipulation that does not affect fecundity—usually for the worse. Among the many mutations that affect the fecundity of Caenorhabditis elegans, some of the most interesting are those that cripple glp-1, a Notch homologue that is required for stem-cell proliferation in the germ (Crittenden et al., 2003). Such mutations produce few or no sperm and eggs and so are more-or-less sterile. Interestingly, recently it has also been found that they are long-lived (Arantes-Oliveira et al., 2002).

Why? The most obvious explanation for the antagonistic pleiotropic effects of glp-1 mutations is the ecologist’s: resource allocation trade-offs (e.g., Barnes and Partridge, 2003). Somatic maintenance (longevity) and gametes (fecundity) both require common, limiting, resources, proteins, lipids and the like. Since a resource allocated to
one trait cannot be allocated to another, “costs of reproduction” and “life-history trade-offs” and, to the degree that allocation alleles segregate in populations exist, “antagonistic pleiotropies” follow (Kirkwood and Rose, 1991).

As it happens, this explanation for glp-1’s antagonistic effects on longevity and fecundity is probably wrong (Leroi, 2001). Recently it has become clear that the gonads of the nematode worm, C. elegans, are the source of several molecular signals that regulate longevity (Hsin and Kenyon, 1999). Surprisingly, while the somatic gonad (the bag that contains the germ-line stem cells, sperm and eggs) is the source of a signal that promotes longevity, the worm’s germ line is the source of a signal that represses it.

The existence of both these signals were inferred by clever experiments in which the minute gonads of worms were ablated using laser microsurgery. A number of genes have been identified that are needed for those signals to function, but the signalling molecules themselves and their receptors are still not known (Hsin and Kenyon, 1999; Gerisch et al., 2001; Arantes-Oliveira et al., 2002). Nevertheless, the source of the germ-line signal has been shown to be the stem cells themselves (rather than differentiated sperm or eggs) and the strength of the signal is roughly proportional to the number of stem cells (Arantes-Oliveira et al., 2002).

The evolutionary function of the germ-line signal, and whether or not it can explain the traditional ‘trade-offs’ detected by ecological experiments is a matter of debate (Leroi, 2001; Lessells and Colegrave, 2001; Barnes and Partridge, 2003). Clearly, resource allocation is also underpinned by (epi)genetic effects (Fig. 1). Thus, to us
it seems just a matter of time before we can describe these genes and determine what their relationship is with the gonad signalling mechanism. To date, no one, however, disputes that it exists and that they can give rise to antagonistic pleiotropic effects of the sort shown by glp-1 alleles. Gonadal signals may, indeed, be the source of other kinds of antagonistic pleiotropies. The nematode germ-line is also the source of signal—perhaps different from the longevity signal that represses growth (Patel et al., 2000).

These results may be quite general. In Drosophila, ecdysteroids are produced abundantly in the follicle cells of the gonads, regulate fecundity, and also—it now seems—longevity (Simon et al., 2003). Humans may have such signals as well. Some data show that castration has a positive effect upon human life expectancy (Hamilton and Mestler, 1969).

4. Insulin-like growth factor signalling

Since the discovery that loss-of-function mutations in the C. elegans insulin-like growth factor receptor homologue, daf-2 spectacularly increase longevity (Kenyon et al., 1993), a great deal of effort has gone into studying the effects of IGF signalling on longevity and health in a variety of organisms. These studies have provided some of the most striking examples of antagonistic pleiotropy.

In C. elegans, insulin signalling appears to act at two stages in the life of the worm. First, during larval development it controls the formation of the stress-resistant dauer stage. Second, in adulthood it appears to regulate life-history as well, albeit in a more subtle way (Dillin et al., 2002). Most known daf-2 alleles show fitness disadvantages at both these stages. First, most known daf-2 alleles are “dauer-constitutive”, that is, they tend to form dauers even in the absence of environmental cues. Not all daf-2 larvae, however, form dauers; some become adults, and it is those adults that are exceptionally long-lived. These long-lived adults also, however, have reduced fecundity. A study of 16 independent daf-2 alleles shows a striking negative correlation between life time fecundity and longevity (Gems et al., 1998; Leroi, 2001)—as fine a demonstration of antagonistic pleiotropic effects between longevity and fecundity as one could hope to find.

