Kujawska Agnieszka, Husejko Jakub, Topka Weronika, Androsiuk-Perkowska Joanna, Skierkowska Natalia, Gajos Małgorzata, Perkowski Radosław, Karpińska Anna, Kromrych Kamila, Kotarska Marta, Zielińska Natalia, Kożuchowski Marcin, Kędziora-Kornatowska Kornelia. What promotes longevity? Journal of Education, Health and Sport. 2017;7(9):142-154. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.888796
http://ojs.ukw.edu.pl/index.php/johs/article/view/4797

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26.01.2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 01.08.2017. Revised: 10.08.2017. Accepted: 31.08.2017.

What promotes longevity?

Agnieszka Kujawska[1], Jakub Husejko[1], Weronika Topka[1], Joanna Androsiuk-Perkowska[1], Natalia Skierkowska[1], Małgorzata Gajos[1], Radosław Perkowski[1], Anna Karpińska[1], Kamila Kromrych[1], Marta Kotarska[1], Natalia Zielińska[1], Marcin Kożuchowski[1], Kornelia Kędziora-Kornatowska[1]

1. Faculty of Health Sciences, Department and Clinic of Geriatrics, Nicolaus Copernicus University

Abstract

Introduction Scientists try to answer on the need of a long life with a full physical capability Nonagenarians, centenarians and their closest family members are characterized by a survival benefit throughout life. Moreover, twin studies of longevity suggest that around 25% of the variation in lifespan in developed countries may be inherited. It is therefore worth to examine the role of inter-relationship between nature vs nurture in longevity increment.

Material and methods Articles in the EBSCO database have been analyzed using keywords: longevity, gene, behavior, environment. The available literature was subjectively selected. Then, the newest version of every paper was searched for.

Results Restriction of calories as well as intake of desirable nutrients can promote adequate control of metabolic pathways and gene expression. APOE, DRD4, Paraoxonase 1, SIRT 3 and SIRT 5 genes can play an important role in longevity.

Conclusions Genetic profile and environmental factors seems to both influence on the longevity. Relationships between genetic profile, behavior pattern, quality of life, years spent free from activity limitations and longevity should be examined, to be able to give a recipe on living a long and happy life.

Keywords longevity, gene, behavior, environment

Introduction

The will to live a long life with a full physical capability is a constantly returning theme in culture. Focusing only on one element; namely the Fountain of Youth, numerous sources from worldwide origin is known in today's cultural heritage which are about water which increase vital force of anyone who drinks or bathes in it. Scientists also joined to the search for the secret of longevity. Nonagenarians, centenarians and their closest family members are characterized by a survival benefit throughout life [1, 2]. Lower risk of the two leading causes of death: coronary artery disease, cancer can translate on longevity [3, 4] as well as lack of type-2 diabetes. Moreover, longevity traits of such as: low glucose levels and preserved insulin sensitivity [5, 6] could reveal itself in middle aged members of long-living families. Therefore, it is worth to examine the background factors which facilitate longevity.

1.1 Molecular mechanism of longevity. Translation of research evidence from animals to humans

Many studies show that the most effective method in prolonging life is calorie restriction (CR), it was confirmed in mice, rats, fruit flies, worms, and yeast [7, 8, 9]. Older rodents with CR diet seems to have similar pattern of gene expression to their younger counterpart with ad libitum diet [10]. The sirtuin pathway can play one of the main roles in beneficial effects of CR diet. Sirtuins are deacetylases that regulate/silence gene expression. The pro-longevity effects of CR in yeast require an intact sirtuin pathway [11, 12]. Another main player in longevity is the mammalian target of rapamycin (mTOR), which is an evolutionarily conserved nutrient-sensing protein kinase. It belongs to the phosphoinositide 3-kinase (PI3K)-related protein kinase family and acts as a central regulator of growth and cell division [13]. Several interventions involving mTOR pathway result in increased longevity of various creatures, such as: inhibition of the mTOR signaling pathway in yeast [14] Caenorhabditis elegans [15] and rodents [16]. Inhibition of this pathway could provide cardiovascular benefits and improved metabolic function [13]. Inhibition of the mTORC1 pathway may be a one of potential causes of CR, what in turn lead to decrease in cancer incidence and growth rate [17], implying that enhanced mTOR signaling plays a central role in cancer progression and in both Type 1 and Type 2 diabetes, with chronic activity of mTORC1 contributing to obesity and insulin resistance [18].

