Open Access Journal of Gerontology & Geriatric Medicine

Juniper Publishers key to the Researchers

Opinion

Volume 2 Issue 1 - July 2017

OAJ Gerontol & Geriatric Med

Genetics, Lifestyles, Environment and Longevity: A Look in a Complex Phenomenon

Pili Roberto[2], Petretto Donatella Rita[1]*

[1]*Department of Education, Psychology and Philosophy, Italy*

[2]*Comunità Mondiale della Longevità, Italy*

Submission: July 15, 2017; **Published:** July 19, 2017

***Corresponding author**: Donatella Rita Petretto, Department of Education, Psychology and Philosophy, State University of Cagliari, Italy, CAP 09127; Email: drpetretto@unica.it

Abstract

In the last decades, the worldwide progressive ageing of population has had as a principal consequence to focus attention of researchers on the study of different variables that can help people to age well [1-6]. The awareness that ageing is a complex phenomenon, that affects different aspects and dominions of life, has led researchers to analyze it from different points of view (physiological one, psychological one, sociological one and so on). From a functional and a physiological point of view, ageing could be seen as a complex process where something changes. The results of these changes can be a reduction of functional abilities; the quantity of this reduction can vary a lot [7]. Nowadays there is a relative agreement between researchers in the findings that genetic and constitutional factors can control about 25%-30% of these changes and of the chance to age well, while other variables, mainly related to lifestyles, can control the remaining 70%-75 [8]. What variables are related to these changes and what can be the real level of reduction of functional abilities is perhaps the consequences of the complex interaction between different variables, genetics or constitutional ones, on one side, and behavioral and environmental ones, on the other side. The study of this complex mechanism is the focus of recent studies, mainly aiming to derive specific models of intervention to promote well-being in people who are ageing. A field of specific interest is the study of genetic basis of longevity [6, 8-18]. In this paper we will describe and analyze some recent findings in this field, also deriving from the experiences of long-lived people and centenarians [15] which can be a sort of "natural experiment" from which we could derive information about ageing and ageing well. Then, we will discuss some issues for future researches and for intervention.

In this paper we will describe and analyze some recent findings in this field, also deriving from the experiences of long-lived people and centenarians which can be a sort of "natural experiment" from which we could derive information about ageing and ageing well. Then, we will discuss some issues for future researches and for intervention.

Keywords: Active ageing, longevity, centenary, oldest olds, genetic, environmental variables, lifestyles, World Health Organization

Introduction

In the last decades, the worldwide progressive ageing of population, the so called "Demographic revolution" or "Demographic transition", has had the principal consequence to focus attention of researchers on the study of different variables that can help people to age well and live a long [1-6]. Ageing is the results of two kinds of processes: primary ageing and secondary ageing. While primary ageing is a genetically programmed process and it is an uncontrollable and irreversible one, the secondary ageing is biologically-based and it is related to the deterioration of physical and biological functions, during different phases of life. So, primary ageing is very difficult to control or modify, while secondary ageing could be influenced by some kind of control, related to lifestyle, psychological, social and environmental factors [15]. Ageing is a very complex phenomenon, the awareness of this complexity, that affects different aspects and dominions of life, has led researchers to analyze it from different points of view (physiological one, psychological one, sociological one and so on). From a functional and a physiological point of view, ageing could be seen a process where something change. The results of these changes can be a reduction of functional abilities, the quantity of these reduction can vary a lot [7]. Nowadays there is a relative agreement between researchers in the findings that genetic or constitutional factors can control about 25%-30% of these changes and also the chance to age well, while other variables, mainly related to lifestyles (like physical activity, diet and not smoking) and healthcare (prevention of age-related disorders or the so called "not-communicable disorders"), can control the remaining 70%-75 [8]. What variables are related to these changes and what can

be the real level of reduction of functional abilities is perhaps the consequences of the interaction between different variables (genetics or constitutional ones, on one side, and behavioral and environmental ones, on the other side) [6, 8-18]. The study of this complex mechanism is the focus recent studies. A field of particular interest is the study of the genetic basis of longevity and the biological basis on the bottom of long-living.

