Genetics and Demography of the Framingham Cohorts: The Joint Influence of Many Small-Effect Genetic Variants on Life Span and Mortality Risk

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Abstract

Background. The genetic studies of human life span produced controversial results. The effects of a number of genes on longevity are confirmed in some studies and are not manifested in others. None of the connections resulting from the genome wide association studies (GWAS) of longevity achieved genome-wide significance level. New approaches are needed to evaluate the roles of genetic factors in longevity from available data.

Method. In this paper we investigate joint influence on life span of a set of genetic variants individually selected in GWAS of life span using Framingham Heart Study data. We use bio-demographic models to investigate possible mechanisms, which are likely to be involved in regulating differences in survival patterns in groups of individuals with different genetic background and at different time points.

Results. We show that difference in genetic background among groups of individuals from the same cohort generates differences in survival/mortality curves resembling those observed during survival/mortality improvement in developed countries in the last century.

Conclusion. Observed similarity in patterns of survival changes in response to radically different factors indicates the presence of important systemic biological mechanisms involved in life span regulation. Although these mechanisms could be different for different stimuli their functional roles could be similar.

Introduction

The genome wide association studies (GWAS) of complex traits have been developed to perform intensive analyses of genetic influence on such traits. These studies helped identify hundreds of genetic variants and provided valuable information about their roles in such traits (Hardy and Singleton, 2009). Despite this evident progress, the approach did not entirely meet expectations of many researchers. Most genetic variants identified so far confer relatively small effects on risks of health disorders and life span. Many of detected effects remain below the levels of statistical significance established to correct the results for multiple comparisons. Such small-effects-low-significance single-nucleotide polymorphism (SNP) alleles were traditionally excluded from further analyses. The small contribution of selected SNP alleles into traits' variability generated debates about "missing heritability" (Hardy and Singleton, 2009; Maher, 2008; Manolio et al., 2009; Slatkin, 2009; Visscher et al., 2008). The use of data from the whole genome scan and the intensive search for rare alleles has been suggested as an alternative to existing GWA approaches. However, the genetic data for population of appropriate size and with such level of genetic details are not yet available for the researchers.

The GWAS of human longevity share all the limitations discussed above. The candidate genes approaches used in genetic association studies of longevity resulted in finding a number of genes whose connection to long life can also be associated with the roles they play in metabolic pathways. The effects of a number of such genes were replicated in some independent studies (Anselmi et al., 2009; Flachsbart et al., 2009; Willcox et al., 2008; Zeng et al., 2010).

Surprisingly, these genes did not show significant effect in the genome wide association studies of human longevity (Lunetta et al., 2007; Newman et al., 2010).

Lunetta et al. (2007) performed GWAS using genetic data on 100K SNPs collected for participants of the original and offspring cohorts of Framingham Heart Study (FHS). The Cox proportional hazards model was used to generate martingale residuals to perform the regression analysis of survival times from age at study entry to age at death. Models were sex-specific and adjusted for a number of observed covariates including birth cohorts, behavioral, and physiological characteristics. Residuals from original cohort and offspring participants were pooled. The authors concluded that longevity and aging traits are associated with SNPs on the Affymetrix 100K GeneChip. However none of the associations achieved genome-wide significance.

Newman et al. (2010) performed a meta-analysis of GWAS in Caucasians from four prospective cohort studies. The authors found 273 SNP associations with $p < .0001$, but none reached the prespecified significance level of 5E-08. The authors concluded that survival studies of larger size or more extreme or specific phenotypes may support or refine these initial findings. Using top 24 alleles, the authors conducted a pathway analysis with the Database for Annotation, Visualization and Integrated Discovery http://david.abcc.ncifcrf.gov/).

In Yashin et al. (2010b), we found that small-effect-low-significance genetic variants, individually selected using methods of GWAS, may jointly influence life span. This influence was substantial and highly statistically significant. The evaluated relationship between genetic dose and life span response explained 21% of life span's variance. The relationship was replicated using data on an independent population. The set of selected genetic variants was able to predict a similar relationship in the other population. In this paper we evaluate age patterns of survival for the subgroups of individuals having different numbers of longevity SNPs in their genomes. We show that survival functions in the subgroups differ substantially, and the dependence of such patterns on the number of respective SNP alleles follows regularities detected in the analyses of age patterns of survival improvement during the last century.