Resveratrol, one of the polyphenols included in many products, inter alia in red wine, is widely examined in terms of possible pro-health activity. In one study, incorporating both in vivo and in vitro methods, resveratrol suppressed AT1R expression through SIRT1 activation

[19 Authors conclude that inhibition of the renin-angiotensin system may play a role in the prolonging of the lifetime and inhibiting atherogenesis effects of resveratrol [19]. Large part of evidence reveals that resveratrol mimics the effects of CR in increasing the longevity, however, the biological background remains unknown. One of possible explanation is that both CR and resveratrol improve insulin sensitivity, what leads glucose levels reduction in the body [20, 21, 22].

1.2 Role of genetic profile in longevity

Twin studies of longevity suggest that around 25% of the variation in lifespan in developed countries may be inherited [23]. One of candidates on "longevity gene" is the Apolipoprotein E (apoE), involved in lipoprotein metabolism and many other crucial functions [24]. The gene on chromosome 19q13.2 has three common alleles, e2, e3, and e4. Carriers of the e4-allele have higher risk of coronary heart disease and Alzheimer's disease, relative to people with the most common genotype, e3e3, and carriers of the e2-allele have lower risk [24, 25, 26]. The APOE e4 allele is commonly found among African-Americans (20%), Caucasians (15%) and Japanese (10%) [26]. Interestingly, there could be some sex differences in relation of APOE alleles and longevity. Results of studies on population from southern region of Italy showed that grouping participants due to sex, greater number of e2 carriers was noted only in elderly and centenarian men and not in women [27]. In addition, studies based on a population of 2118 nonagenarian Caucasian sibling pairs from 15 study centers of 11 European countries showed that APOE locus is a longevity gene. Moreover, Authors declare that additional longevity loci could be possibly identified at 14q11.2, 17q12-q22, and 19p13.3-p13.11 [28]. In line with these results, are conclusions from studies based on another population of 403 nonagenarians and 1670 controls younger than 65 years [29] and in a study of 763 long-lived individuals and 1085 younger controls [30] and by a longitudinal study of 1606 Danes which revealed the highest effect size of APOE allele and longevity in the oldest subgroup [31].

FOXO1 polymorphism can play an essential role in longevity in humans [32]. However, these results were not replicated by studies based on large European sample [28].

Moreover, mitochondrial DNA haplotypes, which in most multicellular organisms is maternally inherited, may play a crucial role in longevity. Population-based studies in Europe and Japan have reported that some mitochondrial DNA haplotypes are more common in centenarians than in the general population [33, 34, 35, 36, 37, 38].

The human sirtuin 3 (SIRT3) gene encodes a mitochondrial protein (SIRT3). Studies based

on a population from southern Italy [39] founded coexistence between a marker of SIRT3 and survivorship in a group of males. Moreover, Sirt1, a potential marker and modulator of the drug resistance phenotype in cancer could play a main role in longevity [40]. In addition, there are some tissue-specific examinations on effects of gene polymorphisms on ageing. For example, one low-expressing polymorphism of a Sirtuin5 (SIRT5prom2). In a cross-cohort microarray examination of several human brain areas, the largest effect of aging was showed in cingulate, but not amygdala [41].

The DRD4 receptor belongs to the D2-like class of receptors, expressed in several brain regions, with high levels in prefrontal cortex [42]. In a studies comparing two populations (n1=310, n2=2902) the oldest-old population had a 66% increase in individuals carrying the 7R allele of the DRD4 gene [43].

