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Viewpoint

Recent advances in human gene–longevity association studies

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Abstract

This paper reviews the recent literature on genes and longevity. The influence of genes on human life span has been confirmed in studies of life span correlation between related individuals based on family and twin data. Results from major twin studies indicate that approximately 25% of the variation in life span is genetically determined. Taking advantage of recent developments in molecular biology, researchers are now searching for candidate genes that might have an influence on life span. The data on unrelated individuals emerging from an ever-increasing number of centenarian studies makes this possible. This paper summarizes the rich literature dealing with the various aspects of the influence of genes on individual survival. Common phenomena affecting the development of disease and longevity are discussed. The major methodological difficulty one is confronted with when studying the epidemiology of longevity involves the complexity of the phenomenon, which arises from the polygenic nature of life span and historical mortality change. We discuss this issue and suggest new methodological approaches.

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1. Introduction

The determinants of longevity have drawn the attention of researchers from a variety of disciplines, such as sociology, biology, psychology and medical science. Life span is a multifactorial quantitative trait, which is affected by genetic and environmental factors. It also contains a stochastic component resulting from the interaction between the individual chances of surviving and unpredictable events that occur throughout the life course (Luciani et al., 2001). Environmental changes that reduce mortality, e.g. advances in medicine, have a profound impact on the life span. Advances in the treatment of fatal diseases and improvements in nutrition and living conditions (environmental hygiene, social welfare and healthcare systems) led to a drastic reduction in death rate at young ages before 1950 and at old ages after 1950 in the developed world (Vaupel et al., 1998). As a result, mean life spans have experienced a remarkable increase in developed countries. With more and more people celebrating their 100th birthday, we need to come up with an explanation for life-span heterogeneity. Why do some people reach advanced ages while others do not? To answer this question we turn to individual factors such as lifestyle, behaviour, socio-economic background and genetic make-up. Using twin data, intensive studies carried out in recent decades (Carmelli, 1982; Harris, 1992; Hayakawa et al., 1992; McGue et al., 1993; Yashin et al., 1999a) have established that there is a genetic correlation between life spans. A well-known Danish twin study (Herskind et al., 1996) estimated the heritabilty of life span to be 0.23 for males and 0.20 for females. However, the molecular basis of the inherited components in human longevity is far from clear.

Two major arguments have to be taken into account in studies on the genetics of longevity. The first involves the definition of the phenotype. Longevity is, in fact, the net outcome of cumulative mortality over all age-classes, and cumulative mortality is historically controlled. For this reason, the introduction of a cut-off in the definition of longevity is quite arbitrary (Wilmoth et al., 2000). Second, classical approaches to the study of human genetics, which are aimed at detecting co-segregation of genetic markers in pedigrees, are not easy to implement. In fact, this requires the sampling of pedigrees that include two or more very old individuals, possibly in more than one generation, which is a very rare occurrence. This difficulty applies equally to parametric (lod score) and non-parametric (sib-pair) methods of assessing linkage. Moreover, the secular trend in the changing of environmental conditions renders a direct comparison between the age of death of parents and that of their offspring virtually meaningless.

For the above reasons, gene-longevity association studies of unrelated individuals, which search for non-random associations between polymorphisms at candidate loci and aging, have been the most popular type up to now, and the literature is growing quickly. This paper aims to review briefly the current literature and then to make some suggestions for possible avenues of future research on gene-longevity association.

2. A brief review of the literature

Table 1 summarises the genes whose polymorphisms have been analysed in more than one gene-longevity association study (only the post-1980 literature is considered).