Data

We used data on life spans of 1173 deceased individuals from the original FHS cohort, as well as data on 550000 SNPs collected for these individuals. The detailed description of the Framingham Heart Study and the FHS genome-wide genotyping data can be found on the dbGaP website (phs000007.v3.p2)

Methods

We use the set of 39 longevity alleles selected in Yashin et al. (2010b) to evaluate the joint influence of the subsets of genetic variants on survival in the groups of study participants carrying respective subsets in their genomes. We constructed an index measuring additive genetic component of life span, as well as other indices capable of representing the joint influence of subsets of genetic variants on survival. Then we fitted the Gompertz-Makeham model to mortality data in respective sub-cohorts and compare obtained estimates and respective survival functions. Then we used Strehler and Mildvan (Strehler and Mildvan, 1960) mortality model (the SM model) to evaluate which parameters of this model can be affected by genetic factors.

Index for measuring additive genetic contribution to life span. There is no need to argue about importance of studying the additive genetic component of phenotypic traits. Evolutionary models of phenotypic traits, theoretical principles of quantitative genetics, breeding experiments, as well as many other aspects related to transmission of genetic effects through generations involve this notion. In the pre-genomic era these effects of additive genetic components of phenotypic traits were estimated indirectly using data on related individuals. The availability of genome wide data nowadays allows for direct evaluation of respective effects. To do this, denote by B the set of 39 *SNP*-alleles (i.e., $SNP_i \in B$ if selected in the allele selection procedure in Yashin et al. (2010b), and let $\hat{\beta}_i$ be the effect size of SNP_i, i= 1, 2,…, 39, estimated in this procedure. Denote by $B_j \subseteq B$ the subset of B consisting of *SNP*-alleles contained in the genome of j^{th} individual, j=1, 2,…, 1173. The additive genetic component of life span of j^{th} individual G_j can be represented as a weighted sum of indicators $I(SNP_i \in B_j)$, $SNP_i \in B$, with normalized weights $\hat{\beta}_i \Big/ \sum_{k=1}^{N} \hat{\beta}_k$:

$$G_j = \sum_{i \in B} \left(\hat{\beta}_i \Big/ \sum_{k \in B} \hat{\beta}_k \right) I(SNP_i \in B_j) \qquad (1)$$

This function is sometimes called “genetic or genomic score function” (Meigs et al., 2008; Paynter et al., 2010; Reeves et al., 2010; Ruiz et al., 2009; Talmud et al., 2010). Thus, by the definition of the additive genetic component, life span of j^{th} individual can be represented as

$$LS_j = \alpha_0 + \alpha_1 G_j + E_j \qquad (2)$$

Here E_j is the environmental component of life span with zero mean value. The function G_j is constructed from genetic data, and is considered as an observed covariate. Parameters α_0 and α_1 have to be estimated from the data. The percent of phenotypic variance explained by the estimated relationship: $\hat{LS}_j = \hat{\alpha}_0 + \hat{\alpha}_1 G_j$ can be used as the measure of goodness of fit.

Note that the values of the effect sizes for individual alleles are never known exactly. Their estimates as well as *p*-values of these estimates may substantially depend on the statistical model describing connection between the genetic variant and the phenotype of interest, and used in the allele selection procedure. This statement was checked by selecting longevity alleles using the Cox, logistic and linear regressions, the GEE method, and the mixed effects models in the allele selection procedure. The use of these methods resulted in different sets of *SNP*-alleles and in different estimates of the effect sizes of *SNP*-alleles from the overlapping sets. Therefore, the values of genetic scores, the estimates of α_0 and α_1 as well as percents of explained phenotypic variance characterizing genetic contribution to life span also differed from one model to the next. The dependence of the results of analyses on the method used in the allele selection procedure may jeopardize interpretation of the research results about the strength of genetic influence on the trait. To avoid the uncertainty associated with different relative values of the estimates of the effects sizes, the values of $\hat{\beta}_i$ were assumed to be about the same $\hat{\beta}_i \approx \hat{\beta}_k$ for each *SNP*-allele from the overlapping set of such alleles produced by different methods. In this case, the genetic score function for j^{th} individual becomes proportional to $N_j = \sum_{i \in B} I(SNP_i \in B_j)$, i.e., the number

of *SNP*-alleles, contained in his/her genome. So, life span of j^{th} individual can be represented as the function of the proportion of the genetic variants $n_j = N_j / N$ contained in his/her genome:

$$LS_j = \alpha_0 + \alpha_1 n_j + E_j \quad (3)$$

The comparison of the percents of phenotypic variance explained by representations (2) and (3) showed that these values are about 19% in both cases.

