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Causes, Effects, and Constraints in the Genetics of Human Longevity

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Jeanne Calment, who died recently in her 123d year, being the oldest human being alive on earth, epitomized our quest for longevity. This deeply rooted quest has been spurred by recent strides in genetics, giving rise to renewed hopes that answers to the puzzle of aging may lie close at hand, in our genome. Indeed, a survey of Jeanne Calment's ancestry revealed a striking aggregation of the longevity trait: 24% of her 55 immediate ancestors have lived to age >80 years, as compared to merely 2% of an adequately paired control group (Robine and Allard 1998). Like other multifactorial traits, longevity aggregates, rather than segregates, in families, displaying a low heritability. Added to the stringent age requirements for probands, this limits practicable strategies for searching for underlying genetic variants in humans.

Centenarians, as examples of extreme longevity, approaching our species' maximum potential life span, exert a strong fascination. While differences in maximum life spans (MLS) among species ultimately relate to their genomes, the existence and extent of a genetic flexibility in this potential within humans is far less obvious. Longevity is the final outcome of aging processes that affect every level of biological organization, interacting and integrated over a lifetime. Finch and Rose (1995) have proposed a hierarchy of biology in five levels that aims to understand the architecture of life history, of which life span is but one component. The genome occupies a central position in this hierarchy, a position that calls for diverse viewpoints.

Genetic Polymorphism of Longevity

The seemingly fanciful hope of finding single mutations that confer long life has been realized in the nematode *Caenorhabditis elegans*. Since the initial discovery of *age-1,* ~10 different gerontogenes—genes involved in life prolongation—have been found (Finch and Tanzi 1997). The life extension displayed by the mutant nematodes may be as much as fivefold in certain double-mutant strains, and it stems at least in part from slower aging. In *Drosophila,* protocols of selection for delayed fertility have yielded strains with a more-than-twofold-increased life span, but so far no individual gene effect has been identified. Rather, it appears that heritable shifts in MLS depend on the natural variability at hundreds of polymorphic loci. In mammalian species, allometric equations link MLS with brain weight and body weight, allowing the former to be deduced from estimates of the latter traits in fossil specimens. Applied to hominid species, this approach suggests a doubling of the MLS within the past 3 million years along the evolutionary line that leads to modern man. This conclusion may indicate that relatively few genes, in the range of 40–250, are involved in controlling MLS (Cutler 1975). The spectacular recent increase in the mean longevity of human populations has not been accompanied by an increase of MLS, which has remained stable, at ~120 years of age, over historically recorded times. A lasting question is whether there exists a polymorphism of MLS in present human populations or only interindividual differences in longevity. In the former case, one might expect to find major-gene effects in centenarians, whereas in the latter case, many genetic variants would contribute to survival through advanced ages.

The impact of apolipoprotein E (APOE) alleles on survival in different pathological contexts has been amply confirmed (Finch and Tanzi 1997). Since causal variants were identified from the outset, these epidemiological data have opened new avenues for probing into molecular mechanisms of cardiovascular and neurodegenerative diseases. Contradictory reports on the human leukocyte antigen (HLA) locus have fueled controversy for >2 decades. A sufficiently large number of long-lived probands has now revealed the influence of three alleles: HLA-DR7, DR11, and DR13 (Ivanova et al. 1998). The first two alleles displayed interactions with sex in their effect on survival, which is most interesting in view of the sex-specific effects on life span of autosomal quantitative-trait loci (QTLs) found in *Drosophila* (Nuzhdin et al. 1997). The QTLs that affect life span in *Drosophila*

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also had age-specific effects on mortality. This is reminiscent of the late-acting (10th decade) effects of HLA-DR alleles on human survival, effects that were missed in previous studies that applied an age cutoff of 80 or 90 years. A study of genetic hemostasis factors in Italian centenarians reported a higher frequency of a variant of the plasminogen activator inhibitor 1 (PAI-1) that has been associated with elevated plasma levels of this protein as well as with heightened risk of myocardial infarction in adults (Mannucci et al. 1997). This finding, like our results on the angiotensin-converting enzyme (ACE) polymorphisms (Schächter et al. 1994), provides a genetic background to the surprising phenotype of hypercoagulability described in centenarians (Mari et al. 1995).