The pervasive effects of insulin signalling in worms are echoed in Drosophila with the additional twist that instead of controlling a dramatic diapause state analogous to the dauer, it controls adult body size. Loss-of-function mutation in InR, an insulin-receptor homolog, and Chico, an insulin-receptor substrate homologue, increase longevity (Clancy et al., 2001; Tatar et al., 2001). These mutations have widespread effects on the fitness of the flies, dwarving them and reducing their fecundity. In both worms and flies, the pervasive effects of IGF signalling appear to be mediated by other steroid hormones. In C. elegans, both the larval dauer response and adult longevity response are mediated by daf-9, which encodes a cytochrome P450 thought to be involved in making a steroid hormone secreted in many tissues throughout the body, and daf-12 which encodes a putative receptor (Hsin and Kenyon, 1999; Gerisch et al., 2001). Analogously in flies, insulin/IGF is thought to regulate the production of juvenile hormone (Tatar et al., 2003).

Perhaps the greatest surprise of recent years, has been the finding that insulin signalling also controls ageing in mammals. Moreover, many of the antagonistic pleiotropic effects seen in worm and fly mutants are also seen in mice. The first indication for this effect came from the study of mutations that delete, to varying degrees, the hypothalamus–pituitary hormone axis. Such mutations (e.g., in the genes encoding pituitary specific transcription factors (Prop-1, Pit-1) and growth-hormone-releasing hormone receptor (Ghrhr), cause mice to be dwarfed, long-lived with reduced fertility (Brown-Borg et al., 1996; Bartke et al., 2001a,b). It was widely supposed that these mutations exercise at least some of their effects by reducing IGF signalling. However, Prop-1 and Pit-1 mutations affect multiple pituitary lineages, and hence the production of several different hormonal systems (notably thyrotrophin). More recently, however, the study of mice heterozygous for a null mutation in the Igf1r gene confirm that IGF signalling controls longevity in mammals—or at least it does in females, since males were not long-lived (Holzenberger et al., 2003; Tatar et al., 2003). Another curiosity of the long-lived Igf1r+/- females is that, extended longevity aside, they appear quite normal, being fertile and having more or less normal body size. This prompted some commentators to wonder if these mutant mice were an example of “cost-free-longevity” (Lithgow and Gill, 2003). A moment’s reflection suggests that this is unlikely to be true. IGF’s roles in the control of mammalian growth and reproduction have long been documented (Liu et al., 1993), and any mutation that cripples a major gene in this pathway would surely have deleterious fitness consequences in the wild.

The subtleties of IGF’s effects on age-specific fitness are, indeed, the focus of studies in humans. As in mice, IGF is needed for proper intrauterine and postnatal growth. During adult life, however, serum levels of IGF decline. Italian centenarians seem to have exceptionally low serum IGF levels (Barbieri et al., 2003). This is generally consistent with the evidence from worms, flies and mice that low levels of IGF during adulthood are a route to relative longevity.

One way in which low levels of IGF might promote longevity comes from its role as a mitogen. Much evidence—of varying degrees of directness—shows that an excess of IGF signalling can cause cancer. For example, people who inherit a single loss-of-function mutation in the tumour repressor, PTEN, which controls IGF-dependent PI3 kinase signalling, are prone to a rich variety of tumours. Analogously, large breeds of dogs, tall-for-age children, and acromegalics all have high IGF serum levels and high risks of cancers (Leroi, 2003, pp. 208, 378).
The costs of having low serum levels of IGF are less obvious. There do not seem to be any studies on, for example, IGF levels and fecundity. However, there is some evidence that low levels of IGF increase frailty, that is, they cause relatively weak soft-tissues and bones. If this is so, then alleles that reduce IGF signalling in young adulthood may have an initial deleterious effect increasing the risk of broken bones and the like, but ultimately have a beneficial effect in the very old (Barbieri et al., 2003).