Note that the joint influence of genetic variance on risk of disease has been tested in several other studies using an aggregated index called "genetic or genomic score" (Meigs et al., 2008; Paynter et al., 2010; Reeves et al., 2010; Ruiz et al., 2009; Talmud et al., 2010). The fact that these researchers combined genetic variants detected in different studies and often in different populations may produce misleading results when genes affecting respective traits are sensitive to external conditions. Moreover, the "genetic score" function in these publications often included only alleles whose effects on the trait were statistically significant. No one of these studies addressed the critical issue that different statistical methods of allele selection will result in different sets of SNP alleles. It is clear that more work is needed to properly select influential alleles and evaluate regularities of their joint influence on health related traits.

Regularities of genetic influence on survival. Fig. 1 (upper panel) illustrates two patterns of survival improvement observed in developed countries during the 21st century. The results of our studies of genetic influence on life span using data from the original FHS cohort showed that dependence of survival curve on the number of minor longevity alleles (i.e., alleles, having positive effects on survival) contained in the genomes of individuals from respective sub-cohorts follows similar patterns (Fig.1, bottom panel). When the number of longevity alleles, contained in individuals' genomes, varies from the total number 0 of such alleles to 22, respective changes in survival functions in the sub-cohorts of individuals with such differences in genetic background follow the rectangularization pattern. When the number of such alleles contained in persons' genomes increases, the changes in survival functions in respective population subgroups show a pattern resembling almost a parallel shift of the entire survival curve to the right (Fig. 1, bottom panel).

Fig. 1 is about here

One more striking similarity is between an almost linear increase of average life span as a function of the number of longevity alleles (Yashin et al., 2010b) and a linear increase in the life expectancy at birth over time (Oeppen and Vaupel, 2002). Fig. 2 shows an increase in average life span for groups of individuals whose number of longevity alleles varies from 0 to 39 (upper panel) and an increase in life expectancy at birth caused by improvements in external conditions (bottom panel).

Fig. 2 is about here

What mechanisms might be responsible for such similarity in survival and life expectancy changes caused by two evidently different reasons?

Strehler and Mildvan correlation. More than 50 years ago the Science magazine published the seminal paper by Strehler and Mildvan (1960), in which the Gompertz mortality rate

$\mu(x) = a\exp(bx)$ was represented as a result of interplay between external disturbances (stresses of life) and the decline in the "vitality" variable describing individuals' resistance to stresses. The model explained striking regularity detected in comparison of the Gompertz mortality rates in different populations: the parameters *a* and *b* of this curve were not changing independently from one population to the next, as one could expect, but showed strong negative correlation, later called the Strehler and Mildvan (SM) correlation. This model was applied to explaining differences in mortality rates among different populations (Gavrilov and Gavrilova, 1991; Strehler and Mildvan, 1960); differences in mortality rates in the same country at different time periods, or in subsequent sub-cohorts (Yashin et al., 2001; 2002), as well as in cause specific mortality rates (Riggs and Millecchia, 1992).

Fig. 3 shows logarithms of the Gompertz mortality rates evaluated for groups of individuals having different numbers of longevity alleles in their genomes (upper panel).

Fig. 3 is about here

One can see that the pattern of changes is typical for rectangularization of survival curves. The mortality rate for non-genotyped population is higher than that in any sub-cohort of the genotyped population. The SM-correlation diagram (bottom panel in Fig.3) shows clear correlation pattern between the Gompertz parameters ln *a* and *b*. Note that the values of these parameters for the non-genotyped individuals are located in the right bottom part of this diagram. One can use this diagram to predict that most likely number of longevity alleles in non-genotyped individuals is about zero. The evaluation of dependence of life span on the number of "longevity" alleles contained in individuals' genomes may shed more light on genetic nature of this trait.