These scattered data should not obscure the fact that association studies aimed at identifying such loci are still in their infancy. However, the four genes so far implicated in longevity, *APOE, ACE, HLA-DR,* and *PAI-1,* share common features: (1) they have an impact on intermediary traits, such as plasma levels of a homeostatic protein or immune response, and (2) they display gene-environment interactions in normal adult populations. These are general features of common multifactorial diseases with polygenic effects and environmental components (Sing and Reilly 1993), which should not surprise us, since such diseases are leading causes of death and thus limit life span. Hence, these genes appear to affect longevity by modulating an individual's responses to life-threatening disorders, not by regulating MLS as an intrinsic physiological trait.

Compensatory Adaptation (CA) in Survival

The "compensation effect on mortality" is one of the more puzzling observations in human gerontology. This term refers to the convergence property of mortalities from various populations. Mortality increases exponentially with age in any population, its dynamics being defined by the two population-specific values of an initial mortality rate (usually given as ~20 years of age) and the mortality-doubling time, which measures aging. The observation is that mortalities converge toward a common value in the 80–90-year range; in other words, differences in rates of increase compensate for initial differences in mortality. This property implies that causes of death should be correlated, which has been extensively documented by Gavrilov and Gavrilova (1991). It also explains why genetic effects are stronger on age-related pathologies than on life span, while they may yet be detected in centenarians.

Genetic associations with longevity are likely to reveal hitherto unsuspected etiologic links among pathologies. For example, considering the impact of APOE on cardiovascular and Alzheimer diseases, it may be worthwhile to investigate its role in cancer, the third major pathology of aging. The effect of APOE alleles on survival may be related to the changing physiological role of serum cholesterol during aging. High cholesterol levels that are a risk factor in the 40s and 50s become beneficial in the 9th decade of life, whereas low cholesterol levels become associated with greater cancer incidence and mortality (Weverling-Rijnsburger et al. 1997). Similarly, thymic involution in conjunction with chronic immune challenge may lead to an expansion of certain T-cell subsets in very aged individuals. A similar pattern has been observed in HIV-infected patients (see Effros 1998 [in this issue]).

These age-related changes in the physiological role of one homeostatic parameter speak of CA, defined as a long-lasting adaptation occurring in any subsystem of an organism in response to a shortcoming in this or another subsystem. CA results in alterations of the values or physiological role of a homeostatic trait; hence, CA differs fundamentally from homeostasis, in that CA implies a durable and often irreversible departure from the state optimized by natural selection. CA therefore eventually leads to some loss of viability in an initially fit organism. Looking at the complete life cycle, one may distinguish the early portion of the phenotype, which has been sculpted by natural selection, from the late portion, when the organism continues to survive beyond the realm of optimized fitness. This is when natural selection pressure has decreased to nearly zero, after menopause for women, in the 5th decade of life for both sexes.

At the population level, aging represents an acceleration in mortality with age; this effect may be understood, at the individual level, as a decline over time in the ability to respond to external or internal perturbations. An organism survives in the face of various kinds of stress by reorganizing its physiological responses, but it is constrained in its ability to make such adjustments, by its resources and its patterns of homeostasis. These homeostasic response patterns are molded by the evolutionary history of the organism and are finely honed to handle perturbations that arise in early life. The same patterns may become harmful in later life, if they operate in a physiological environment for which they were not selected. These evolutionary considerations may explain some of the apparent paradoxes encountered in studying the very old. For example, cardiomyocytes die off progressively during aging, so that sinus-node cells, which entrain other cardiac cells, are ~90% depleted by the eighth decade of life (Wei 1992). The compensatory effort in maintaining the cardiac rhythm may account for enlargement of the remaining cells. Higher plasma levels of ACE, which have been associated with left-ventricular hypertrophy (Schunkert et al. 1994), may favor this adaptation. The *ACE* D/D genotype is known to confer

an increased risk of myocardial infarction, but it may also favor the CA of cardiac hypertrophy: such an effect might be evident in a study of the *ACE* genotype in a group of elderly athletes trained in aerobic sports. Similarly, the hypercoagulability in centenarians' blood (Mari et al. 1995) may represent an adaptation to damaged vasculature, chronic inflammation, and atherosclerosis (Ross 1993), but this feature is inextricably linked with an increased danger of clotting and strokes. The associations found in long-lived groups with HLA-DR alleles, which are arguably the causal variants, may be taken as clues to molecular interactions of these variants in mediating life-limiting immune responses (Ivanova et al. 1998). Indeed, we found a highly significant association of the DR11 allele with rapid progression of disease in HIV-infected patients, the association being stronger in women (F. Schächter, S. Caiilat-Zucman, J. Rappaport, and J.-F. Zagury, unpublished data).

