as our international ethics and intellectual property committees remain the only international committees duly constituted to evaluate, direct and meet such needs. Indeed, in the future, HUGO might well assist in achieving globally acceptable diagnostic and therapeutic standardization.

HUGO has largely completed its first mission—assisting the Human Genome Project in the mapping phase, at least in so far as this has been possible in times of equally dire funding for mapping and mapping databases (one can only pray that this will not backfire on the popularity of the Genome Project in the medical genetics community, or on the timely achievement of the genome sequencing targets). Now, HUGO is poised to begin its next mission as the global, free-standing genomics organization: the dissemination of functional genomics and provision of responsible guidance with genomic applications and implications.

If life begins at 40, HUGO's perceived mid-life crisis and earlier growing pains should pass, now that younger scientists and responsible corporations are encouraging us to take up our role in making sense of the interface between genome science and society.

Gertjan van Ommen[1], Bartha Maria Knoppers[2], Richard Cotton[3], Joseph Strauss[4], Sue Povey[5], Norman Doggett[6] & Luca Cavalli-Sforza[7]

[1]President of HUGO, [2]Chair HUGO Ethics committee, [3]Treasurer of HUGO and Chair HUGO Mutation Database committee. HUGO, One Park Square West, London NW1 4LJ, UK. [4]HUGO IP Committee. [5]HUGO Nomenclature Committee. [6]HUGO HGM Committee. [7]HUGO HGD Committee. e-mail: hugo@hugo-international.org

1. Cotton, R. McKusick, V.A. & Scriver, C. *Science* **279**, 10–11 (1998).
2. Antonarakis, S. *et al. Hum. Mutat.* **11**, 1–3 (1998).

A putative gene causes variability in lifespan among genotypically identical mice

Ageing is a complex process during which damage to multiple organ systems accumulates[1]. The time at which impairment of critical bodily functions becomes incompatible with life determines organismal longevity and is usually measured in a population as mean or maximal lifespan. Our current understanding of the genes affecting longevity, particularly in mammalian species, is rudimentary at best[2]. Here we studied the range of lifespans among individual animals within genetically identical recombinant inbred (RI) strains of mice. We found that the time between the deaths of the first and last members of a given strain fell into two temporal groups, despite the fact that strains may have had similar mean or maximal lifespans. The segregation of RI strains into wide and narrow ranges that roughly corresponded to characteristic lifespan ranges of the progenitor strains, suggested a genetic component. We therefore mapped a putative gene accounting for more than 60% of the phenotype to a genomic segment near the centromere on chromosome 11. This locus causes variability in the rate at which genetically identical members of a population die and, from a practical standpoint, affects the slope of a death curve for a population.

During the course of studies in which we genetically linked cell-cycle kinetics and organismal lifespan[3] in mice, we re-examined the extensive study of lifespan in BXD recombinant inbred mouse strains[4]. Despite comprehensive efforts to standardize environmental conditions during the several years of the study (which involved usually 20 mice per strain), one of the most striking findings was the extensive variation in lifespan encountered among genetically identical members of individual BXD strains. In a scatter plot of the mean lifespan *versus* the range of lifespan obtained for the 22 individual BXD strains studied, it is apparent that there is no correlation between the two parameters; that is, short-lived strains may have a wide range and *vice versa* (Fig. 1*a*). We then asked if this range could have a genetic basis by comparing the strain distribution pattern (SDP) for this parameter with existing SDPs for previously mapped traits or markers in BXD mice, of which there are now more than 1700. A genome-wide search for linkage with previously mapped loci, carried out with MapManager QT (b15) software[5] (a method which does not take into account non-distinguishable markers)