In this paper we will describe and analyze some recent finding in the field of study on genetics of longevity, also deriving from the experiences of "longevity people", "centenarians" and "supercentenarians" [15] which can be a sort of "natural experiment" from which derive a lots of information about different aspects of ageing, also genetic ones. The term "longevity people" refers to people older than 85 years. The term "centenarians" refers to people older than 100 years. The word "supercentenarians" refers to people older than 110 years. The term "exceptional longevity" refers to people who are 100 years old and over and it is a very rare phenomenon (about 0.7/1 person in 10.000 people as a mean in the worldwide population) [17]. Other study considered "exceptional longevity" when people are 95 years old and over [8]. There are some zones in the world where the exceptional longevity is more frequent. One of this is the island of Sardinia, in Italy, that in late 1990 were the first to be named Blu Zone [19-21]. Now a day, Sardinia has 1.658.138 inhabitants with 483 centenarians on January, 1 2016 (about 3 persons in 10.000 people). In Sardinia there also lives the oldest man of Italy, a 111 years old man whose name is Mister Valerio Piroddi. He was born on November, 11 1905 in Villamassargia and now he lives with his family in Assemini, a city near Cagliari.

Genetics of Longevity

There are at least three different kinds of studies on the genetics of the longevity: one kind is related to the study of longevity twins, another is related to the study of siblings or familiar person of longevity people, a third kind of study is related to study directly the genome of long-lived people (compared with a control-group). A first test of genetic aspects of longevity is its heritability, that is estimated in about 0.20-0.30 in general population (with gender differences, higher in men), and it increases with ages, so in centenarians the level is about 0.33 in women and 0.48 in men, showing that this component is higher in older ages and it shows gender differences [8, 15, 17]. A second test is the study of siblings of long-lived people, the so called "familiar effect". Dato and colleagues [17] reported that when we study the survival curves of a member of a cohort born in the same geographical area, siblings of long-lived people show a clear advantage for survival in any age. Also the risk to have age-related disorders or the so-called "not-communicable disorders" (like cardiovascular diseases, diabetes and cancer) is reduced in siblings of longevity people and they are healthier than controls from the same cohort. Santos-Lozano and colleagues [15] reported, for example, some studies on siblings of centenarians and revealed a greater chances to become centenarians between siblings and birth cohort (16.95 times greater chance for male siblings and 8.22 for female siblings). The role of biological components of longevity in this "familiar effect" is clearer when the studies analyzed the "brothers in law" of long-lived people, who share the same environment but do not share the same survival advantage. This data highlights the effect of genetic factors in longevity, estimated in about the 25% [17].

The third type of study is about the genome. The genetics of longevity, as a complex of quantitative traits, is supposed to be influenced by many genes (polygenic), located in the nuclear and in the mitochondrial genome. For this reasons, genetics of longevity has been studied (and it now studied) mainly by candidate gene analysis, linkage and linkage disequilibrium mapping and whole genome sequencing, and more recently by the study of exome and whole gene sequencing [9]. These different kinds of studies aim to study the genetic variation in longevity people and to describe genetic variants (mutations or polymorphisms, on specific genes, locus and with specific alleles) related to longevity [15]. According to Dato and colleagues [17] the identification of specific genes could be done by different methodological approaches: the candidate approach, by which a set of SNPs are studied in longevity people and younger control, from the same geographical zone and other kind of studies are performed with long-lived people from different geographical zone as control-group. As this type of studies has revealed inconsistent results (only consistent results on a few SNPs), new approaches are needed to overcome difficulties. One possibility is related to inform GWAS, a method based to the use of previous data deriving from large study on age-related disorders, used then to study longevity [17].

Results

Budowsky and colleagues [22] have reported between 300 and 750 genes related to longevity. Some years ago, Shadyab and LaCroix [8] described many genes with findings on influencing longevity, like APOE1, ATM, BCL, CETP, eNOS, FOXO1A, FOXOEA, KLOTHO, LMNA, TERC, HSPA, SOD1, SOD2, SOD3, NIOS1, NIOS2, NIOS3, P53, RAGE and others (Govindaraju et al., 2015). From this group, some genes are related to metabolic functions (FOXO1), oxidative stress (SOD3), lipid metabolism (APOE, CETP), and glucose metabolism (IGF1) [9].

In a recent review, Santos-Lozano and colleagues [15] revised and analyzed in general the impact on longevity of twenty most investigated single nucleotide polymorphisms (SNPs). They found that some SNPs have a positive impact (rs429358 in APOE gene, rs2802292 in FOXO3A gene, rs13217795 in FOXO3A gene, rs2764264 in FOXO3A gene, rs1042522 in TP53 gene, rs7762395 in FOXO3A gene, rs1800896 in IL10 gene), some have negative impact (rs7412, rs662, rs2755209, rs1050450), and others have no impact on longevity (rs3758391 and rs266729) [15]. Shadyab and LaCroix [8] revealed that there are consistent results only on the relationship between APOE (apolipoprotein

How to cite this article: Pili R, Petretto D R. Genetics, Lifestyles, Environment and Longevity: A Look in a Complex Phenomenon. OAJ Gerontol & Geriatric Med. 2017; 2(1): 555576.

