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Centenarians as extreme phenotypes: An ecological perspective to get insight into the relationship between the genetics of longevity and age-associated diseases

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ABSTRACT

In this review, we address the genetic *continuum* between aging and age-related diseases, with particular attention to the ecological perspective. We describe the connections between genes that promote longevity and genes associated with age-related diseases considering tradeoff mechanisms in which the same genetic variants could have different effects according to the tissue considered and could be involved in several biological pathways. Then we describe mechanisms of antagonistic pleiotropy, focusing on the complex interplay between genetic variants and environmental changes (internal or external). We sustain the use of centenarians as "super-controls" for the study of the major age-related diseases, starting from the concept that the maximization of the phenotypic differences in the considered cohort, achieved by selecting the most divergent phenotypes, could be useful for increasing the significant differences observed in the genetic association study. We describe the potential impact of the population genetic variability in the study of human longevity and the possible contribution of the past selective pressures in shaping the current genomic background of individuals. In conclusion, we illustrate recent findings emerged from whole-genome sequencing of long-lived individuals and future perspectives for interpreting the huge amount of genetic data that will be generated in the next future.

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1. Aging populations

Population aging is a widespread phenomenon that occurs from the combination of different factors, including the increase in life expectancy and the decline in fertility that is often linked to the social-economic development. For instance, the United Nations World Population Prospects (2015) revealed that today's Europe is the most aged continent, having 24% of the population aged over 60 years. Europe was the first to experience the demographic transition, but population forecast estimates that, for the other countries, this phenomenon is only delayed. Population aging is referred to the last decades of life and, in particular, to the fact that the elderly population ages further and the number of long-lived individuals (including centenarians) increases. This eventually leads to a burden of non-communicable diseases, such as cardiovascular and neurodegenerative diseases, cancers, diabetes, respiratory diseases, that have huge implications for the healthcare system and the welfare state (Christensen et al., 2009). In this framework, population aging implies that mortality is significantly delayed and a big increase in lifespan, mainly due to medical and lifestyle changes (better education and healthier food habits), is observed (Oeppen, 2002)

Aging is considered the major risk factor for common age-related pathologies (Niccoli and Partridge, 2012). However, these two mechanisms could be considered two side of the same coin, as they could be mutually exclusive. This concept is supported by recent theories (Kennedy et al., 2014) that suggested that there is a continuum between aging and chronic aging diseases (such as neurodegenerative and metabolic syndromes, most cancers, and cardiovascular disease). The authors placed emphasis on the fact that aging promotes disease as well as diseases may accelerate aging pathologies (as in the case of long-term cytomegalovirus infection, human immunodeficiency virus, HIV). Nevertheless, the presence of certain risk variants for age-related diseases has been proved not to influence longevity (Bonafè et al., 1999; De Benedictis and Franceschi, 1998; Sebastiani et al., 2012; Yashin et al., 1999), opening a wide range of considerations that we will address in the following paragraphs.

2. Centenarians: Do the genes that promote longevity protect from diseases?

Longevity is a complex trait and the genetic variants involved in this process could be classified as follows:

1. variants located in genes that may have an impact on more than one phenotypes: the same genetic variant could have different effects according to the tissue considered and could be involved in several biological pathways (*tradeoffs*). One of the most representative examples is APOE e4, for which opposite roles in Alzheimer's disease onset, in cancer, and in heart diseases have been demonstrated (Kulminski et al., 2013; Ukraintseva et al., 2010). For example, it has been observed that APOE e4 may reduce cancer risk and, at the same time, may increase heart diseases risk in a sex-, age-, and population-specific way. From an evolutionary point of view, the tradeoff mechanisms represent the cost paid in term of fitness when a beneficial change in a trait is linked to a detrimental change in another (that can occur in a different period of the life, a classical example is a mutation that promotes calcium deposition might accelerate bone growth early in life, but then lead to hardening of the arteries later in life) (Partridge and Gems, 2002). This mechanism is at the basis of the selection of certain variants that could be associated to diseases (Stearns et al., 2010). In the case of longevity, tradeoffs are influenced also by the huge environmental changes occurred in the last centuries during epidemiological revolution, meaning that present and past environmental pressures must be considered to better understand tradeoffs. The example of APOE is self-explaining. It is known that in certain populations—such as Finns—the risk variant for Alzheimer's disease (APOE e4) is at a very high frequency (but the incidence of Alzheimer's disease is not as high as would be expected) and it has been suggested that temperature-driven differences in metabolic rate may have influenced the requirements for cholesterol, thereby driving the selection for the most "appropriate" APOE alleles in certain human populations (Eisenberg et al., 2010).
2. variants that exert different functions according to the period of life: genes may change their effect according to the remodeling process that occurs in the human organism during aging (Franceschi et al., 1995) and that involves metabolism, body composition, and hormones, leading to a new internal environment. In this framework, genetic variants that exert beneficial effects in the early stages of life may turn out to be detrimental at older ages and vice versa (De Benedictis and Franceschi, 2006; Yashin et al., 2001). This phenomenon is known as "*antagonistic pleiotropy*" (Kirkwood and Rose, 1991). It refers only to those variants that go from "*good*" to "*bad*" and it differs from the concept that certain variants have negative effects in the first part of life and neutral or beneficial roles in the last decades (i.e. from "bad" to "good") extensively described in Ukraintseva et al. (2016).