How SM model explains observed patterns in survival improvement over time. One of the key variables in the SM model is "vitality", $V(x)$, where x denotes individuals' age. The decline in vitality with age is described by a linear function and interpreted as aging associated reduction in capacity to withstand stresses:

$$V(x) = V_0(1 - Bx) \tag{4}$$

The external disturbances are described by the Poisson-like stochastic process, which is characterized by two parameters: the frequency, K, and the average magnitude of stresses, εD, respectively (here we follow the original notation by Strehler and Mildvan). The function $V(x)$ is characterized by the intercept, or initial value of this index, V_0, and the slope, V_0B. The model represents parameters of the Gompertz mortality curve $\mu(x) = a\exp(bx)$ (describing the typical pattern of human mortality rates between ages 30 and 85 years) in terms of V_0, B, K, and εD:

$$a = K\exp(-V_0/\varepsilon D); \qquad b = V_0 B/\varepsilon D\,. \tag{5}$$

In the framework of the SM model the observed rectangularization pattern of survival improvement over time (upper panel in Fig. 1) can be explained by the decline in average magnitude of external stresses, εD. The parallel shift of the entire survival curve to the right over time (the same panel in Fig. 1) can be explained by the decline in the frequency of external disturbances, K. This is because εD, and K are the only parameters characterizing properties of external disturbances. Changes in V_0 and B are not expected, because these parameters represent properties of individual genetic background, significant changes of which require evolutionary time.

How SM model explains differences in survival for groups of individuals with different genetic background. Note that explanations given above are no longer valid for the patterns shown in the bottom panel of Fig. 1. This is because instead of considering of how changes in external conditions over time influence human survival we consider how such survival is affected by differences in genetic parameters of individuals taken from the same population cohort (original FHS cohort), and exposed to the same external conditions. Therefore, different age patterns of survival (mortality rates) for these sub-cohorts are likely to be associated with differences in parameters V_0 and B of the vitality function, $V(x)$, which are likely to depend on the genetic backgrounds of individuals from respective sub-cohorts. The analyses of parameters of the Gompertz mortality curve given by (2) together with the spectrum of survival functions shown in the bottom panel of Fig. 1 indicate that the rectangularization pattern of changes in survival, in this case, can be observed if the initial value of vitality, V_0, increases with the decline in the number of longevity alleles contained in individuals' genomes. In populations with such genetic background, the parameter B remains unchanged, so the rate of vitality decline (which is characterized by the product, V_0B) increases. As we mentioned earlier, such a pattern of changes in survival takes place in the groups of study participants when the number of longevity alleles varies from 0 to 22 (Fig. 1, bottom panel). The almost parallel shift in the entire survival curve to the right (Fig. 1, bottom panel) with further increase in the number of longevity alleles in genomes of individuals from respective sub-cohorts could be obtained by simultaneous changes in parameters V_0 and B but in opposite directions, so that the initial vitality, V_0, continues to increase, but the slope, V_0B, of the vitality curve remains the same.

This connection between genetic changes and modifications of the hypothetical vitality curve, estimated from the real data, indicates that changes in the genetic background of individuals may affect dynamic parameters of aging related changes in physiological indices measured in longitudinal data. The use of the SM model shows what types of effects on dynamic parameters of the age trajectories of physiological indices can be expected (e.g., improvement in survival may take place with and without changes in the rate of aging-related changes in respective biomarkers) when the genetic backgrounds of respective individuals change. Better understanding of the roles of such genetic factors in biomarkers of aging may also shed light on the role of gene-environment interaction in the survival changes over time (upper panel in Fig. 1). The new environmental conditions may activate new genes, which may modulate parameters of vitality curve.

Discussion

The presence of SM correlation in the Gompertz parameters is associated with the "rectangularization" pattern of survival improvement also called the "compression of mortality" (Myers and Manton, 1984). Respective decline in mortality rate can be represented by counter clock-wise rotation of the logarithms of respective mortality rates around some point, so the parameter a declined and the parameter b increased. The insights about possible biological mechanisms responsible for such patterns of changes can be gained by comparing these curves with those resulting from the model of "saving lives" (Vaupel and Yashin, 1987; Yashin et al., 2000), where the rectangularization pattern of survival changes corresponds to an increase in the number of times "individuals' lives have been saved." "Saving lives" can be achieved by providing living organisms with necessary resilience, redundancy, and robustness, which increases their ability to withstand stresses. It is interesting that analyses of data factors and conditions experienced by centenarians brought researchers to the same conclusion: Resilience

makes substantial contribution to exceptional longevity in humans (Zeng and Shen, 2010).