E) gene and the FOXO3A (forkhead box O3A) gene with longevity [8].

Apolipoprotein E gene (and its three polymorphical alleles 2, 3 and 4) is the main carrier of cholesterol and it is useful for the transport of lipid, for the repair of injury in the brain and for the neural plasticity [8, 15]. It is also related to Alzheimer's disease (allele 4 is related to enhanced risk of onset of the disease and allele 2 protects from the disease) and cardiovascular disease (allele 4 and 2), mainly by their involvement in oxidative stress, inflammation and high level of lipid. The allele 2 is enhanced in frequency in centenarians, while allele 4 is related to early mortality (with inconsistent results between different centenarian studies) [8,15]. FOXO3A gene is related to the insulin/insulin-like growth factor 1 signaling pathway, and it is also related to oxidative stress and insulin sensitivity [8,15,17]. Govindaraju and Colleagues [9] reported that this gene is over represented in long-lived people from Okinawa (one of the BLUE-Zone). TP53 gene is related to the control of stress-response and it has a recognized role in the risk of cancer, hepatitis C, schizophrenia and ageing [15]. IL10 (immunoregulatory cytokine) gene has a role in limiting and terminating inflammatory responses with consequences for longevity, with different results on gender differences [15].

Also mitochondrial factors are related to longevity, for their role in the regulation of cellular metabolism and apoptosis and in the regulation of reactive oxygen species, which has been related to ageing as results of DNA damage. The consequences of oxidative stress are the enhanced risk of infection, age-related disease and disability and death [8].

Some methodological issues in genetic studies: According to Santos-Lozano and colleagues [15] the studies in this field show only modest effects of many genes. There is also a great debate on the consistency of the results of studies on genetic factors associated with longevity, and not all findings have been replicated [8,15]. As we have just said before, there are only consistent results only on the relationship between APOE and FOXO3A with longevity.

According to Shadyab and LaCroix [8], the inconsistency of results could be related to the fact that longevity is a polygenic trait, influenced by a lots of genetic and environmental factors and by the joint effects of multiple genetic variants: the nature of the longevity phenomenon as a complex polygenic trait enhance the level of difficulty in studying it, but perhaps the inconsistency of the results could be reduced by modifying some methodological issues. First, the candidate gene association study is the most common design used, but the use of different kind of control groups could increase the consistency of results between studies (younger people versus birth cohort groups that could help to control for environmental factors and life experiences). Also Dato and colleagues [17], state that the use of younger control can be a cause of inconsistent results: in different ages, the allele frequency of SNPs could change in a sort of U-shaped pattern, and not in a simple monotonic fashion. So, young and very old people could have similar higher allele frequencies, while 80 years olds could have a lower level. So, it could depend on the age of the control whether or not single researches could find different allele frequencies between centenarians and controls.

Both the authors state that the use of larger samples of exceptionally long-lived people and different population could permit to confirm some results [8,15]. Also the study of rare variants of genes associated with longevity, the study of different phenotypes, and the taking into account of gender differences could help to increase the consistency of the results [8].

Centenarians as distinct region of demographic distribution and as "super control group

Govindaraju and colleagues (9) state that centenarians represent a sort of "distinct region of demographic distribution" in the population, as they live about one generation more than other people (about 25 years more) and they have a healthier status than other people. Moreover, some genetic factors related to longevity are more enriched among them (like APOE, FOXO3A and others) and their genome shows more integrity, with low level of chromosomical aberrations, as a consequence of genomic stability and as a factor that contributes to their possibility to live longer. Their progeny also lives longer and also shows reduced level of age-related disorders, as cardiovascular disorders. Another aspect is that they have a greater frequency in specific geographical regions, like Blue Zone, where people share similar lifestyle and environment (9, 23). Govindaraju and colleagues (9) use for them the "Black Swan metaphor", comparing them to the presence of black swans in a zone where there are mainly white swans. For these and for other reasons, some authors decide to study centenarians as a specific group in genetic studies and to consider them as a sort of "super control group" for the study of age-related disorders (24).