Consequently, the identification of those genes that promote longevity and those that protect from diseases depends upon environmental interactions, as the same variant could be protective, neutral, or detrimental according to the specific environmental conditions (internal or external). Recently, a meta-analysis of longitudinal studies aimed at identifying genetic variants with pleiotropic effects on common age-related diseases and endophenotypes (i.e. intermediate phenotypes that are associated to specific conditions but cannot be considered as a symptom of a disease) (He et al., 2016). By including five different datasets, the authors took into account different endophenotypes (blood glucose, blood pressure, lipids, hematocrit, and body mass index) and the age-at-onset of some age-related conditions (T2D, cancer, cardiovascular diseases, and neurodegenerative diseases) and identified seven novel genome-wide significant loci (<5e−08), many of which seem to have a regulatory role on gene expression.

Another layer of complexity should be added and consists of the fact that the genetics of longevity is characterized by both public (common) and private mechanisms as demonstrated by a study on the mitochondrial DNA (mtDNA) heteroplasmy (Giuliani et al., 2014). The analysis of mitochondrial heteroplasmy of an 853 bp mtDNA fragment in centenarians and their offspring showed that some heteroplasmic positions are shared by all parent–offspring couples whereas others are characteristic of one family or common to few families (Giuliani et al., 2014).

3. Centenarians as "super-controls" for the studies of the major age-related diseases

The approach of "extreme phenotypes" is based on the identification of subjects with very peculiar and/or clinically relevant phenotypes to maximize the efficiency in identifying the molecular pathways and the genetic characteristics underlying such phenotypes. The selection of these people can be focused both on harmful phenotypes (i.e. patients suffering from age-related diseases and complications) and on favorable phenotypes (i.e. healthy long-lived subjects). In the field of longevity, a frequent approach is to compare centenarians with younger subjects as "controls", whereas for

the study of age-related diseases the comparison often included affected and unaffected individuals. A recent paper published by Sebastiani et al. (2017) addressed the problem of how to define cases and controls in longevity studies as the definition of age of controls could be challenged. In particular, the authors suggest that, besides taking into account parameters such as sex and population, it would be extremely useful to identify the age threshold to be considered on the basis of percentile survival, according to the reference birth cohort tables. Also the random selection of controls proved to be extremely important as it has been reported that centenarians for non-genetic reasons will increase and only a small percentage of persons will reach extreme longevity.

However, only a small proportion of the available results from longevity studies was reliable and replicated in independent cohorts, probably because of several factors including methodological issues, the different population genetic structures of the considered populations, and, above all, the heterogeneity of the selected phenotypes. The strategy of the "extreme phenotypes" overcomes, at least in part, this last issue because it reduces the heterogeneity (centenarians are "real" controls as they have never developed the disease), focusing on the most divergent phenotypes and selecting individuals according to very stringent criteria. This method leads to the identification of more robust associations, with no need to increase the sample size to obtain more significant *p*-values in GWAS.

This model has a further advantage because it could be exploited from two points of view to obtain complementary information, as shown in the two sides of the spectrum in Fig. 1.

- SIDE #1: centenarians could be crucial for identifying genes involved in age-related diseases; a case–control study is performed comparing persons affected by a specific age-related disease and the general unaffected population to identify risk/protective variants; then centenarians are added as a "super-controls" group and genetic variants emerged from the first comparison are validated also in this cohort to get insight into the biological role of those variants (Garagnani et al., 2013);
- SIDE #2: age-related diseases could be crucial for identifying genes involved in longevity; in this case, subjects affected by different age-related diseases and the general population are compared and a weight is assigned to the statistically significant variants; then centenarians and the general population are compared and a weighted value (calculated according to the previously obtained one) is associated to each variant, highlighting those that may be important in healthy aging and longevity (Fortney et al., 2015).