Demographers studying trends in mortality and survival in developed countries paid attention to the fact the concept of "mortality compression" became no longer valid in the second part of the last century. Myers and Manton (1984) brought evidence that at the second part of the 20^{th} century the tail of survival curve in the United States has a tendency to increase with years. Horiuchi and Wilmoth (1997; 1998) confirmed an increase of the tail of life span distribution in the population of the United States. Wilmoth and Horiuchi (1999) found that the decline in variability of life span, associated with the rectangularization pattern of changes in survival curves ended up around 1950 in Sweden and United States. These evidences were summarized in the papers by Yashin et al. (2001; 2002) which found that the process of "rectangularization" of the survival curve, which took place in the first half of the last century, was later replaced by an almost parallel shift of the entire survival curve to the right (Fig. 1, upper panel). It was clear that human survival improves in response to changes in environmental and living conditions, which include ameliorations in health care and medications. However, factors and mechanisms responsible for such an improvement remained poorly understood. The analyses performed in this paper indicate that observed differences in survival (mortality) curves can be generated by modulating individual resistance to stresses. Importantly, such modulation can be done by genetic factors, and, what is even more important, by favorable changes in external conditions. An increase in individual resilience by providing adequate medical help and health care facilities in critical situations is likely to make an important contribution to exceptional life span.

Thus the use of the SM model in the analyses of genetic data shows that genetic factors may modify values and dynamic properties of variables describing aging related transformations in the human body, and these modifications influence life span. In Yashin et al. (2006) we found associations between values of physiological indices at ages between 40 and 60 years and life span. Extending these analyses (Yashin et al., 2010a) we also found that not only values of these variables, but also their dynamic characteristics, are associated with life span, and healthy life span. These findings together with the insights from the SM analyses suggest that at least some of the detected associations may be caused by the joint influence of the number of genetic variants individually selected for their effects on health and survival outcomes.

The observed patterns in survival/mortality changes have important interpretation from the reliability theory point of view. Indeed, the parallel shift of the mortality curve to the right corresponds to proportional modification of respective hazard rate. Such changes are expected when in the series connection of N sub-systems with similar age patterns of hazard rates one or several systems became invulnerable (e.g., by providing them with high levels of redundancy, or repair capacity). The rectangularization (mortality counter clock-wise rotation) pattern corresponds to providing a limited redundancy (or limited additional repair capacity) to one or more subsystems. This analogy stimulates systems biology approaches to studying aging and longevity with identifications of respective systems blocks, connections, mechanisms and capacities for reservation and repair at different levels of organism's biological organization.

Note that even if the differences in survival functions/mortality rates in the two panels in Fig. 1 look similar, the mechanisms responsible for them are not necessarily the same. An improvement in survival over time involves influence of advancing health care and medical technology (e.g., proper access to emergency care, implantation of pacemakers, performing by-pass surgery, etc.), which could extend life without affecting genetic mechanisms, for example by increasing reliability of functioning in certain biological organs, or subsystems. An important

finding of this study is that selected genetic variants may jointly influence reliability of biological subsystems, and that this influence depends on the number of respective genetic variants contained in genomes of respective individuals.

Acknowledgements

The FHS project is conducted and supported by the NHLBI in collaboration with Boston University (N01 HC25195). The FHS data used for the analyses were obtained through dbGaP (phs000007.v3.p2).The authors acknowledge the investigators that contributed the phenotype and genotype data for this study. This manuscript was not prepared in collaboration with investigators of the FHS and does not necessarily reflect the opinions or views of the FHS, Boston University, or the NHLBI. This work was partly supported by NIH/NIA grant R01AG030612. The authors acknowledge University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany) for developing and maintaining Human Mortality Database (available at www.mortality.org or www.humanmortality.de; data downloaded on 07/15/2008).