The first conclusion one can draw from Table 1 is that, in most cases, different studies have furnished contradictory results. This can be explained by considering the problems which affect the reliability of case/control longevity studies (Caruso et al., 2000). Firstly, the assumption underlying association studies is that all individuals in a population are fundamentally related to each other, and the degree of their relationship has not been diluted by mutation rates or recombination between the marker and the functional variant. Therefore, studies carried out in genetically heterogeneous populations may be severely biased. Furthermore, the linkage disequilibrium between marker and functional variant may be different in different populations, depending upon the genetic history of the population itself. Secondly, longevity does not necessarily imply good health. In fact a careful examination of centenarians revealed that a substantial proportion of them reach the extreme limits of human life span although they exhibit important functional/cognitive disabilities (Forette, 1999; Franceschi et al., 2000a). Thus, the different results shown in Table 1 may be the consequence of different criteria of recruitment on the basis of health status. Thirdly, since drastic changes in the incidence and prevalence of a number of diseases have occurred in the past century, mortality for genotypes may depend on the birth year of the cohort, and the real controls to oldest-old people should consist of subjects who were born in the same year as the cases and who died before the age chosen as the longevity cut-off. The recently introduced genetic–demographic approach, which combines demographic information with data on genetic markers, may overcome this last problem and permit an estimation of hazard rates and survival functions for candidate genes and genotypes in unrelated individuals (Yashin et al., 1998; Toupance et al., 1998; Yashin et al., 1999b; Tan et al., 2001). In any case, the different results obtained in different studies strongly suggest that the influence of single genes on the overall population mortality is rather slight, and that this is probably affected by the genetic and environmental history of the population (Caruso et al., 2000). Despite the above-mentioned problems, the data in Table 1 seem to show a consistent association with longevity for some genes (APOE, APOB, APOA-IV, mtDNA). In particular, the current literature suggests that APOE is the locus that can most consistently and reliably affect longevity. Indeed, APOE genotype/allele distributions vary between centenarians and young people in a variety of populations, as recently reviewed in Gerdes et al. (2000). In this regard, it has been proposed that the e4 allele is a frailty gene, i.e. the APOE e4 carrier has an increased rate of mortality compared to the rest of the population. Moreover, the lack of association for other markers located in P53 and PARP genes also seems to be quite replicable (De Benedictis et al., 1998b; Muiras et al., 1998b; Bonafè et al., 1999a,b; Cottet, 2000).

Table 1
Genes whose polymorphisms have been analysed in association with longevity in more than one study[a]

Gene	Function	Disease associated	Longevity association
ApoE	Lipoprotein metabolism (apoprotein of HDL, VLDL)	AD, CVD	Yes (Louhija et al., 1994; Kervinen et al., 1994; Schachter et al., 1994; Zhang et al., 1998; Gerdes et al., 2000) No (Bader et al., 1998)
ApoB	Cholesterol homeostasis (sole apoprotein of LDL)	CAD	Yes (Kervinen et al., 1994; De Benedictis et al., 1997, 1998a)
ApoA-IV	Lipoprotein metabolism (apoprotein of HDL, VLDL)	AD?	Yes (Merched et al., 1998; Pepe et al., 1998)
ACE	Angiotensin converting Enzyme	MI, CI, AD, EH	Yes (Schachter et al., 1994; Faure-Delaneff et al., 1998) No (Bladbjerg et al., 1999; Heijmans et al., 1999a)
CYP2D6, CYP2C19	Cytochrome P450 gene family	PD? cancer susceptibility	Yes (Bathum et al., 1998) No (Agundez et al., 1997; Yamada et al., 1998; Muiras et al., 1998a)
HLA class I and class II	Immune response	Immune disorders	Yes (Proust, 1982; Takata et al., 1987; Dorak et al., 1994; Ma et al., 1997; Akisaka et al., 1997; Ivanova et al, 1998a; Ricci et al., 1998) No (Izaks et al., 1997)
P53	Tumor suppressor gene	Cancer susceptibility, Apoptosis	No (Bonafè et al., 1999a,b)
Factors V, VII, PAI-1	Blood coagulation and fibrinolysis proteins	MI, thromboembolia	Yes (Mari et al., 1996; Mannucci et al., 1997) No (Bladbjerg et al., 1999; Heijmans et al., 1999a; Meiklejohn et al., 2000)
Fibrinogen	Plasma coagulation factor	CAD	Yes (Mari et al., 1996) No (Mannucci et al., 1997; Bladbjerg et al., 1999)
Prothrombin	Blood coagulation and prothrombin protein	MI	Yes (Mari et al., 1996) No (Bladbjerg et al., 1999)
MTHFR	Homocysteine methylation	CVD Cancer susceptibility?	Yes (Faure-Delaneff et al., 1997; Matsushita et al., 1997; Kluijtmans et al., 1999; Todesco et al., 1999) No (Galinsky et al., 1997; Harmon et al., 1997; Brattstrom et al., 1998; Bladbjerg et al., 1999; Rea et al., 2000)

Table 1 (*Continued*)

Gene	Function	Disease associated	Longevity association
Mitochondrial DNA	Oxidative Phosphorylation	Mitochondrial diseases, CAD?, diabetes?, PD?, AD?	Yes (Tanaka et al., 1998; Ivanova et al., 1998b; De Benedictis et al., 1999)
PARP	DNA repair, apoptosis	???	No (De Benedictis et al., 1998b; Muiras et al., 1998b; Cottet, 2000)

[a] AD, Alzheimer's disease; CVD, Cardiovascular disease; CAD, Coronary artery disease; MI, Myocardial infarction; CI, Cerebral infarction; EH, Essential hypertension; PD, Parkinson disease.