One of the most representative studies that apply the SIDE #1 approach was published by Garagnani et al. (2013). It is a proof of principle based on one of the major age-related diseases, the type 2 diabetes (T2D). The study considered a wide spectrum of different phenotypes that span from diabetic patients with micro- and macro-vascular complications to healthy centenarians that have never had T2D. A total of 1349 individuals were selected and 31 SNPs in or nearby 16 different genes that were previously strongly associated with T2D and metabolic diseases were analysed. The paper starts from the assumption that the presence of risk alleles at the same frequency in T2D patients with or without complications and in centenarians suggests that those variants alone do not represent a strong biological risk, being compatible with exceptional longevity. These variants likely need to interact with other risk alleles and/or specific environmental conditions to give a certain phenotype. The most interesting result of this study involves the rs7903146 located in the TCF7L2 gene. Genotypic frequencies of this SNP vary proportionally according to the decrease of health/longevity and the increase of T2D severity. Moreover, the OR and *p*-values showed the most significant results when centenarians were compared with T2D patients, and a further increase in OR was observed when centenarians and patients with complications (the extreme phenotypes) were compared. The interactome analysis supports the biological relevance for Tcf7l2 not only in the T2D pathogenesis but also in a variety of age-related pathologies such as Alzheimer's disease, cardiovascular diseases, and colorectal cancer, all sharing vascular alterations.

For the second approach (SIDE #2), the most representative study has been recently published by Fortney et al. (2015) and applies a cross-diseases analysis to the traditional longevity studies, deriving specific weights for each genetic variant that will be used in the GWAS on longevity. Basically, the authors weight the *p*-values calculated from longevity association according to their impact in age-related diseases in order to identify SNPs associated to longevity. The authors distinguish between "disease SNPs" that are specifically identified for one disease and the "aging SNPs" that are indirectly involved in many age-related diseases with different etiologies. SNPs located in APOE/TOMM40 locus seem to be involved in the "general aging mechanisms" as they are associated to several age-related diseases.

The extreme phenotype approach seems to increase the possibility to identify biological interesting signals, also with a higher statistical significance. The study performed by Freudenberg-Hua et al. (2016) compared coding region variants of 53 healthy centenarians and 45 patients with Alzheimer's disease of Ashkenazi Jewis ancestry, considering centenarians as "super-controls". APOE4 risk variant reached genome-wide significance despite the modest samples number. In this study, the approach of extreme phenotype, together with the peculiar characteristics of this population (that likely experienced a recent bottleneck, shaping the allele frequency spectrum), led to the conclusion that AD patients are characterized by a burden of rare protein truncating mutations when compared with centenarians.

4. The ecology of centenarians clarifies the relationship between healthy aging, longevity, and age-related diseases

Many factors still need to be investigated and included in the study of human longevity and healthy aging. Among these, there are the "population genetic variability" and the analysis of the past selective pressures that have shaped genomic background of the populations.

Evolutionary dynamics (such as migration, mutation, admixture, and natural selection) do not directly shape gene pool of long-lived individuals because longevity (and age-related diseases) is a post-reproductive trait as Haldane suggested for the first time in 1941. However, recent studies based on genome-wide data showed that evolutionary dynamics could indirectly play a role in shaping the genetic variability of many key pathways in longevity and age-related traits such as inflammation or lipid metabolism (Brinkworth and Barreiro, 2014; Jostins et al., 2012; Voight et al., 2006).