Conclusion

In recent years, the study of genetics of longevity has been (and it is now) the focus of a great number of researches. There is the awareness that longevity is a very complex phenomenon, and that it is very important to study if from different points of view. From the genetic point of view, there is now only a relative agreement on the role of some SNPs, located in some particular gene and an agreement on the statement that longevity is surely a polygenic trait. Mainly, some of these genes are related to age-related disorders and to specific physiological and pathological processes, like inflammation, oxidation and lipid metabolism. But longevity is a complex phenomenon, where there is a close relationship between different levels and when the search of single aspects could lead to inconsistent results [17]. "It takes two to tango" (that is also the intriguing title of a recent paper [11] describes the recent debate on the interaction between genetic variables and lifestyles in influencing the individual chance to become oldest old and also centenarian and it well

How to cite this article: Pili R, Petretto D R. Genetics, Lifestyles, Environment and Longevity: A Look in a Complex Phenomenon. OAJ Gerontol & Geriatric Med. 2017; 2(1): 555576.

describes the multidisciplinary approach needed to afford this topic of research.

For our opinion, the study of genetics bases of longevity is in its advanced step but there is a great work to be done, mainly in the study of the complex relationship between genetics and lifestyles and environment and the study of the so called "niche construction", also with reference to novel dimensions of "constructed environments" [25-29]. What are the next steps. According to Capri and colleagues [30] another step to be done is related to the study of all the components of the complexity of human longevity genetic, like the interactions with essential genomes, culture and microbiome, because the study of longevity-related genes does not explain the mechanisms of healthy aging and longevity rather highlight the role of the epigenetic contribution.

Another step, from a more general perspective is, perhaps, the development of specific studies starting from biological point of view and reaching a biopsychosocial point of view. The general aims of all the study in the field of ageing and longevity is to elaborate specific interventions aiming to modulate the interaction between genetic and environmental aspects of ageing and longevity, and to guarantee well-being and good quality of life of people in different phases of life and to guarantee each person to age with dignity.

Acknowledgment

The Authors wish to thanks all the oldest olds and their families who collaborated to the researches and, especially, Mr. Valerio Piroddi and his family, the dean man of Sardinia and Italy. The Authors also wish to thanks Ing. Andrea Domenico Petretto for English revision.

This study is supported by RP's grant from Fondazione di Sardegna and by DRP's personal research grant from University of Cagliari DRP. DRP and RP equally contributed to the design of the study, to the qualitative analysis of literature, they have drafted the paper, have revised the paper and have approved the final manuscript.

References

[1]. Rowe J.W., Khan R.L. (1987), Human aging: usual and successful, Science, 237, 143-149.

[2]. Rowe J.W., Kahn R.L. (1988), Successful aging, New York, Random House.

[3]. Rowe J.W., Kahn R.L. (1998), Reply to Letter to Editor, The Gerontologist, 38(2), 151.

[4]. Petretto D.R., Pili R., Gaviano L., Matos Lòpez C., Zuddas C., Active ageing and success: a brief history of conceptual models, Envejecimiento activo y de éxito o saludable: una breve historia de modelos conceptuales, Revista Esp. Geriatr Gerontol, jul-aug, 51(4), 229-41, 2016a.

[5]. Petretto D.R., Pili R., Le vie dell'invecchiamento attivo e di successo: modelli concettuali, International Congress on Active Ageing and Longevity, Giornate di Studio sull'invecchiamento Attivo e di Successo in un'ottica biopsicosociale Cagliari, 15-16 Aprile 2016b.

[6]. Pili R., Promuovere l'invecchiamento attivo alle frontiere della longevità: giornata di studio internazionale tra Sardegna, Spagna e Bielorussia – To promote active ageing in the frontiers of longevity: International conference on Sardinia, Spain and Republic of Belarus, Cagliari, 24 giugno, 2017.

[7]. Petretto D.R., Pili L., Gaviano L., Pili R., On the Semantic of Ageing: from Successful Ageing to Dynamic and Developmental Model of Ageing, Open access Journal of Gerontology and Geriatric Medicine, 2017. 1(3), 555562.

[8]. Shadyab A.H., LaCroix A.Z., Genetic Factors associated with longevity: a review of recent findings, Ageing Research Reviews, 19, 1–7, 2015.

[9]. Govindaraju D., Atzmon G., Barzilai N., Genetics, lifestyle and longevity: lessons from centenarians, Applied & Translational Genomics, 4, 23-32, 2015.

[10]. Minster R.L., Sanders J.L., Singh J., Kammerer C.M., Barmada M., Matteini A.M., Zhang Q, Wojczynski M.K., Warwick Daw E., Brody J.A., Arnold A.M., Lunetta K.L., Murabito J.M., Chiristensen K., Perls T.T., Province M.A., Newman A.B., Genome-wide association study and linkage analysis of the healthy aging index, Journals of Gerontology: Medical Sciences, 1003-1008, 2015.

[11]. Passarino G., De Rango F., Montesano A., Human Longevity: genetics or lifestyle? It takes two to tango, Immunity and Ageing, 13: 12, 2016.