Moreover, studies examining Paraoxonase 1 (PON1) is one of the most commonly examined genes in terms of cardiovascular risk, oxidative stress and inflammation. Results show that PON1 gene variants at codon 192 impact on the probability of attaining longevity, and that subjects carrying RR and QR genotypes (R+ carriers) are favored in reaching extreme ages [44].

In addition, two studies based on the same population from Finland it was shown that subgroup characterized by the high producer genotype of Interleukin-6 (IL6) is associated with increased mortality [45] and that characterized by the high produce of C-reactive protein (CRP) genotype had shorter life expectancy [46]. Curcumin may protect against oxidant- and lipid-induced damage in the inflammatory cells of the vascular system, thus reducing the risk for age-associated cardiovascular disease by increasing FoxO3 activity [47]. The concept of inflammAGING have both solid theoretical background [48] which was later appreciated in experimental studies on interaction of the longevity and genetic profile [49].

1.3 Role of diet in longevity

A study on a sample of 7989 men aged 65 to 83 years from Perth, Western Australia has verified that a “healthy lifestyle”, which included diet, allows for a lengthening of the average life by a nearly five years [50]. The researchers from Denmark came to similar conclusions, studying a group of women aged 60 to 69 years, where they emphasize the importance of the type of diet. According to the results, a Healthy Traditional Dutch Diet, with high intakes of vegetables, fruits, nonalcoholic drinks, dairy products and potatoes, can reduce mortality risk by 30%, compared to diet with high intakes of meat, potatoes, vegetables and alcoholic drinks [51].

There are currently many studies on the effects of the Mediterranean Diet (MD), which is combination of fruit and vegetables, fish, cereals and polyunsaturated fats, on longevity, and its meaning has been declared by United Nations Educational, Scientific and Cultural Organization (UNESCO) in 2010 [52, 53]. Recent studies indicate the impact of MD on reducing cancer progression and the incidence of obesity and obesity-related diseases, such as metabolic syndrome, which prolongs the life expectancy [53]. MD appears to be more effective in terms of longevity promotion, than traditional diet for a given area and should be widely recommended, for example in Great Britain [54]. However, studies from Denmark show that a Healthy Traditional Dutch Diet is even more beneficial than MD in terms of longevity and pro-health effects [51].

The effects of particular types of food on aging process seems to be important also. Results of studies conducted in Shanghai shows that eating fruits and drinking milk at a young age lower the risk of developing high blood pressure in middle and old age [55]. Other studies underline the importance of eating fruits and vegetables in preventing the development of osteoporosis [56] and high levels of LDL cholesterol [57], which can significantly prolong human life and improve its quality.

1.4 Methodological problems in researches on longevity

Based on the above reviewed results, one can suppose that years of staying healthy/without diseases life is a crucial factor in longevity. Indeed, other Authors proposed three ways to becoming a centenarian: surviving one or more potentially fatal age-related diseases, delaying their onset, or staying healthy [58]. In contrary to that, Eurostat statistics show “gender gap” in longevity in favor for greater longevity of women. Men longevity are on average shorter, although greater proportion of life is spent free from activity limitations [59].

However, studies on longevity are not free from methodological problems. Lewis et al propose that two of commonly stated assumptions in such studies are very labile [60]. The first assumption, that allele frequencies in the different age groups are similar do not take into account, inter alia, various migrations of populations. Another assumption of independency between genotype and year of birth in terms of risk of mortality [60]. This assumption may be broken, especially when taking into account that often examined population is the European one which the date birth is around a second world war or around, when unusual environmental factors occurred.

Moreover, studies on p66Shc in relation to the coronary artery disease occurrence concluded,

that variations of this gene which could have potential influence on patients health state are so rare in a examined population, that this gene is not involved in the mechanism of coronary artery disease [61].