Table 2 summarises the genes whose polymorphisms have been analysed in association with longevity in one study only.

Taking into account the contrasting findings within Table 1, both negative and positive results require caution. It is worth noting however that, while all the genes in Table 1 (except PARP) are known as potential risk factors in complex age-related diseases, three out of seven genes in Table 2 have been analysed only in regard to their biological role, without considering possible disease associations. Particularly intriguing are the roles played by TH and SOD2 genes, which were found to be associated with longevity although they are not associated with any known disease. TH encodes the rate-limiting enzyme for the synthesis of cathecolamines, which are aminoacid-derived molecules that act both as hormones (adrenalin) and neurotransmitters (dopamine and noradrenalin). The TH gene is therefore a master gene in the immune–neuro-endocrine system. Similarly crucial is the function of SOD2, which encodes the mitochondrial superoxide dismutase specifically responsible for reactive oxygen species (ROS) scavenging in mitochondria. It should be noted, however, that the same SOD2 data set was analysed using two different methodological approaches: the gene frequency method (De Benedictis et al., 1998b) and the relative risk method (Tan et al., 2001). Only the second approach, which is more sensitive, was able to reveal an allele-specific association with longevity. This new approach is based on the idea of combining data on genetic markers with demographic information. This allows for the evaluation and comparison not only of frequencies of selected alleles or genotypes but also of survival functions and mortality rates for groups of individuals carrying selected candidate

Table 2
A brief review of genes whose polymorphisms have been analysed in association with longevity in one study only[a]

Gene	Function	Disease associated	Longevity association
TPA (Tissue plasminogen Activator)	Fibrinolytic/thrombolytic response	MI? Stroke	No (Bladbjerg et al., 1999)
AGT (Angiotensinogen)	Renin–angiotensin system	EH, CVD, CAD, CHD	No (Bladbjerg et al., 1999)
GP2b3a	Blood coagulation	CVD	No (Bladbjerg et al., 1999)
TPO (Thyroid Peroxidase)	Thyroid metabolism	???	No (De Benedictis et al., 1997)
TH (Thyrosine Hydroxilase)	Catecholamine Synthesis	???	Yes (De Benedictis et al., 1998b)
SOD2 (Superoxide dismutase 2)	ROS scavenging, apoptosis	???	Yes (Tan et al., 2001)
WRN (Werner)	DNA helicase	Werner syndrome	No (Castro et al., 1999)

[a] MI, Myocardial infarction; EH, Essential Hypertension; CVD, Cardio-vascular disease; CAD, Coronary artery disease; CHD, Coronary heart disease.

genes or genotypes (Yashin et al., 1998). Several modifications of this method have been developed and applied to the analysis of data on genetic markers. They include parametric, semiparametric, non-parametric, and relative risk methods (Yashin et al., 1999b, 2000). In contrast to the Gene Frequency (GF) method, which assumes monotonous changes in genetic frequencies with age, this method can deal with non-monotone age-specific trajectories of the frequencies of a genotype. Such trajectories arise when mortality rates for groups of individuals carrying different genotypes intersect. The reasons for such an intersection and examples illustrating this phenomenon are discussed in Yashin et al. (1999b).

3. Do genetic risk factors affect longevity?

How can the negative findings be explained for genes whose variants are well-recognised risk factors in age-related diseases? Insights on this point could be furnished by some recently published studies. Heijmans et al. (1999b, 2000) confirmed that the homozygosity for the Val-allele of the MTHFR gene is associated with increased mortality for male carriers, with consistent results from both cross-sectional and prospective studies. This can be largely explained by an increased risk of death due to cancer. However, polymorphisms at the ACE and PAI-1 loci, which are associated with an increased risk of cardiovascular disease, failed to show any influence on mortality since individual genes make only a minor contribution to the mortality of the general population (Bladbjerg et al., 1999; Heijmans et al., 1999a). In this situation, cross-sectional studies should be capable of revealing a gene/longevity association only for those genes whose variability contributes significantly to general mortality. The data in Table 1 shows that this contribution is controversial for some risk factors of specific age-related diseases. Stronger effects should be observed if the gene itself played a major, age-sensitive biological role. For example, the positive association found between APOB polymorphisms and longevity would not depend solely on the APOB/CAD association (Table 1) but also on the role played by Apolipoprotein B in cholesterol homeostasis, which in turn could exert pleiotropic effects in a number of pathophysiological situations (Goldstein et al., 1989). Likewise, the positive association between mitochondrial DNA (mtDNA) inherited variability and longevity would not refer to specific mtDNA-associated diseases but to the master role (oxidative phosphorylation) played by the mitochondrial genome in cell metabolism. Time-related stochastic events could deteriorate master functions, and different polymorphic variants of the related genes could have different capabilities of coping with such time-related stress factors. Therefore, a decrease or increase in specific gene variants in the genetic pool of the oldest-old (as compared to those of younger individuals) would mirror the capability of these variants to compensate time-related damages in crucial cell pathways. In line with this hypothesis are the positive findings at the TH and SOD2 loci, although these findings require further confirmation. In contrast, the negative result obtained for the PARP gene is rather disappointing (De Benedictis et al., 1998b; Muiras et al., 1998b). Indeed, PARP encodes a zinc