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Figures:

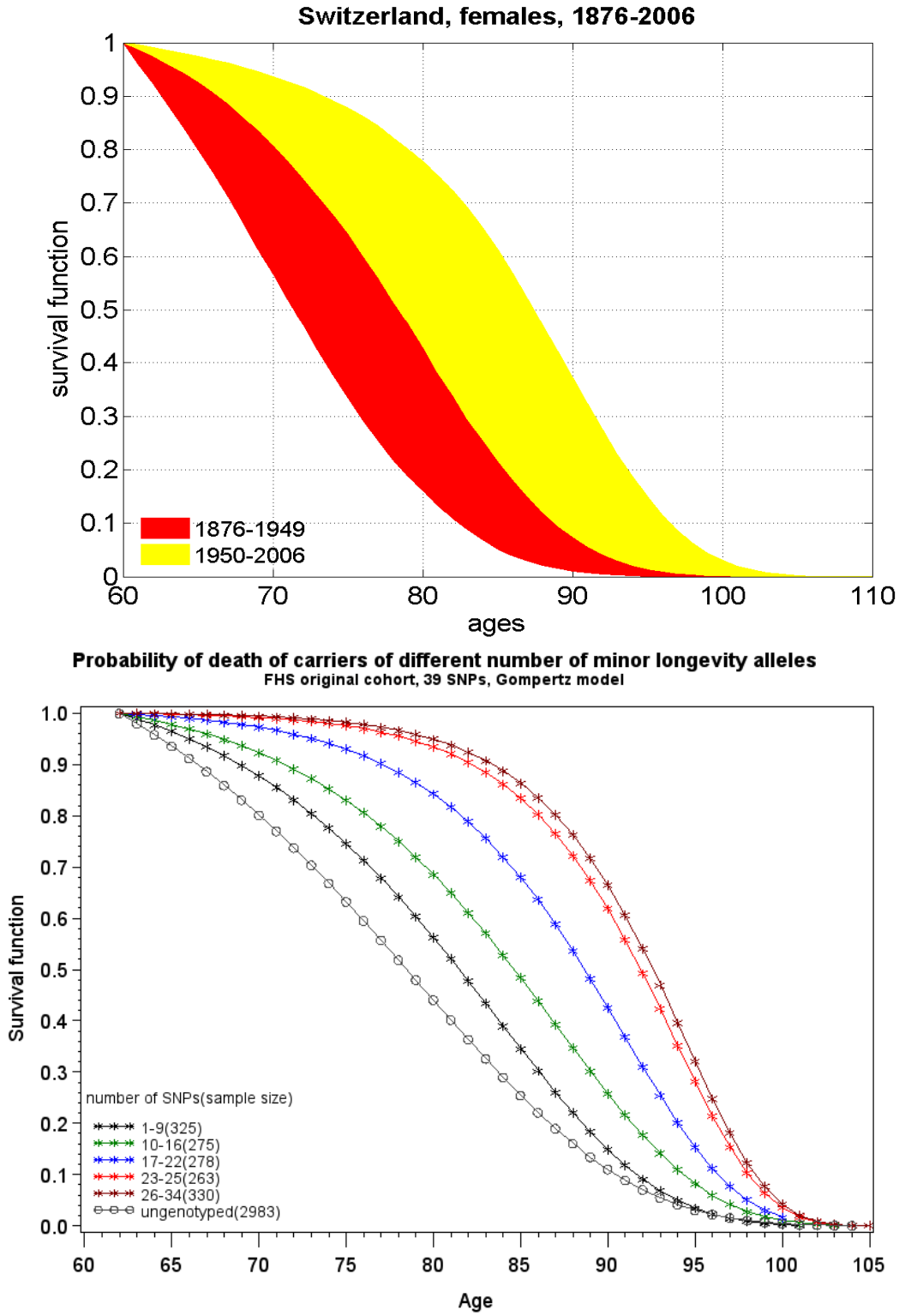

Fig. 1: ***Upper panel:*** Two patterns of survival improvement for females in Switzerland (data source: Human Mortality Database). ***Bottom panel:*** Two patterns of changes in survival of carriers of different number of longevity alleles detected in our GWAS of the original FHS cohort.