When physiological responses cause irreversible, ultimately life-threatening damage in older individuals, they shall be referred to as "CA." CA might therefore be defined as a trade-off between present and future survival—which is really another way to say aging. This concept may be helpful in allowing primary aging processes to be disentangled from secondary changes, a lasting conundrum in the field of gerontology. Primary aging processes encompass various types of irreversible structural damage, at the core of which is damage incurred by the genome. It is expected that gene-specific and tissue-specific patterns of damage will ultimately appear to be related to changes in the alleles' survival values during aging. For example, if a vital gene becomes progressively inactivated by damage, structural or regulatory variants that favor compensatory overexpression will confer an advantage in late survival.

CA may arise whenever homeostatic mechanisms are inadequate to respond to various kinds of stress. A novel strategy for finding candidate genes in longevity follows directly from this observation: quantitative traits under homeostatic control should be examined for interindividual variation not only in their mean value but also in their variance. Indeed, the pattern of response to perturbations and its alteration by CA may be even more relevant to aging than is the average value of the trait. For example, serum dehydroepiandrosterone sulfate (DHEAS) levels (1) are variable among comparable subjects, (2) are stable in each subject, (3) decrease sharply with aging, and (4) are believed to influence susceptibility to multiple age-related pathologies. Therefore, it should prove interesting to identify the genetic variants underlying serum DHEAS variations and to look at their distributions in long-lived groups.

Toward a Genetics of Chronobiology

Homeostatic quantitative traits are often characterized only by their average value and variance, but in fact they also have a temporal structure, and this is the domain of "chronobiology." Body temperature and blood levels of various hormones, for example, are subject to daily cyclic fluctuations. These cycles become disrupted during aging. Examples abound of age-related disturbances of biological rhythms, in sleep-wake cycles, in circadian and monthly cycles of hormone production, etc. The major-histocompatibility-complex genotype has been shown to influence estrous cycles, as well as fertility and life span, in mice (Finch and Rose 1995). Whether such genetic effects exist in women's menstrual cycles might be worth investigating.

Much work and attention have been devoted to the melatonin cycle, which displays not only changes in periodicity but also decreased amplitudes in aged persons (Reiter 1995). Still more subtle changes occur as well. Any periodic signal may be analyzed in terms of complexity, as measured by the entropy of the signal (Pincus et al. 1991). This entropy reflects the degree of "unpredictability" of the signal. It has been found to decrease with aging, for various physiological functions, especially cardiovascular control, leading to the concept that aging is associated with a pervasive loss of complexity (Lipsitz and Goldberger 1992). Measures of complexity for various biological rhythms, and the rate at which they decline during an organism's lifetime, may therefore be added to the list of meaningful homeostatic traits, qualifying as potential biomarkers of aging. Their genetic determinants should be investigated. The ideal biomarker would faithfully reflect aging, and its rate of change would predict life span. Such biomarkers exist in *C. elegans,* where life-extending mutations in the *Clock* genes decrease aging by generally slowing down the pace of living in the nematodes (Finch and Tanzi 1997). One may still wonder whether this might be possible in humans.

"Longevity Genes": Regulating MLS or Disease Susceptibility?

Existing evolutionary theories of aging fail to provide a mechanism for age-related changes in the relative survival values of genetic variants; they merely state that such changes are expected. The basic argument is that since the force of natural selection decreases sharply after (and even during) the reproductive period, deleterious gene action with onset in that portion of the life cycle is not counterselected and therefore should have accumulated in the course of evolution. "Antagonistic pleiotropy" further suggests the concept that early beneficial

and late deleterious effects may be correlated. The disposable-soma theory, meaning that the soma may be disposed of as long as the survival of the germ line is assured, treats the problem of resource allocation between reproduction and somatic maintenance (Kirkwood and Rose 1991). Under this theory, the level of somatic maintenance depends in part on the life expectancy of the species in its natural evolutionary environment. Since they view aging as the consequence of a randomly accumulated genetic load, all of these theories predict that the effects of aging should be manifold and species specific. They also predict that aging and sex should be intimately related: the former would appear as a passive by-product of the evolution of a life-history strategy, and life span would be constrained only to the extent of compatibility with a reproductive schedule. The scope of the genetic epidemiology of aging would then be to characterize our species' genetic load, which limits the range of physiological states available to older individuals.