Some reviews elucidate the importance of adaptive and demographic history for new insight into the genetic basis of complex diseases (Crespi, 2011; Di Rienzo, 2006; Quintana-Murci, 2016). Past selection, indeed, can lead to high frequencies of certain variants/haplotypes that confer susceptibility to modern pathologies (Brinkworth and Barreiro, 2014; Di Rienzo, 2006; Fumagalli et al., 2011; Sazzini et al., 2016; Vasseur and Quintana-Murci, 2013). Inflammation, crucial in longevity and in age-related pathologies (Franceschi et al., 2000, 2007; Franceschi and Campisi, 2014), is an intensively studied mechanism in terms of adaptive events and some data showed that recent positive selections have shaped a portion of genetic variation influencing inflammatory-disease sus-

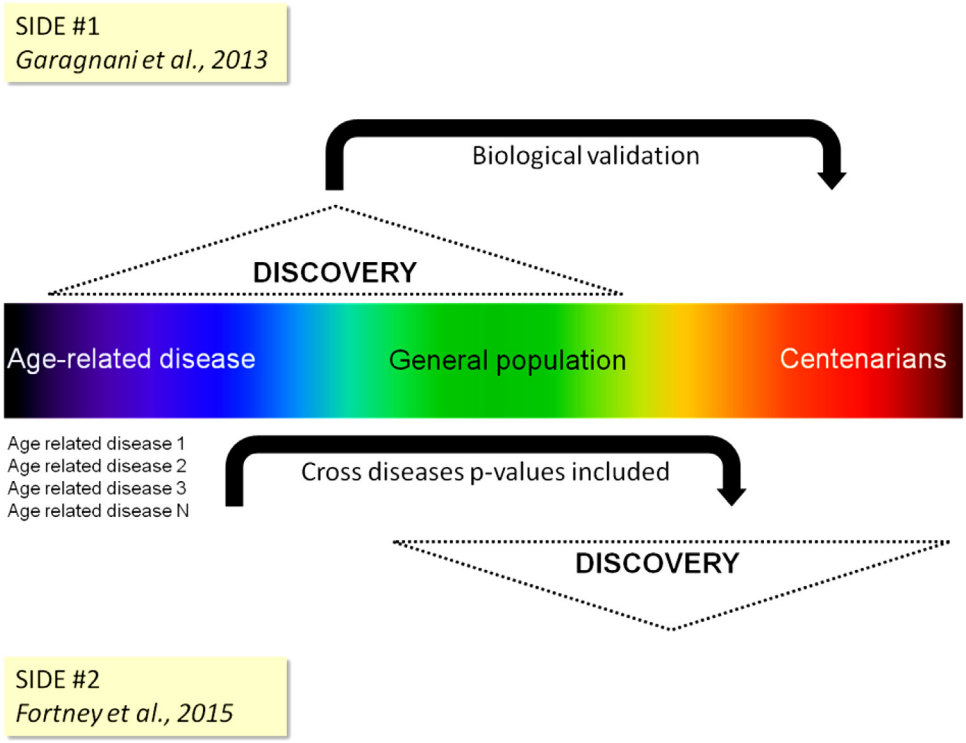

Fig. 1. The approach of extreme phenotypes. Centenarians could be analysed as a super-controls group (SIDE #1) to evaluate the biological relevance of variants identified in association studies on age-related diseases. Age-related diseases could be included in the longevity studies to identify longevity variants (SIDE #2).

ceptibility to a greater extent than genetic variation associated with other common diseases (Raj et al., 2013). However, as many factors changed dramatically in the past century, one can expect that the cost–benefit tradeoff of the inflammatory response in modern human populations is not optimized to the current environment (Okin and Medzhitov, 2012).

In the study published by Sazzini et al. (2016), more than 500,000 SNPs were genotyped in 780 Italian individuals recruited according to demographic criteria in 20 provinces equally distributed in four geographical macro-areas representative of Italy. The study revealed that the past local adaptations and the different admixture events with continental and Mediterranean populations have contributed to shape the frequency of the risk variants for complex pathologies (such as T2D and cardiovascular diseases) in the Italian subpopulations (especially from North to South). This is an example that demonstrates that each individual/population/cohort is the result of a complex process of adaptation in which biological (genetics) and non-biological (cultural and anthropological) factors act together in shaping genetic susceptibility to age-related diseases in different populations (and in this case also according to geographic cline). This implies that certain variants can become detrimental because of recent and substantial cultural "transition" (Fig. 2). Within this scenario, it is to consider that the Italian centenarians' birth cohort ranges from 1904 to 1906, meaning that they have experienced very different environmental conditions during the course of their life, as indicated in Fig. 2. In this context, an environment that can change so fast strongly influenced the risk variants, and the study of centenarians' genetics could not be kept separated from the environmental condition that they have lived in the past and that they currently live.