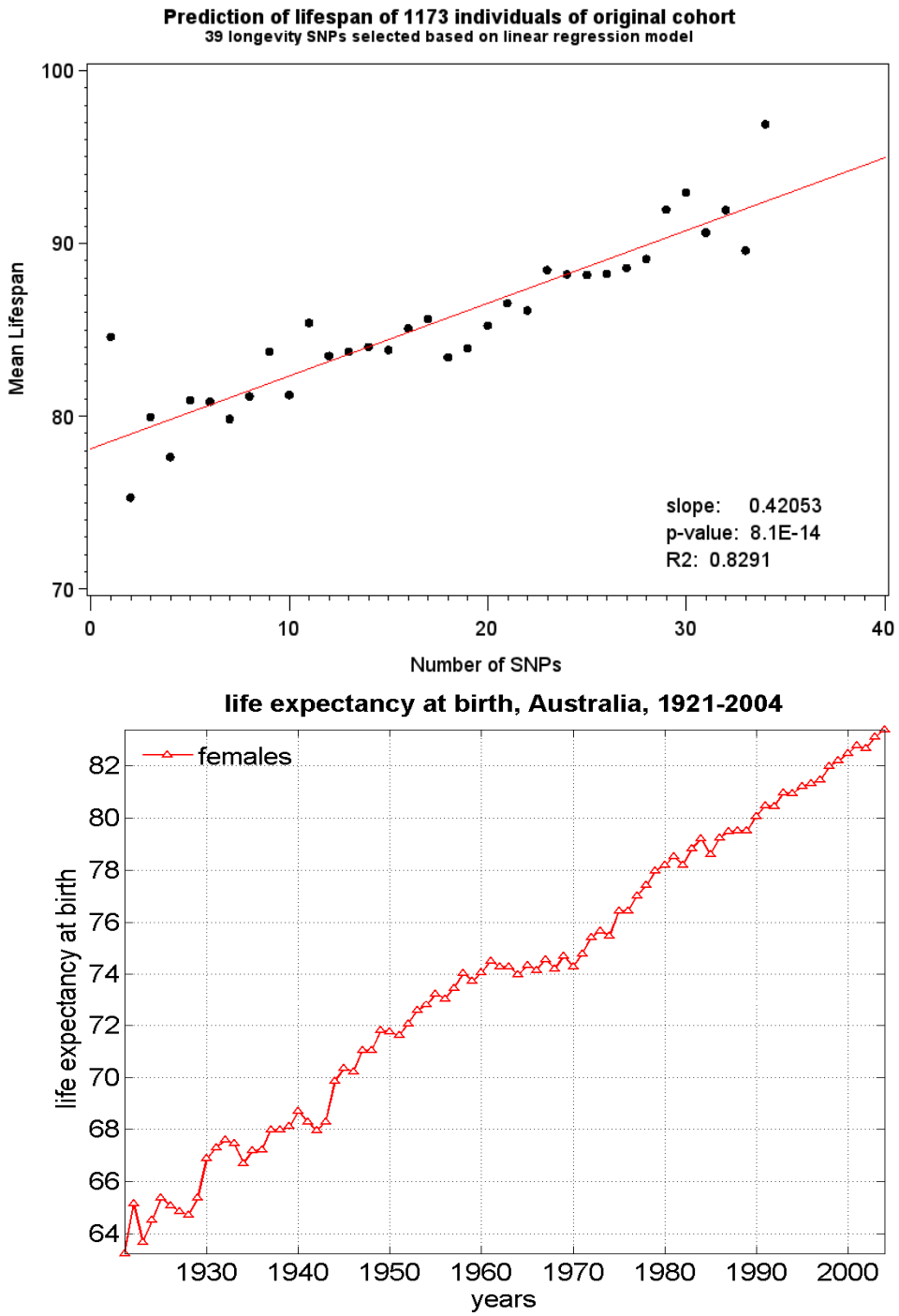

Fig. 2: ***Upper Panel:*** The "genetic dose – phenotypic response" relationship between the numbers of selected "longevity" alleles (39 total) contained in individuals' genome and mean life span of individuals carrying a given number of longevity SNPs in their genomes (analyses of 500K SNP data, original FHS cohort). Dots represent real data, dashed line represents respective linear regression. Longevity alleles were selected using a linear regression procedure, which involved comparison of characteristics of life span distributions among carriers and non-carriers of each of 500K genetic variants. ***Bottom Panel:*** life expectancy at birth in Australia, females, 1921-2004 (data source: Human Mortality Database).