One can suppose that empirical evidence on methodological weaknesses of studies on longevity can be revealed by the French paradox. It is understood as a high intake of dietary cholesterol and saturated fat but low coronary heart disease death rates and has several potential explanations [62]. Pattern of attitude and behavior such as pleasure-centered attitude to food and regular, moderate wine drinking pattern could possibly explain in part this paradox [62]. Moreover, the pattern of leisure time physical activity can play a significant role as well [62]. Most importantly, it show to scientists how much is yet to-be discovered.

Conclusion

Both genetic profile and environmental factors seems to influence on longevity. Most importantly, longevity seems to be more dependent on the second factor, which means that it is worth to conduct epidemiological studies on longevity, which results could be translated to popular science sources available to laymen which want to gain the knowledge, especially about potentially modifiable factors that increase longevity. It seems that the target group of recipients of such information should not be restricted to older people only: longevity seems to be a result from life-long daily pattern of behaviors, what was confirmed by the results of researches, with important point in the mid-life. In terms of longevity, diet plays a crucial role. Restriction of calories as well as intake of desirable nutrients can promote adequate control of metabolic pathways and gene expression.

Further studies on the role of the genetic profile in longevity should incorporate large populations to ensure proper size of subgroups with even the most uncommon alleles. Moreover, diet pattern, for example: alcohol consumption should not be measured in quantity only manner; it seems reasonable to measure the time of intake (wine to dinner pattern in Mediterranean diet vs binge drinking at night). In addition, the level of social contacts, approach to coping with daily life problems etc. might be included into analysis also. The role of physical activity, which description was beyond of the scope of above review, could also be examined due to the fact of well-known disease prevention effects, what in turn can potentially promotes longevity. Last but not least, relationships between behavior pattern, quality of life, years spent free from activity limitations and longevity should be examined to give a clues on living a long and happy life.

References

1.Perls, T. T., Wilmoth, J., Levenson, R., Drinkwater, M., Cohen, M., Bogan, H., Joyce, E., Brewster, S., Kunkel, L., Puca, A. Life-long sustained mortality advantage of siblings of centenarians. *Proc. Natl Acad. Sci*. 2002, USA 99, 8442–8447.

2. Schoenmaker, M., De Craen, A.J., de Meijer, P.H., Beekman, M., Blauw, G.J., Slagboom, P.E., Westendorp, R. G. Evidence of genetic enrichment for exceptional survival using a family approach: the Leiden Longevity Study. *Eur. J. Hum. Genet*., 2006, 14, 79–84.

3. Terry, D. F., Wilcox, M., Mc Cormick, M. A., Lawler, E., Perls, T. T. Cardiovascular advantages among the offspring of centenarians. *J. Gerontol. A Biol. Sci. Med. Sci*. 2003, 58, M425–M431.

4. Westendorp, R. G, van Heemst, D., Rozing, M. P., Frolich, M., Mooijaart, S. P., Blauw, G. J., Beekman, M., Heijmans, B. T., De Craen, A. J., Slagboom, P. E. Nonagenarian siblings and their offspring display lower risk of mortality and morbidity than sporadic nonagenarians: the Leiden longevity study. *J. Am. Geriatr. Soc.,* 2009, 57, 1634–1637.

5. Rozing, M. P., Westendorp, R. G., De Craen, A. J., Frolich, M., de Goeij, M. C., Heijmans, B. T., Beekman, M., Wijsman, C. A., Mooijaart, S. P., Blauw, G.J., Slagboom, P. E., van Heemst, D. Favorable glucose tolerance and lower prevalence of metabolic syndrome in offspring without diabetes mellitus of nonagenarian siblings: the Leiden longevity study. *J. Am. Geriatr. Soc.,* 2010, 58, 564–569.

6. Slagboom, P. E., Beekman, M., Passtoors, W. M., Deelen, J., Vaarhorst, A. A., Boer, J. M., van den Akker, E. B., van Heemst, D., De Craen, A. J., Maier, A. B., Rozing, M., Mooijaart, S. P., Heijmans, B. T., Westendorp, R. G. Genomics of human longevity. Philos. Trans. R. Soc. Lond. *B Biol. Sci*., 2011, 366, 35–42.