The lack of replication across independent longevity studies could be due to population genetic structure and/or to peculiar local adaptations between the environment and the genetic background of an organism. A paper published by Yashin et al. (2016) properly addresses this point. They consider one aspect of the population stratification, that is the linkage disequilibrium (LD), and showed that for each population, the patterns of LD in regions including the causal SNP may confound the associations identified by GWAS in complex traits, such as longevity. They suggest that this may result in misleading interpretation particularly in US populations that include mixtures of subpopulations with different ancestry. Another study (Predazzi et al., 2013) considered a different aspect of population differentiation, i.e. pattern of selection, sustaining that differential selection dynamics between populations may make the replication of association even more difficult.

It is likely that the longevity could be achieved in a population-specific way and involving both public—shared across distantly related evolutionary lineages—and private mechanisms—those peculiar to particular evolutionary lineages (Partridge and Gems, 2002). Longevity could be seen as a sort of "convergent phenotypic trait" reached through context-specific mechanisms (genetic and non-genetic) that in part shared between individuals (at least for biological functions) and in part are private of each population and of each family. The importance of population genetic structure in relation to their specific environment is clearly depicted in the evolutionary concept of *niche construction* (Govindaraju et al., 2015; Laland et al., 2010; Odling-Smee et al., 2013). In this perspective, individuals' genotypes interact with the natural environment and with the environment constructed by themselves. In the case of human beings, it has been estimated that four aspects of niche construction mainly influence longevity: (i) the urbanization, (ii) the industrial revolution, (iii) the modern medicine, and (iv) the nutrition.

The strength of the environment in shaping the relationship between the genetics of longevity and age-related diseases is sustained by many recent studies (Corella et al., 2013, 2006; Corella and Ordovás, 2014; Do et al., 2011; Fumeron et al., 1995; Yang et al., 2007). In particular, the study by Corella et al. (2013) pointed the attention toward the TCF7L2 gene (rs7903146). This study found

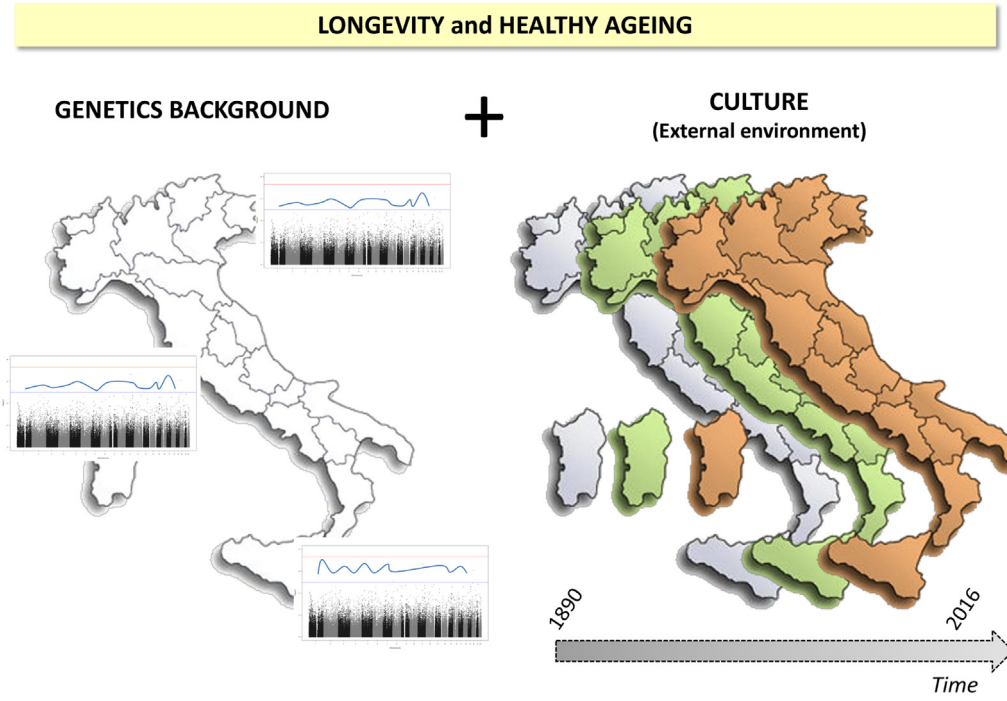

Fig. 2. Longevity is correlated to age-related disease in a population- and context-specific way. On the left an example of genetic structure of Italy that leads to peculiar genetic backgrounds along the peninsula, on the right the environmental shifts occurred in the last centuries and that Italian centenarians (born form 1904 to 1906) experienced during the course of their lives, are indicated.