Patterns of allele frequencies in elderly groups should reflect these constraints. We have shown elsewhere how the sheer mathematics of increased mortality should permit the identification of allele-specific effects on survival in advanced age groups, and how the compensation effect on mortality emerges as a general property, with a turning point at ~90 (Toupance et al. 1998). While providing a bridge between genetic epidemiology and a demography of aging, these calculations still do not explain how, at the individual level, a given gene becomes relatively deleterious to survival. The idea of CA suggests that the effects of longevity-associated alleles will depend on the specific environment and history of each cohort examined. For example, cohorts of centenarians who lived through the great Spanish influenza epidemic at ages of 1 or 5 years may not share the same genetic structure. This in turn has two consequences: (1) we should be forewarned against inadequate comparisons between different long-lived cohorts, and (2) it is worth investigating candidate genes in different cohorts. Martin et al. (1996) have proposed a distinction between "private" species-specific mechanisms of aging and "public" mechanisms that would be widely shared across species. CA provides clues to the private set of genes. The gradual emergence of these gene effects in old individuals is driven by primary aging processes, which involve the genome as a target, rather than a determinant, of aging.

The Ambiguous Role of the Genome

Although, 2 decades ago, damage to mtDNA was postulated to occur with aging, its quantitative detection had to await PCR and the design of specific primers. The nakedness of the mitochondrial genome and its topological exposure to reactive oxygen metabolites render the mtDNA particularly vulnerable to damage. The most frequent mutations involve deletions of portions of the genome that are flanked by direct sequence repeats, but point mutations also accumulate with aging (Wallace 1992). These accumulate in nondividing cells within tissues that have high respiratory rates, such as neurons and muscle cells, notably in cardiomyocytes. The appearance and multiplication of defective mitochondria provides an example of detrimental CA at the cellular level; it seems that energy demands on the cell stimulate mitochondrial division specifically in cells that already carry defective mitochondria, eventually leading to overproliferation of these defective mitochondria and to loss of cell function.

Mitochondria with a defective genome lose control of oxidative phosphorylation, which becomes uncoupled. This produces more free radicals, which in turn increase damage to mitochondrial and other components in the cell, setting up a vicious cycle. The rate of oxidative damage is proportional to the metabolic rate and increases with aging (Sohal and Weindruch 1996), in accordance with the classic "rate-of-living" theory of aging, which addresses the inverse correlation between basal metabolic rate and life span. The life-prolonging effect of antioxidative enzymes in flies and of caloric restriction in rodents has been interpreted in this light. Martin et al. (1996) have reviewed data supporting the general role of oxidative stress in aging, such as the observation that life-extended mutants in *C. elegans* and *Drosophila* share an increased resistance to oxidative and other stresses. All macromolecules—DNA, RNA, proteins, lipids—are targets of oxidative damage. Among the most common and mutagenic by-products of such damage are the oxidized nucleotides 8-oxo-dGTP and 8-oxo-rGTP. In a recent report, Taddei et al. (1997) have shown that the *E. coli* MutT protein, which has mammalian homologues, is able to efficiently remove not only 8-oxo-dGTP but also 8-oxo-rGTP, thereby enhancing both DNA replication and transcription fidelity. Transcription errors may contribute to the accumulation of modified proteins with altered enzyme activities, independently of genomic mutations.

The nuclear genome staves off relentless attack, with powerful and versatile systems of DNA editing. Ranking among the classic theories of aging is the somatic mutation–accumulation hypothesis. In spite of extensive evidence (gathered, for the most part, 2 decades ago) on gross chromosomal abnormalities in old cells, the data for somatic mutation in aging are astonishingly scanty when compared with the abundance generated in the somatic genetics of cancer. Although there is good evidence for global alterations of the genome in terminally

senescent fibroblasts (Macieira-Coelho 1995), we still lack specific examples of age-related genomic damage, aside from the well-known telomere story (see Effros 1998).

From mitochondria, we have learned that we need to focus on specific tissues and specific genes if we are to detect and quantify age-related alterations, but we have only begun to apply this lesson to the nuclear genome. Tischfield (1997) recently proposed a broad definition of loss of heterozygosity (LOH) as the loss of a functional gene product encoded by a particular locus, and he showed that mitotic recombination leads to extensive LOH in normal human T cells and fibroblasts. This clearly qualifies as a candidate primary mechanism of cellular aging in vivo and in vitro. Tischfield focused, for experimental ease, on the adenine phosphoribosyltransferase (*APRT*) locus, which maps to the subtelomeric region of 16q. His conclusions may be broadly applicable to other genes in autosomal subtelomeric regions, where rates of mitotic recombination in aging cells may be influenced by cis-acting effects of shortened telomeres (Meltzer et al. 1993). Many other loci within the nuclear genome are expected to undergo age-related damage in the form of broad-sense LOH (Tischfield 1997). For example, both the hypoxanthine guanine phosphoribosyltransferase (HPRT) gene on the X chromosome and HLA-A2 in the HLA region have high somatic-mutation rates and are prone to age-related LOH in dividing cells. Indeed, a linear decrease of the enzyme-activity ratio of HPRT/APRT has been reported in aging fibroblast cultures (Paz et al. 1981).