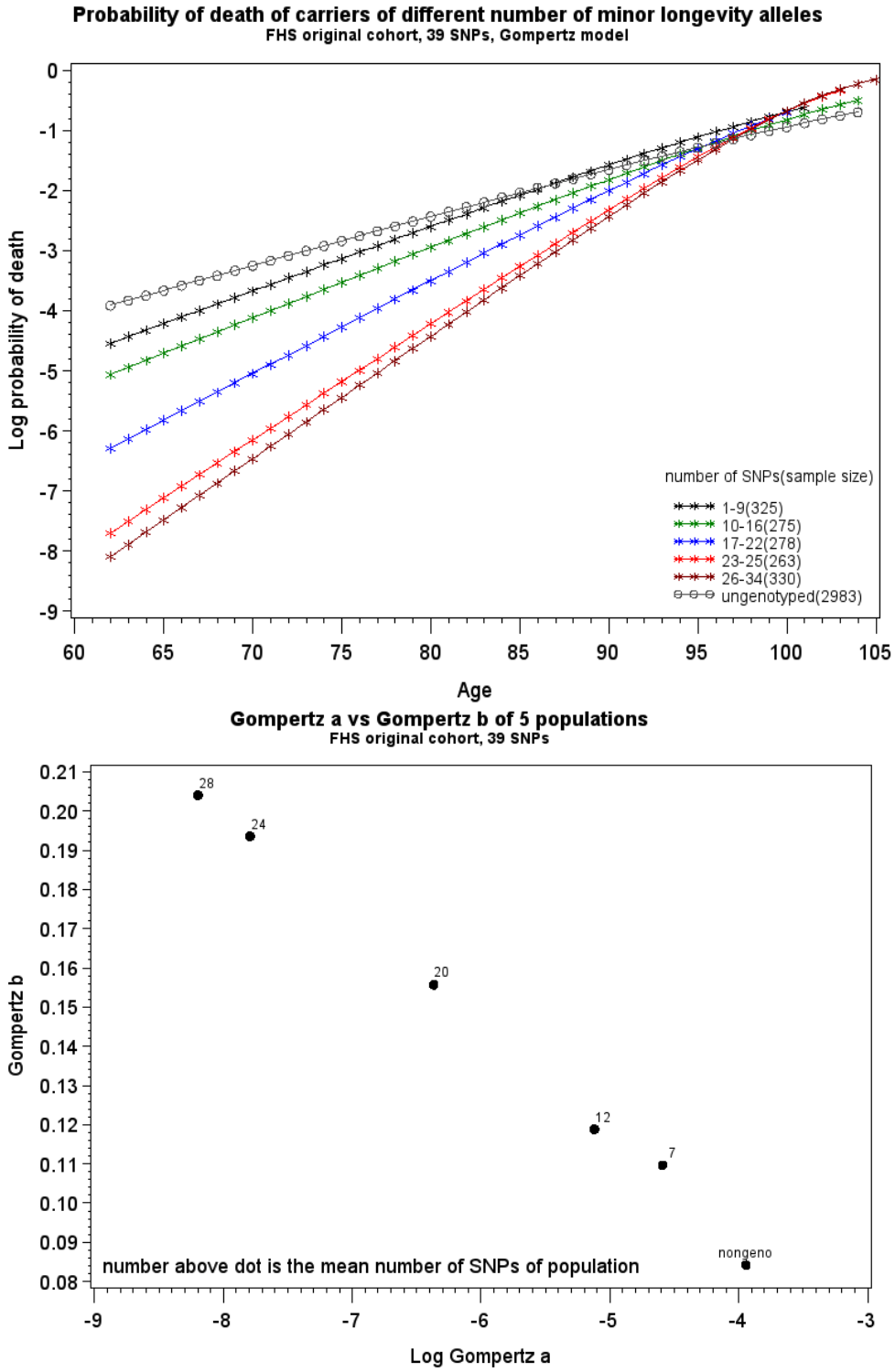

Fig. 3: ***Upper Panel:*** The logarithms of the estimates of mortality rates approximated by the Gompertz curves in the groups of individuals having different numbers of longevity alleles in their genomes. ***Bottom Panel*****:** The Strehler and Mildvan correlation between the Gompertz parameters of mortality rates in the groups of individuals having different numbers of longevity alleles in their genomes.