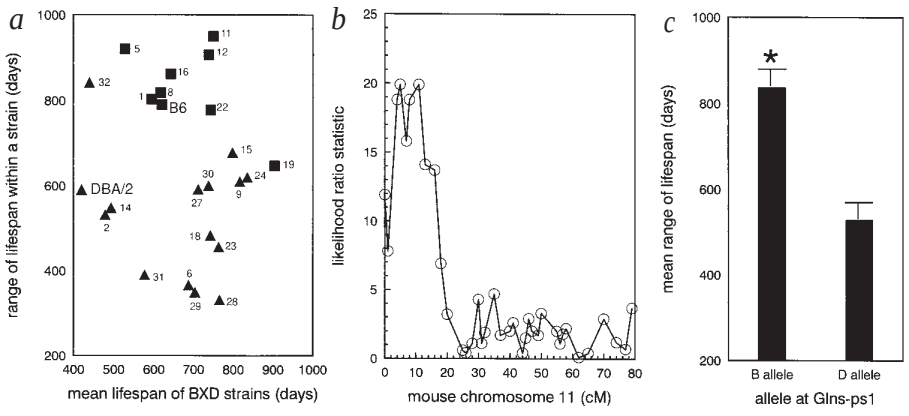

Fig. 1 Mapping a locus conferring variability on organismal longevity. ***a***, Longevity data in which intra-strain lifespan range is plotted against mean lifespan for each of the 22 BXD recombinant strains used in the study. The numbers correspond to the BXD strain designations. Symbols refer to the genotype for which each strain types at *Glns-ps1* (the locus most tightly linked to range of lifespan): squares, type 'B' strains; triangles, type 'D' strains. Values for the C57BL/6 and DBA/2 progenitor strains were previously described[4]. ***b***, Likelihood-ratio statistic plot showing the results of the interval mapping of intra-BXD longevity range on chromosome 11. ***c***, Mean range of lifespan for BXD strains carrying the B-allele (n=8) or D-allele (n=14) at *Glns-ps1*. Error bars reflect ± 1 s.e.m; the asterisk indicates significant difference ($P<0.001$), using the Wilcoxon-test.

a

Parameter	Likelihood ratio statistic	LOD score	Point-wise probabilty
Range of lifespan[a]	19.9	4.33	9.7×10^{-6}
Slope of survival curve[b]	18.0	3.91	2.2×10^{-5}
Mean quartile range[c]	14.1	3.06	1.7×10^{-4}
Standard deviation[d]	14.8	3.22	1.2×10^{-4}