[12]. Brooks-Wilson A. R., Genetics of Healthy ageing and longevity, Human Genetics, 132, 1323-1328, 2013.

[13]. Ostan R., Monti D., Gueresi P., Bussolotto M., Franceschi C., Baggio G., Gender, aging, and longevity in humans: an update o fan intriguing/ neglected scenario paving the way to a gender-specific medicine, Clinical Science, 130, 1711-1725, 2016.

[14]. Sen P., Shah P.P., Nativia R., Berger S.L., Epigenetic Mechanisms of longevity and aging, Cell, 166, 822-839, 2016.

[15]. Santos-Lozano A., Santamarina A., Pareja-Galeano H., Sanchis-Gomar F., Fiuza-Luces C., Cristi-Montero C., Bernal- Pinor A., Lucia A., Garatachea N., The Genetics of exceptional longevity: insights from centenarians, Maturitas, 90, 49-57, 2016.

[17]. Dato S., Rose G., Crocco P., Monti D., Garagnani P., Franceschi C., Passarino G., The genetics of human longevity: an intricacy of genes, environment, culture and microbiome, Mechanisms of Ageing and Development (2017).

[18]. Montesanto A., De Rango F., Pirazzini C., Guidarelli G., Domma F., Franceschi C., Passarino G., Demographic, genetic and phenotypic characteristics of centenarians in Italy: focus on gender differences, Mechanisms of Ageing and Development, 2017.

[19]. Pes G.M., Research Workshop on "Genes, genealogy and longevity", Montpellier, 1999.

[20]. Deiana L., Ferrucci L., Pes G.M., Carru C., Delitala G., Ganau A., Mariotti S., Nieddu A., Pettinato S., Putzu P., Franceschi C., Baggio G., AkentAnnos. The Sardinia Study of Extreme Longevity, Aging, 11(3), 142-149, 1999.

[21]. Poulain M., Pes G.M., Grasland C., Carru C., Ferrucci L., Baggio G., Franceschi C., Deiana L., Identification of a geographic area characterized by extreme longevity in the Sardinia Island: the AKEA study, Experimental Gerontology, 2004, 39(8), 1423-29.

[22]. Budowsky A., Craig T., Wang B., Tacutu R., Csordas A., Lourengo J., Frailed V.E., de Magalhaes J.P., longevity Map: a data base of human genetic variants associated with longevity, Trends in Genetic, 29, 539-560, 2013.

[23]. Govindaraju D.R., Evolutionary genetic bases of longevity and senescence, 847:1-44, 2015.

[24]. Giuliani C., Pirazzini C., DelleDonne M., Zumerle L., Descombes P.,

How to cite this article: Pili R, Petretto D R. Genetics, Lifestyles, Environment and Longevity: A Look in a Complex Phenomenon. OAJ Gerontol & Geriatric Med. 2017; 2(1): 555576.

Marquis J., Mengozzi G., Monti D., Bellizzi D., Passarino G., Luiselli D., Franceschi C., Garagnani P., Centenarians as extrem phenotypes: an ecological perspective to get insight into the relationship between genetics of longevity and age-associate diseases, Mechanisms of Ageing and Development, 2017.

[25]. Odling-Smee F.J., Laland K.N., Feldman M.W., Niche construction. Am Nat 147:641–648, 1996.

[26]. Odling-Smee F.J., Laland K.N., Feldman M.W., Niche construction: the neglected process in evolution. In: Monographs in population biology, vol 37. Princeton University Press, Princeton, 2003.

[27]. Odling-Smee F.J., Erwin D., Palkovacs E., Niche construction theory: a practical guide for ecologists. Q Rev Biol 88:3–28, 2013.

[28]. Matthews B., De Meester L., Jones C.G., Ibelings B.W., Boume T.L., Nuutinen V., Van de Koppel J., Under niche construction: an operational bridge between ecology, evolution and ecosystem science, Ecological Monograph, 84(29), 245-263, 2014.

[29]. Laland K., Matthews N., Feldman M.W., An introduction to niche construction theory, Evo Ecol, 30: 191-202, 2016.

[30]. Capri M., Santoro A., Garagnani P., Bacalini M.G., Pirazzini C., Olivieri F., Procopio A., Salvioli S., Franceschi C., Genes of human longevity: an endless quest? Current Vascular Pharmacology, 12(5), 707-717, 2014.

How to cite this article: Pili R, Petretto D R. Genetics, Lifestyles, Environment and Longevity: A Look in a Complex Phenomenon. OAJ Gerontol & Geriatric Med. 2017; 2(1): 555576.