Many human IGF signalling pathway polymorphisms have been found, and various studies have detected—with varying degrees of reproducibility—associations with bone density, growth and risk of cancers (e.g., Kato et al., 2003; Rosen et al., 2003; Rivadeneira et al., 2003). Furthermore, at least two polymorphisms, one in IGF1-R, and the other near PIK3CB, which encodes a IGF signal transducer homologous to C. elegans age-1, are associated with reduced serum levels of IGF-1 and increased longevity or at least ‘successful ageing’ (Bonafe et al., 2003). Thus while the antagonistic pleiotropic effects of any single polymorphism in a human IGF pathway gene have yet to be convincingly demonstrated, a range of evidence suggests that when such effects are sought they will be found.

Why is antagonistic pleiotropy so pervasive in the IGF pathway? Many workers argue that IGF signalling is an ancient device to control alternate life-history strategies in the face of environmental vicissitudes. The most blatant example of such an alternative strategy is the dauer stage in C. elegans. But flies and mammals also modulate their investment in growth and reproduction in response to food ration—and do so at a gain or cost to somatic maintenance. Direct evidence for the role of IGF in controlling these environmental responses remains scant (but see Tu and Tatar, 2003; Zwaan, 2003). In C. elegans and Drosophila melanogaster the importance of gene-environment interactions for interpreting the function of the INS pathway has been demonstrated by manipulating environmental conditions. Under experimental conditions designed to mimic the natural environment, age-1 (phosphatidylinositol 3-OH kinase catalytic subunit) mutants suffered a 23% reduction in fitness relative to wild type worms (Walker et al., 2000); this had remained unnoticed under “standard” laboratory conditions. Furthermore, mutants of the Drosophila homologue of IRS (insulin-receptor substrate, Chico) exhibited a longer life span only when the adults were kept on concentrated food; they showed a shorter life span than wild type flies when kept under diluted food conditions more likely to mimic their natural habitat (Clancy et al., 2002). Moreover, the Indy (I’m not dead yet, a membrane protein involved in the transport of Krebs cycle intermediates) mutation doubles the life time, but shows decreased fecundity only under caloric restricted adult food conditions (Marden et al., 2003). If these results are general, then we should not be surprised if polymorphisms in the IGF signalling pathway frequently have antagonistic effects on early and late-life fitness components.

5. Free radicals

The free-radical theory of ageing proposes that ageing is caused by the accumulated damage that reactive oxidative species inflict upon cells over the course of years. Since these molecules are produced by mitochondria as a by-product of respiration, a great deal of attention has been given to the effects of mitochondrial genes—be they encoded in the nuclear or mitochondrial genomes—on ageing.

Broadly consistent with the free-radical theory, several human mtDNA polymorphisms are associated with differences in longevity. Mitochondrial DNA polymorphisms have traditionally thought to be selectively neutral. But the mitochondrial genome encodes 37 genes, 13 of which are proteins involved in oxidative phosphorylation (OXPHOS), and some mtDNA haplogroups (groups of evolutionarily related molecules) share mutations that alter the coding sequences of those genes. For example, one common European haplogroup, haplogroup J, is defined by (among others) missense mutations in several genes encoding OXPHOS components. That these mutations have consequences is suggested by the finding that centenarians more commonly have the J haplotype than expected (De Benedictis et al., 1999; Ross et al., 2001; Niemi et al., 2003). Similarly, in the Japanese population the C5178A missense mutation (characterizing the Asian haplogroup D) has been reported to be associated with longevity (Tanaka et al., 1998).

Do these longevity-associated haplogroups have any effect on early-life fitness? Some evidence indicates that particular haplogroups may have fitness consequences. Two European haplogroups, T and H, for example, are associated with sperm defects, and the very presence of certain haplogroups, but not others, in high latitudes is thought to be the result of adaptation to particular climates (Mishmar et al., 2003; Ruis-Pesini et al., 2004).