b

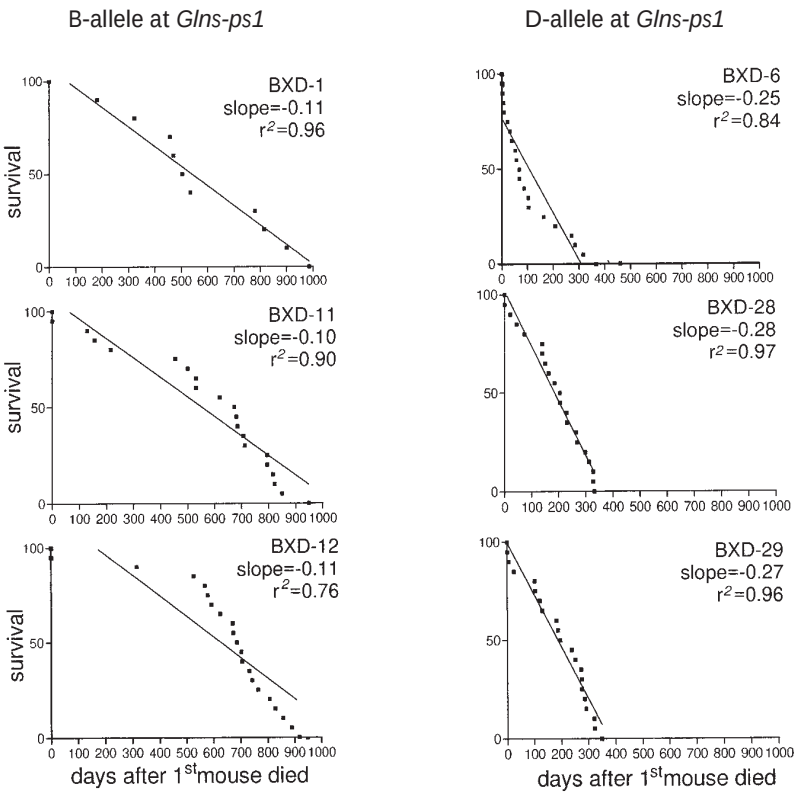

Fig. 2 Phenotypic consequences of allelic variation at the putative locus conferring longevity variability. ***a***, Linkage statistics at *Glns-ps1* using different mapping parameters. [a]The range of lifespan is defined as the number of days between which the first and the last mouse died. [b]The slope of the survival curve was calculated by linear regression analysis of the data starting from the day at which the first mouse died. [c]To obtain mean quartile range, data from each strain were grouped into quartiles, and the range in days between the mean of the first and the last quartile was used as the trait. [d]Standard deviation is that of the mean lifespan within each strain. ***b***, Graphical representation of the phenotype imparted by the putative variability locus. Mortality curves are shown for three BXD strains with the 'B' allele and for three strains with the 'D' allele. Linear regression lines were calculated using all mice per strain and the resulting slope was used for mapping. Note (i) that there is a greater than two-fold difference in the slopes between the two groups, (ii) that high r^2 values demonstrate good data fit to the regression lines, and (iii) that the scales of X-axes in all six panels are identical.

revealed strong linkage to one genomic interval—a near-centromeric segment of chromosome 11 (Fig. 1*b*), and weaker linkage to segments on chromosomes 5 and 8. The peak likelihood ratio statistic (LRS) for linkage to chromosome 11 was 19.9 ($P<9.7\times10^{-6}$) and only two strains, BXD 32 and BXD 19 (Fig. 1*a*), deviated from complete concordance with the SDP for the strongest linked markers (*D11Buy1* and *Glns-ps1*, at 5.0 and 11.0 cM, respectively). BXD strains that carry a 'B' allele (n=8) at one of these markers had a significantly ($P<0.001$) wider range (approximately 300 days) than strains carrying the 'D' allele (n=14; Fig. 1*c*). As lifespan range is by necessity dependent on the longevity of only two mice in a given strain—the shortest and longest living—three other parameters were used for parametric and non-parametric re-analyses: range of means in survival between the first and last quartiles within a strain, standard deviations of the mean lifespans per strain, and the slopes of the mortality curves for each BXD strain. In concordance with the mapping results using lifespan range, the other three parameters show tight linkage to the same marker on chromosome 11 (Fig. 2*a*). Range of lifespan and the slope of survival curves map to the common interval with the best statistics because they most accurately reflect the phenotype. The other two parameters are related but not identical to the trait and therefore show somewhat weaker linkage scores.

The phenotypic consequences of allelic variation at the putative quantitative trait locus (QTL) for six representative BXD strains—three with the 'B' allele and three with the 'D' allele (the best and worst fit in each case)—as reflected in the slopes of survival curves, is shown in Fig. 2*b*. To correct for the previously noted differences in mean lifespan among strains, we calculated the slopes of the curves starting on the day on which the first mouse within a given strain died. The intra-strain death rate (after the first death) was significantly higher in strains with the 'D' allele (Fig. 1*c*) comparing lifespan ranges. A simple linear regression model was found to best fit the mortality data and consequently the slopes of the regression lines for all strains were used to obtain the mapping result (Fig. 2*a*).