Qian and Germino (1997) have proposed that somatic mutations, which sensitize a tissue to the effects of a "second hit" at the same locus, may explain the focal and highly variable progression of many diseases. Such progression is also a generic feature of aging at the tissue level. For example, the discovery, by histochemistry, of isolated cytochrome c oxidase–negative fibers in aged cardiac tissues was seminal in triggering the search for mtDNA deletions. A most interesting example of age-related local cellular alteration is the appearance of revertant neurons in the homozygous Brattleboro rat (Finch and Goodman 1997). In these rats, the vasopressin gene is inactivated by a single-base deletion, conferring a phenotype of diabetes insipidus. Heterozygosity appears gradually and in a linear fashion with aging, only in those neurons that are under chronic hyperosmotic stress for the synthesis of vasopressin. The mechanism seems to involve posttranscriptional mutations leading to phenotypic reversion, including hybrid mRNA molecules with the neighboring homologous oxytocin gene. This remarkable case of CA in individual neurons could be generalized to other genes (Finch and Goodman 1997).

Homologous recombination provides for a certain genomic plasticity in meiosis and mitosis and even in nondividing cells. The expression of this plasticity is controlled by genes of the mismatch-repair system (MRS) and depends on the genomic region as well as on the cellular context. Data are growing on the variability, according to the region, genotype, or haplotype, of recombination rates within the genome (Robinson 1996). A case in point is again the HLA region, where haplotypes carrying the DR11 allele have the highest recombination rates. Homologous recombination, as modulated by the set level of the MRS, regulates both the rate of germ-line mutations giving rise to genetic diseases and the rate of somatic mutations. Defects in the MRS account for a diverse array of genome mutations (Radman et al. 1995). On the other hand, adaptation requires a degree of genomic plasticity, and the same plasticity also serves in cellular ontogeny and differentiation. Obviously, the mutation rate that maximizes population fitness depends on the environment. The discussion leads us to the thesis that this set rate of genomic plasticity is also a central determinant of aging and life span.

X-chromosomal loci may provide a crucial test for models of DNA damage in aging. Since these genes are functionally hemizygous in both males and females, effects on longevity of lesions on the X chromosome may be relatively easy to observe. The genealogical study recently published by Gavrilov et al. (1997) provides cogent support for the impact that aging has on the somatic load on the X chromosome. Investigating correlations between parental age at conception and children's longevity, the authors reported a highly significant decrease in the life span of daughters—but not sons—born to elderly fathers. Their data suggest that X-chromosome damage accumulates with age in both the male germ line and somatic tissues and that it may limit life span. These findings shed light on a hitherto unexplained oddity in the familial pattern of transmission of longevity—namely, the weak father-daughter correlation (Abbott et al. 1974). A maternal-grandfather effect on the longevity of males would then also be expected. A hint to that effect may come from a study of the Duchenne muscular dystrophy locus on Xp21, which reported that the mean age of maternal grandfathers, at birth of the carrier daughter, was 33.7 years, compared with a value of 29.5 years for the general population and intrapedigree controls (Bucher et al. 1980). Similar effects may be sought in pedigrees segregating for X-linked phenotypes. A more direct test of the hypothesis would be to quantify mutations according to relevant parameters at specific loci on the X chromosome, for which there are already clues of increased fragility with aging.

These findings and hypotheses have important evolutionary implications. Loci on the mammalian X chromosome spend two-thirds of their time in oocytes rather than in sperm cells. In addition to other mutation-reducing mechanisms, this accounts for a slower mutation

rate of these loci (McVean and Hurst 1997), which harbor precious genes in particularly well-conserved syntenic groups (Ohno 1973). On the other hand, X-chromosome loci are more sensitive to damage than are autosomal loci in somatic cells, because they lack a partner for repair by homologous recombination, and such damage has a dominant cellular phenotype. Thus, the X chromosome is at the same time protected in the germ line and critically vulnerable in the soma, whereas its rate of damage accumulation in sperm cells may limit male reproduction. This may represent the case par excellence of trade-off between germ-line propagation and somatic maintenance, the very exemplification of the cost of sex in terms of aging.

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