Of course, since any given mtDNA haplogroup carries many substitutions that others do not, it is hard to demonstrate the causal role of any given substitution on longevity, much less fitness. This is not the case for nuclear genes encoding mitochondrial proteins—and mutations in these genes frequently reveal antagonistic pleiotropic effects. Among the many mutations that confer increased longevity on the nematode, C. elegans, are loss of function mutations in clk-1, which encodes a mitochondrial hydroxylase required for the synthesis of ubiquinone UQ9. These mutations extend longevity by up to 40% but slow cellular proliferation, extend the time to maturity and reduce fertility. Similarly, RNAi surveys of nuclear-encoded proteins involved in mitochondrial OXPHOS frequently yield increases in longevity and multiple developmental pleiotropies (small size, slow growth, and even infertility)—though whether reduced free-radical production accounts for the longevity effect was not definitively shown (Lee et al., 2003). These antagonistic
effects are even seen in chemical manipulations of mitochondrial OXPHOS: worms fed bacteria lacking coenzyme Q show an increase in late-life survivorship, but a decrease in early-life survivorship (Larsen and Clarke, 2002).

Beyond the mitochondrion, free-radical production is regulated by various cytoplasmic proteins such as the free-radical scavengers, superoxide dismutase and catalase—and these, too, influence longevity. One of the few Drosophila loss-of-function mutations that confers increased longevity, Methuselah, encodes a G-protein coupled receptor that functions in neuronal synapses and may regulate such pathways since it confers resistance to Paraquat, a free-radical generator (Lin et al., 1998). More directly, transgenic Drosophila carrying unusually active versions of superoxide dismutase and catalase—these, too, in adults, when heat-shocked larvae are returned to normal temperatures, they have reduced survivorship and they grow slowly as well. And heat-shocked mothers have reduced fecundity, apparently due to embryonic mortality.

Thus heat shock proteins seem to exhibit the sort of physiological relations that we might expect to give rise to alleles with antagonistic pleiotropic effects. Genetic experiments suggest that this is so. Each wild type D. melanogaster genome carries six, closely related, hsp70 genes; but transgenic strains have been made that carry another six besides. When heat-shocked, these super-hsp70 flies show all the fitness costs and benefits that wild type flies do—but more so (Krebs and Feder, 1998; Silbermann and Tatar, 2000). The fitness burden of high hsp70 expression is further illustrated by population genetic studies. Natural populations of D. melanogaster are polymorphic for a transposable element insertion located between two of the wild type’s hsp70 genes; a polymorphism that affects HSP70 protein expression levels. Hot environments, both in the laboratory and wild, appear to select against the more active allele—on the face of it, a surprising result (Bettencourt et al., 2002). One explanation looks to antagonistic pleiotropy. Cool environments are often variable, but hot environments are often constantly so. The fitness costs of high hsp70 expression may, then, exceed its benefits when both are relentless.

6. Heat shock proteins

Heat shock proteins are induced by, and protect against, heat stress. They do this in diverse ways: by aiding protein folding, mediating signal transduction pathways, and protecting cells from protein denaturing stress (Silbermann and Tatar, 2000). A great deal of work in D. melanogaster shows that they also affect fitness.

Fruit-flies exposed briefly to stressfully high temperatures rapidly, if transiently, express heat shock proteins. This, in both larvae and adults, accounts at least in part for their subsequent resistance to even higher, otherwise lethal, temperatures. More surprisingly, mild heat shock in adults also causes them to be long-lived even when returned to normal temperatures—and this, too, is generally attributed to the protective effects of HSP induction. However, the blessings of HSP induction are not unmixed. In contrast to adults, when heat-shocked larvae are returned to normal temperatures, they have reduced survivorship and they grow slowly as well. And heat-shocked mothers have reduced fecundity, apparently due to embryonic mortality.