What are the implications of this finding? The results suggest the presence of a QTL whose phenotype is the generation of variability in a complex trait, here organismal lifespan, among genetically identical individuals. The actions of modifiers, suppressors and epistatic genes, as well as the effects of incomplete penetrance and variable expressivity are all well-established factors that, in concert with environmental influences, modulate phenotypic expression of genes in populations where there is genetic variability. However, because of the genotypic uniformity of members of individual BXD strains and the uniform and carefully regulated housing conditions of all mice in the study, these factors do not offer a satisfying explanation for intra-strain variability. We cannot exclude the possibility that environmental influences on lifespan were imparted early postpartum before mice were weaned and segregated into cage groups for the duration of the lifespan study. However, if the variability was caused by the environment (or by chance), it is difficult to see how a genetic determinant that accounts for 62% of the observed phenotype could have been mapped with the statistical analysis described here. A similar genotype-dependent range in survival is observed when large cohorts of commonly used inbred strains of mice are similarly evaluated[6]; thus mice from one inbred strain may be phenotypically more homogenous, irrespective of the nature of the trait, than mice from another strain.

What might be the mechanism of action? Much recent attention has been focused on the role of telomeres in the process of ageing and in tumorigenesis[7,8]. A sensitive and

quantitative fluorescence *in situ* hybridization technique has been developed and used to analyse telomeres of individual chromosomes of inbred mouse strains[9]. No discernible genetic determinant appeared to regulate telomere lengths between littermates of the same strain. Rather, telomere length on individual chromosomes was highly variable among siblings despite genotypic identity. This is reminiscent of the effect of the locus reported here, and may be a possible mechanism. At present, however, the role of telomere shortening in organismal ageing, as opposed to cellular replicative senescence[10], is unclear[11], and deserves further study. The existence of genes affecting variability in expression of other phenotypes in genotypically identical populations has been suggested by others[12,13], but to our knowledge this is the first locus to be mapped. An alternate mechanism of action for this type of gene invokes a heightened sensitivity to environmental factors that leads to extended phenotypic variation[13]. The unique nature of the trait complicates cloning and obscures potential paths to understanding its mechanism of action, primarily because it can only be studied in populations and not in individuals. The simplest cloning strategy is usually the candidate gene approach, which in this case is frustrated by the lack of solid clues concerning a mechanism. If a sequence difference was detected in a candidate gene between the DBA/2 and C57BL/6 progenitor strains, obtaining proof that it was responsible for the phenotype would likely be very time-consuming, but should be achievable. Similarly, a positional-cloning strategy, requiring extensive progeny testing of mice segregating critical recombinant events, would be difficult and require considerable patience. However, the broad implications of this trait for genetic studies in general, and in genetic studies of ageing in particular, may warrant the effort.

Acknowledgements

This work was supported by the Lucille P. Markey Cancer Center, the University of Kentucky Hospital and the Department of Internal Medicine. The original lifespan studies were carried out with support of NIH grant AG02329.

Gerald de Haan[1,4], Rebecca Gelman[2,3], Ada Watson[2], Edmond Yunis[2,3] & Gary Van Zant[1]

[1]Blood and Marrow Transplant Program, Lucille P. Markey Cancer Center, University of Kentucky Medical Center, 800 Rose Street, Lexington, Kentucky 40536-0093, USA. [2]Dana-Farber Cancer Institute, Boston, Massachusetts 02115, USA. [3]Harvard Medical School, Boston, Massachusetts 02115, USA. [4]Department of Physiological Chemistry, University of Groningen, The Netherlands. Correspondence should be addressed to G.V.Z. e-mail: gvzant1@pop.uky.edu