that the gene–diet interaction between TCF7L2 genotypes and the Mediterranean diet modulates the stroke risk. These results reinforce what has been reported in a previous study (Garagnani et al., 2013) in which authors observed a decrease in the frequency of TCF7L2 risk variants in Italian centenarians (rs7903146-TT = 0.104) and an increase in diabetic patients with macro-vascular complications (rs7903146-TT = 0.234). The interactome analysis supports its contribution in apparently different age-related diseases, as described earlier. The natural consequence of these observations is that genes that are responsible for extreme longevity today may differ from those that were responsible for extreme longevity in the past: this is indeed supported by a simulation study on APOE that showed that selection is still acting on this gene (Drenos and Kirkwood, 2010). In particular, the study of Drenos and Kirkwood based on Western population environmental conditions showed a gradual increase with each generation of the e2 and e3 alleles of the gene at the expense of the e4 allele. This is a clear example that recent evolutionary history has a big relevance in determining the frequency of alleles involved in human longevity.

5. The study of extreme phenotypes: New insight from whole-genome sequencing and future perspectives

The complex relationship between longevity and age-related diseases has been recently addressed also by a study that analyses the whole-genome sequences of US centenarians (Erikson et al., 2016). The paper points out the diversity between (i) individuals older than 80 years who experienced healthy aging (called "wellderly") without any chronic disease and (ii) long-lived individuals. In this paper, the authors—for the first time—support the hypothesis that healthy aging and longevity rely on two distinct mechanisms and sustain that healthy aging seems to be related to a reduced genetic susceptibility to Alzheimer's disease and to coronary artery disease and not to known longevity variants. These first results foster the idea that the study of rare variants—that still represents a promising component of the whole-genome sequencing analysis—is not crucial, at least for longevity and healthy aging as well as for some age-related diseases such as T2D (Fuchsberger et al., 2016). Nevertheless, a recent pedigree-based study successfully identified rare variants important for longevity (Druley et al., 2016). What emerges from all these recent studies is the urgent need of combining the right experimental design with the proper mathematical/statistical model to clearly demonstrate the role of rare variants in healthy aging.

The use of extremes phenotypes in the study of longevity is just beginning and many other questions and models need to be addressed. In particular, the combined and integrated analysis of mtDNA and nDNA (nuclear DNA) seems to be very promising. In an interesting paper, Ma et al. (2014) use publicly available datasets from Human Microbiome Project to investigate the relationship between human mtDNA genomic variants and microbiome profiles, finding an association between host ancestral genome and the structure of its microbiome. A recent letter published in Nature by Latorre-Pellicer et al. (2016) describes the effect of mtDNA–nDNA crosstalk in organism physiology by studying conplastic mice, i.e. mice bred so that their nuclear and mtDNAs derive from different strains. The authors first crossbred female mice with male mice and, for the subsequent 20 generations, they mated the resulting female offspring with the same strain of the male (same nDNA) in order to "dilute" the nuclear DNA of the female mice strain. The resulting "conplastic" mice had the mtDNA from the original female mice and the nDNA from the strain of male mice. They observed that these conplastic mice have a general better health status and they age healthier than normal mice, they have fewer tumors at death and maintain more steady cholesterol levels with age. Surprisingly, these mice are characterized by an increase in oxidative stress that seems to be linked to the phenomenon of "hormesis" where a bit of little stress could be beneficial. Also epistatic mechanisms need to be elucidated in the field of longevity considering the "three genetics" of each individual (mtDNA, nDNA, and microbiome) (Garagnani et al., 2014). All these data need to be investigated and integrated with particular atten-

tion to gender-specific mechanisms. The case of interleukin-6 (IL6) is the most striking example of gender influence. A genetic variant located in the IL6 gene, also known as "cytokine for gerontologists" (Ershler, 1993), has been recently identified (and replicated) in a longevity study that included 2178 Han Chinese long-living individuals (rs2069837). A different variant (rs1800795) located in the same gene was studied previously (Bonafè et al., 2001) in Italian centenarians and was found to have a detrimental effect only in male. Recently, these data were supported by the analysis of the whole-genome peripheral blood mononuclear cell gene expression in nonagenarian men and women. The study identified 62 transcripts whose expression levels were significantly correlated with the plasma IL-6 levels in men, whereas no correlations were observed in women, suggesting that inflammaging could manifest differently in nonagenarian men and women (Nevalainen et al., 2015).

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