7. Masoro, E. J., Caloric restriction and aging: an update. *Exp Gerontol.,* 2000;35:299-305.

8.Sohal, R. S., Weindruch, R. Oxidative stress, caloric restriction, and aging. *Science,* 1996;273:59-63.

9.Mair, W., Goymer P., Pletcher, S. D., Partridge, L. Demography of dietary restriction and death in Drosophila. *Science,* 2003;301:1731-3.

10. Lee, C. K., Klopp, R., Weindruch, R., Prolla, T. Gene expression profile of aging and its retardation by caloric restriction. *Science,* 1999;285:1390-1393.

11. Howitz, K. T., Bitterman, K. J., Cohen, H. Y., et al. Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. *Nature,* 2003;425:191-6.

12. Anderson, R. M., Latorre-Esteves, M., Neves, A. R., et al. Yeast life-span extension by calorie restriction is independent of NAD fluctuation. *Science,* 2003;302:2124-6.

13.Stanfel, M. N., Shamieh, L. S., Kaeberlein, M., Kennedy, B. K. The TOR pathway comes of age. *Biochim. Biophys*., Acta 1790, 2009,1067–1074.

14. Kaeberlein, M., Powers, R. W. III., Steffen, K. K., Westman, E. A., Hu, D., Dang, N., Kerr, E. O., Kirkland, K. T., Fields, S., Kennedy, B. K. Regulation of yeast replicative life span by TOR and Sch9 in response to nutrients. *Science*, 2005,310, 1193–1196.

15. Vellai, T., Takacs-Vellai, K., Zhang, Y., Kovacs, A. L., Orosz, L., Muller, F. Genetics: influence of TOR kinase on lifespan in C. elegans. *Nature*, 2003, 426, 620.

16. Harrison, D. E., Strong, R., Sharp, Z. D., Nelson, J. F., Astle, C. M., Flurkey, K., Nadon, N. L., Wilkinson, J. E., Frenkel, K., Carter, C. S., Pahor, M., Javors, M.A., Fernandez, E., Miller, R. A. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature, 2009*, 460, 392–395.

17. Spindler, S. R. Rapid and reversible induction of the longevity, anticancer and genomic effects of caloric restriction. *Mech. Ageing Dev.,* 2005, 126, 960–966

18. Newgard, C. B., An, J., Bain, J. R., Muehlbauer, M. J., Stevens, R. D., Lien, L. F., Haqq, A. M., Shah, S. H., Arlotto, M., Slentz, C. A., Rochon, J., Gallup, D., Ilkayeva, O., Wenner, B. R., Yancy, W. S. Jr., Eisenson, H., Musante, G., Surwit, R. S., Millington, D. S., Butler, M. D., Svetkey, L. P. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metab. 9*, 2009, 311–326.

19. Miyazaki, R., Ichiki, T., Hashimoto, T., Inanaga, K., Imayama, I., Sadoshima, J., & Sunagawa, K. SIRT1, a longevity gene, downregulates angiotensin II type 1 receptor expression in vascular smooth muscle cells. *Arteriosclerosis, thrombosis, and vascular biology*, 2008, *28*(7), 1263-1269.

20. Baur, J. A., Pearson, K. J., Price, N. L., Jamieson, H. A., Lerin, C., Kalra, A., Prabhu, V. V., Allard, J.S., Lopez-Lluch, G., Lewis, K., Pistell, P. J., Poosala, S., Becker, K. G., Boss, O., Gwinn, D., Wang, M., Ramaswamy, S., Fishbein, K. W., Spencer, R. G., Lakatta, E. G., Le Couteur, D., Shaw, R. J., Navas, P., Puigserver, P., Ingram, D.K., de Cabo, R., Sinclair, D. A. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*, 2006, 16:337–342.