finger nuclear enzyme which is strongly activated by DNA breaks and which promotes DNA repair (Satoh et al., 1992). It is to be expected that such a function is crucial in ageing since the time-related accumulation of somatic DNA damages requires an efficient DNA repair activity. What is more, a correlation between PARP gene expression and longevity in mammals is well established (Grube et al., 1994). The negative association between PARP variability and human longevity is not likely to depend on the lack of linkage disequilibrium between the markers used in the analysis, since other putative functional variants along the PARP gene have yielded similar negative results. In any case, these data reveal another difficulty in gene/longevity association studies, which is the choice of the markers. The ideal marker should have high Polymorphic Information Content (high PIC index) and provide information on a large part of the surrounding DNA region. Haplotypes, possibly including microsatellites and SNPs, seem to offer the best opportunity for this.

As one of the polygenic features of life span, some studies have reported the sex-dependent genetic influences on life span (Proust, 1982; Dorak et al., 1994; Ivanova et al, 1998a; De Benedictis et al., 1998b; Heijmans et al., 1999b). The gene–sex interaction suggests that the effect of a gene on a multifactorial trait depends on the physiological background in which the gene is expressed. If the age-related physiological scenario changes in males and females differently, the effects of a certain gene on disease or survival could vary between the sexes, which indicates that males and females may follow different trajectories toward extreme longevity (Franceschi et al., 2000a). More sophisticated statistical models aimed at detecting the gene–sex and gene–environment interactions are thus needed for genetic studies on longevity (Yashin et al., 2000; Tan et al., 2001).

On the whole, the data in Table 1 shows that gene polymorphisms, which are risk factors for severe diseases, either failed to reveal any association with longevity or they yielded completely unexpected results, such as the high incidence in centenarians of the D/D ACE genotype (Schachter et al., 1994; Faure-Delaneff et al., 1998) or the 4G/4G PAI-1 genotype (Mannucci et al., 1997). These findings may become more clear if they are viewed in the light of recent conceptualisations of human ageing and longevity (Franceschi et al, 2000b). Experimental data from model organisms (yeast, *C. elegans*, *Drosophila*) indicate that ageing and longevity are related, in a complex way, to the ability to cope with a variety of stressors. Vertebrates have developed a complex system, the immune–neuro-endocrine system, which modulates their ability to maintain an efficient network of highly integrated complex functions despite continuous, intrinsic and extrinsic disturbances, which consequences accumulate with time. From this perspective, many features of mammalian ageing could be considered to be the consequence of the long-term effects of chronic stress (Franceschi et al., 2000c). The capacity of the organism to recover from stress-induced modifications decreases in the elderly (Castellani et al., 1998). Furthermore, ageing exposes the organism to possible deleterious effects of stress-response molecules such as cathecolamines, which are highly toxic compounds probably responsible for the selective loss of dopaminergic neurons (Yang et al., 1999). In a heterogeneous population, such as human

population, the ability to maintain stress-response within a range compatible with good health might be age-dependent resembling dependence of survival function on age. Healthy centenarians (Franceschi et al., 2000a) may represent the extreme tail of such curve, which is formed by *the best adapted* individuals, who are able to remodel themselves continuously in the face of time-related challenges.

At any rate, studies both of model organisms and of healthy centenarians indicate the importance of an equilibrated capacity to cope with stress for attaining longevity. As a consequence, common genetic risk factors defined on the basis of specific diseases are probably not the key to longevity. Their effect on the mortality of the overall population is most likely to be negligible in comparison to the effect of master genes located at the knots of the ageing network. In light of these considerations, the next steps in human longevity research could be to search for stress-response genes that have been conserved by evolution. In any case, multidisciplinary approaches integrating demographic, genetic, biochemical, and clinical methods are needed to disentangle the complex network that controls ageing and longevity in higher organisms.

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