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7. Apoptosis

Of all the phenomena considered here apoptosis is perhaps the furthest removed from fitness. And yet in many ways it is the most interesting since it impinges on two of the deeper causes of ageing: cancer and the failure of organs to maintain themselves.

Any system that regulates apoptosis might be expected to have antagonistic pleiotropic effects. Early in life, apoptosis is an anti-cancer mechanism; late in life, as stem cells no longer exist in sufficient quantity to maintain cell populations, it is supposed to contribute to the failure of tissue integrity. Any genotype, therefore, that increases late-life tissue integrity by repressing apoptosis does so at the expense of an increased risk of cancer—or at least it does so in principle.

There are well established links between ageing and apoptosis. Several laboratories have shown that apoptosis is decreased during ageing both in vitro and in vivo (Spaulding et al., 1999; Suh et al., 2002; Monti et al., 2000; Radziszewska et al., 1999, 2000). This resistance to apoptosis may explain why senescent cells can accumulate in tissues with age.

But who are the players? Bcl-2 is responsible for resistance to apoptosis of senescent fibroblasts (Wang, 1995). Interestingly, Bcl-2 also contributes to premature senescence of normal rat and human fibroblasts (Tombor et al., 2003; Rincheval et al., 2002). ApoJ/CLU is a gene implicated in both ageing and apoptosis. High ApoJ/CLU
levels have been recorded during ageing and senescence in several tissues and species (Gonos et al., 1998; Trougakos et al., 2002). ApoJ/CLU gene silencing by RNAi sensitizes cells to apoptosis and results in the down-regulation of anti-apoptotic Bcl-2 and the induction of pro-apoptotic bax (Trougakos et al., 2004).

A good example of an apoptosis-resistance genotype comes from gain-of-function mutations in the tumour-suppressor, p53. Mice heterozygous for an activating mutation in p53 have increased resistance to tumours but show premature ageing: reduced longevity, osteoporosis, organ atrophy and diminished stress tolerance (Tyner et al., 2002). In humans, p53 is polymorphic for proline and arginine at codon 72. The polymorphism is ancient and global and so may well be maintained by natural selection. Many studies have searched for an effect of the polymorphism on cancer risk and a few have searched for an effect on longevity, but claimed associations remain controversial (Bonafe et al., 1999; Sun et al., 1999).

8. Conclusion

Would Alexander Graham Bell’s gerontocrats have paid a cost for their increased longevity? Would they, as 20-year-old, have been sluggish, cautious and sexless? Would they have had stronger bones but more cancers? Or fewer cancers but weaker bones?

Large amounts of data from a variety of model organisms shows that severe mutations that confer increased longevity often show decreases in early-life fitness-related traits such as growth and fecundity. These, combined with detailed cellular studies demonstrating the causal basis of the pleiotropies, convince us that the physiological connections envisioned by Williams when he proposed his theory are common in animals. In this sense, at least, antagonistic pleiotropy genes are ubiquitous.

If, however, we consider the evidence for the existence of natural polymorphisms with antagonistic pleiotropic effects in the wild—the kind of polymorphisms most relevant to evolutionary theory and human health—the evidence becomes much thinner. Exclude Drosophila genes (e.g., Geiger-Thornsberry and Mackay, 2004) and it becomes negligible. Many human loci have been implicated in longevity, but evidence on early-life fitness components is available for only a few. Fertility data are non-existent.

In part, this is due to the technical difficulties of carrying out longitudinal studies. One possible solution might be to carry out life-history studies on the children of the many centenarians who have now been recruited into longevity-assurance studies. Another solution might be to re-examine cohorts from early studies such as the participants of the Framingham study who are now 50 years old.

In summary, we conclude that it quite possible that genes or interventions that increase longevity may well have deleterious effects early in life—even reducing survivorship. We suggest that the study of such effects—in vitro, in model organisms and, above all, in human populations—should be a priority in the search for ways to postpone ageing.

References