21. Blu¨her, M., Kahn, B. B., Kahn, C. R., Extended longevity in mice lacking the insulin receptor in adipose tissue. *Science*, 2003, 24:572–574.

22. Lagouge, M., Argmann, C., Gerhart-Hines, Z., Meziane, H., Lerin, C., Daussin, F.,

Messadeq, N., Milne, J., Lambert, P., Elliott, P., Geny, B., Laakso, M., Puigserver, P., Auwerx, J. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. *Cell*, 2006, 15:1109–1122.

23. Cournil, A., Kirkwood, T. B. L. If you would live long, choose your parents well. *Trends Genet.*, 2001, 17, 233–35.

24. Davignon, J., Bouthillier, D. , Nestruck, A. C., Sing, C. E., Apolipoprotein E polymorphism and atherosclerosis: insight from a study in octogenarians. *Trans Am Clin Climatol Assoc. 99*, 1987, 100–10.

25. Wilson, P. W. F., Schaefer, E. J., Larson, M. G., Ordovas, J. M., Apolipoprotein E alleles and risk of coronary disease: a meta-analysis. *Arterioscler Thromb Vasc Biol.*, 1996, 16, 1250–5.

26. Farrer, L. A., Cupples, L .A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., Myers, R.H., Pericak-Vance, M. A., Risch, N., Van Duijn, C. M. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease MetaAnalysis Consortium. *JAMA 278*, 1997, 1349±1356.

27. Seripa, D., Franceschi, M., Matera, M. G., Panza, F., Kehoe, P. G., Gravina, C., ... & Pilotto, A. Sex differences in the association of apolipoprotein E and angiotensin-converting enzyme gene polymorphisms with healthy aging and longevity: a population-based study from Southern Italy, *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 2006, *61*(9), 918-923.

28. Beekman, M., Blanché, H., Perola, M., Hervonen, A., Bezrukov, V., Sikora E., ... & Rea I. M., Genome-wide linkage analysis for human longevity: Genetics of Healthy Aging Study, *Aging cell*, 2013, *12*(2), 184-193.

29. Deelen, J., Beekman, M., Uh, H. W., Helmer Q., Kuningas, M., Christiansen L., Kremer, D., Van der Breggen, R., Suchiman, H. E. D., Lakenberg, N., Van den Akker, E. B., Passtoors, W. M., Tiemeier, H., van Heemst D., De, C. A., Rivadeneira, F., De Geus, E. J., Perola M., van der Ouderaa, F. J., Gunn, D. A., Boomsma, D. I., Uitterlinden, A. G., Christensen, K., van Duijn, C. M., Heijmans, B. T., Houwing-Duistermaat, J. J., Westendorp, R. G., Slagboom, P. E. Genome-wide association study identifies a single major locus contributing to survival into old age; the APOE locus revisited. *Aging Cell 10*, 2011, 686–698.

30. Nebel, A., Kleindorp, R., Caliebe, A., Nothnagel, M., Blanche, H., Junge, O., Wittig, M., Ellinghaus, D., Flachsbart, F., Wichmann, H.E., Meitinger, T., Nikolaus, S., Franke, A.,

Krawczak, M., Lathrop, M., Schreiber, S. A genome-wide association study confirms APOE as the major gene influencing survival in long-lived individuals. *Mech. Ageing Dev*., 2011, 132, 324–330.

31. Jacobsen, R., Martinussen, T., Christiansen L., Jeune, B., Andersen-Ranberg, K., Vaupel, J.W., Christensen, K. Increased effect of the ApoE gene on survival at advanced age in healthy and long-lived Danes: two nationwide cohort studies. *Aging Cell 9*, 2010, 1004–1009.

32. Chung, W. H., Dao, R. L., Chen, L. K., Hung, S. I. The role of genetic variants in human longevity. *Ageing Res. Rev. 9(Suppl 1)*, 2010, 67–78.