1. Jazwinski, S.M. *Science* **273**, 54–59 (1996).
2. Martin, G.M., Austad, S.N. & Johnson, T.E. *Nature Genet*. **13**, 25–34 (1996).
3. de Haan, G. & Van Zant, G. *J. Exp. Med.* **186**, 529–536 (1997).
4. Gelman, R., Watson, A., Bronson, R. & Yunis, E. *Genetics* **118**, 693–704 (1988).
5. Manley, K.F. *Mamm. Genome* **4**,303–313 (1993).
6. Russel, E.S. in *Biology of the Laboratory Mouse*, (ed Green, E.L.) 511–519, (McGraw-Hill, New York, 1966).
7. Harley, C.B., Futcher, A.B. & Greider, C.W. *Nature* **345**, 458–460 (1990).
8. Blasco, M.A., Rizen, M., Greider, C.W. & Hanahan, D. *Nature Genet*. **12**, 200–204 (1996).
9. Zijlmans, J.M.J.M. *et al. Proc. Natl. Acad. Sci. USA* **94**, 7423–7428 (1997).
10. Bodnar, A.G. *Science* **279**, 349–352 (1998).
11. Blasco, M.A. *et al. Cell* **91**, 25–34 (1997).
12. Berg, K. *Ciba Foundation Symposium* **130**, 14–33 (John Wiley & Sons, Chichester, UK, 1987).
13. McClearn, G.E. *Exp. Gerontol.* **12**, 49–54 (1997).

Accelerated accumulation of somatic mutations in the senescence-accelerated mouse

The somatic mutation theory of ageing proposes that the accumulation of mutations in somatic cells is an important cause of ageing. One prediction of the theory, namely that somatic mutations will be observed to accumulate, has been confirmed for a variety of loci in human and mouse cells[1]. Another prediction is that manipulations that alter the rate of ageing will be associated with a corresponding alteration in the rate of mutation accumulation. This has been confirmed for dietary restriction[2], which prolongs lifespan in rodents. Here, we report on further confirmation obtained from our study of the senescence-accelerated mouse (SAM) strain. SAM mice constitute a mouse model of accelerated senescence, produced by selective inbreeding, in which the features of senescence become apparent at four months[3].

Mutation frequency (MF) in splenic lymphocytes at the hypoxanthine phosphoribosyl transferase (*Hprt*) locus was measured as previously described[4] at various ages in one strain of SAM-prone (SAMP1) mice, which have a median lifespan of 9.9 months, in the corresponding strain of SAM-resistant (SAMR1) mice, which have a median lifespan of 18.9 months[5] and in a group of Balb/cA mice (Fig. 1). Analysis of variance on the logarithmically transformed data showed a significant effect of strain (SAMP1 *versus* SAMR1, $P<0.0001$), age ($P<0.0001$) and sex ($P<0.0001$) on MF. Balb/cA mice showed a significant ($P<0.0001$) effect of age but not of sex on MF. There were no significant differences in the cloning efficiency between mutation assays of any of the groups.

In adult animals (in which the total number of lymphocytes remains approximately constant), the mutation rate (per cell per unit time) equals the rate of increase of MF (ref. 6). We observed a plateau in the relationship between MF and age in surviving SAMP1 mice. This may indicate a true plateau in the underlying relationship between MF and age, which would suggest that MF increases with age in approximately a Gompertzian fashion. Alternatively, because the median lifespan of SAMP1 mice is 9.9 months, the 9-and 11–12-month data may have been biased if mice with higher MF die early. Given the difficulty in interpreting the observed plateau, we restricted our analysis to the first part of life by using the 3- and 6-month data from SAMP1 mice and the 3-, 6-, 9- and 11–12-month data from the SAMR1 and Balb/cA mice. We modelled an exponential increase of MF by calculating linear regressions between the logarithm (base 10) of MF and the age in months (Fig. 1). There was no significant differences in mean of mutation frequency between SAMP1 and SAMR1 mice at three months (Mann-Whitney U-test) but the gradients of the regression lines for SAMR1 mice differed significantly (t-test, $P<0.01$) from those for SAMP1 mice. The slopes of the regression lines indicate that the fractional increase in mutation rate per month in SAMP1 mice was approximately five-fold greater than that in SAMR1 mice during the early part of life. The time at which the increase in MF was observed in SAMP1 mice paralleled the time at which the phenotypic features of ageing developed.