33. Tanaka, M., Gong, J., Zhang, J., Yamada Y., Borgeld H. J., Yagi, K. Mitochondrial genotype associated with longevity and its inhibitory effect on mutagenesis. *Mech. Ageing Dev.*, 2000, 116; 65-76.

34. De Benedictis, G., Rose, G., Carrieri, G., et al. Mitochondrial DNA inherited variants are associated with successful aging and longevity in humans. *Faseb Journal*, 1999; 13:1532-6.

35. Ivanova, R., Lepage, V., Charron, D., Schachter, F. Mitochondrial genotype associated with French Caucasian centenarians. *Gerontology*, 1998 ;44:349.

36. Ross, O. A., McCormack, R., Curran, M. D., et al. Mitochondrial DNA polymorphism: its role in longevity of the Irish population. *Exp Gerontol.*, 2001;36:1161-78.

37. Niemi, A. K., Hervonen, A., Hurme, M., Karhunen, P. J., Jylha, M., Majamaa, K. Mitochondrial DNA polymorphisms associated with longevity in a Finnish population. *Hum Genet.*, 2003;112:29-33.

38. Zhang, J., Asin-Cayuela, J., Fish J., et al. Strikingly higher frequency in centenarians and twins of mtDNA mutation causing remodeling of replication origin in leukocytes. *Proc Natl Acad Sci U S A*, 2003, 100:1116-21.

39. Rose, G., Dato, S., Altomare, K., Bellizzi, D., Garasto, S., Greco, V., ... & BonaFe M. Variability of the SIRT3 gene, human silent information regulator Sir2 homologue, and survivorship in the elderly. *Experimental gerontology*, 2003, *38*(10), 1065-1070.

40. Chu, F., Chou, P. M., Zheng, X., Mirkin, B. L., & Rebbaa, A. Control of multidrug resistance gene mdr1 and cancer resistance to chemotherapy by the longevity gene sirt1. *Cancer research*, 2005, *65*(22), 10183-10187.

41. Glorioso, C., Oh, S., Douillard, G. G., & Sibille, E. Brain molecular aging, promotion of neurological disease and modulation by Sirtuin5 longevity gene polymorphism. *Neurobiology of disease*, 2011, *41*(2), 279-290.

42. Oak, J. N., Oldenhof, J., Van Tol, H. H. The dopamine D4 receptor: one decade of

research. *Eur J Pharmacol.*, 2000, 405:303–327.
43. Grady, D. L., Thanos, P. K., Corrada, M. M., Barnett, J. C., Ciobanu, V., Shustarovich, D., ... & Wang, G. J. DRD4 genotype predicts longevity in mouse and human. *Journal of Neuroscience*, 2013, *33*(1), 286-291.
44. Lescai, F., Marchegiani, F., & Franceschi, C. PON1 is a longevity gene: results of a meta-analysis. *Ageing research reviews*, 2009, *8*(4), 277-284.
45. Hurme, M., Lehtima¨ki, T., Jylha¨, M., Karhunen, P. J., Hervonen, A., Interleukin-6-174G/C polymorphism and longevity: a follow-up study. *Mech. Ageing Dev*., 2005, 126, 417–418.
46. Hurme, M., Kivimäki, M., Pertovaara, M., Lehtimäki, T., Karhunen, P. J., Jylhä, M., ... & Eklund, C. CRP gene is involved in the regulation of human longevity: a follow-up study in Finnish nonagenarians. *Mechanisms of ageing and development*, 2007, *128*(10), 574-576.
47. Zingg, J. M., Hasan, S. T., Cowan, D., Ricciarelli, R., Azzi, A., Meydani, M. Regulatory effects of curcumin on lipid accumulation in monocytes/ macrophages. *J Cell Biochem.*, 2012; 113: 833–840.
48. Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., & De Benedictis, G. Inflamm-aging: an evolutionary perspective on immunosenescence. *Annals of the New York Academy of Sciences*, 2000, *908*(1), 244-254.
49. Franceschi, C., Olivieri, F., Marchegiani, F., Cardelli, M., Cavallone, L., Capri, M., ... & Caruso, C. Genes involved in immune response/inflammation, IGF1/insulin pathway and response to oxidative stress play a major role in the genetics of human longevity: the lesson of centenarians. *Mechanisms of ageing and development*, 2005, *126*(2), 351-361.
50. Spencer, C. A., Jamrozik, K., Norman, P. E., Lawrence-Brown, M. A Simple Lifestyle Score Predicts Survival in Healthy Elderly Men. *Preventive Medicine*, 2005, 40(6), 712-717.
51. Waijers, P. M. C. M., Ocke, M. C., van Rossum, C. T. M., Peeters, P. H. M., Bamia, C., Chloptsios, Y., van der Schouw, Y. T., Slimani, N., & Bas Bueno-de-Mesquita, H. Dietary patterns and survival in older Dutch women. *The American Journal of Clinical Nutrition*, 2006, 83(5), 1170-1176.
52. Medina, X. Mediterranean diet, culture and heritage: challenges for a new conception. *Public Health Nutrition*, 2009, 12(9A), 1618-1620.
53. Di Daniele, N., Noce, A., Vidiri, M. F., Moriconi, E., Marrone, G., Annicchiarico-Petruzzelli, M., D'Urso, G., Tesauro, M., Rovella, V., & De Lorenzo, A. Impact of Mediterranean diet on metabolic syndrome, cancer and longevity. *Oncotarget.*, 2017, 8(5), 8947-8979.

54. Hamer, M., McNaughton, S. A., Bates, C. J., & Mishra, G. D. Dietary patterns, assessed from a weighed food record, and survival among elderly participants from the United Kingdom. *The European Journal of Clinical Nutrition*, 2012, 64(8), 853-861.

55. Lee, S. A., Cai, H., Yang, G., Xu, W. H., Zheng, W., Li, H., Gao, Y. T., Xiang, Y. B., & Shu, X. O. Dietary patterns and blood pressure among middle-aged and elderly Chinese men in Shanghai. *British Journal of Nutrition*, 2011, 104(2), 265-275.

56. Qiu, R., Cao, W. T., Tian, H. Y., He, J., Chen, G. D., & Chen, Y. M. Greater Intake of Fruit and Vegetables Is Associated with Greater Bone Mineral Density and Lower Osteoporosis Risk in Middle-Aged and Elderly Adults. *Public Library of Science One*, 2017, 12(1).

57. Djousse, L., Arnett, D. K., Coon, H., Province, M. A., Moore, & L. L., Ellison, R. C. Fruit and Vegetable consumption and LDL cholesterol: the National Heart, Lung and Blood Institute Family Heart Study. *The American Journal of Clinical Nutrition*, 2004, 79(2), 213-217.

58. Evert, J., Lawler, E., Bogan, H., Perls, T. Morbidity profiles of centenarians: survivors, delayers, and escapers. *J Gerontol A Biol Sci Med Sci.*, 2003;58:232-7.

59. Eurostat. Healthy life years statistics. Avaliable at: http://ec.europa.eu/eurostat/statistics-explained/index.php/Healthy_life_years_statistics#Main_statistical_findings.

60. Brunner, E. J. Methodological problems in genetic association studies of longevity—the apolipoprotein E gene as an example. *International Journal of Epidemiology*, 2004, *33*(5), 962-970.

61. Sentinelli, F., Romeo, S., Barbetti, F., Berni, A., Filippi, E., Fanelli, M., & Baroni, M. G. Search for genetic variants in the p66 Shc longevity gene by PCR-single strand conformational polymorphism in patients with early-onset cardiovascular disease. *BMC genetics*, 2006, *7*(1), 14.

62. Ferrières, J. The French paradox: lessons for other countries. *Heart*, 2004, *90*(1), 107-111.