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The role of genetic variants in human longevity

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Human longevity is a complex phenotype with a strong genetic predisposition. Increasing evidence has revealed the genetic antecedents of human longevity. This article aims to review the data of various case/control association studies that examine the difference in genetic polymorphisms between long-lived people and younger subjects across different human populations. There are more than 100 candidate genes potentially involved in human longevity; this article particularly focuses on genes of the insulin/IGF-1 pathway, FOXO3A, FOXO1A, lipoprotein metabolism (e.g., APOE and PON1), and cell-cycle regulators (e.g., TP53 and P21). Since the confirmed genetic components for human longevity are few to date, further precise assessment of the genetic contributions is required. Gaining a better understanding of the contribution of genetics to human longevity may assist in the design of improved treatment methods for age-related diseases, delay the aging process, and, ultimately, prolong the human lifespan.
and longevity, many case/control association studies have been carried out on genotyping the candidate genes of this pathway. When searching for the genetic antecedents of human longevity, polymorphisms of FOXO3A (forkhead box O3A) showed the most notable association and have been replicated across different human populations. In this article we review the relevant data of genetic polymorphisms contributing to human longevity and describe the candidate genes potentially involved in the aging process. In particular, we focus on data from the case/control association studies of single nucleotide polymorphisms (SNPs) of candidate genes of the insulin/IGF-1 signaling pathway, including IGF1, IGF2, IGF1 receptor (IGF1R), insulin (INS), insulin receptor (INSR), insulin receptor substrate 1 (IRS1), AKT1, FOXO3A, and FOXO1A (Table 1). In addition, we also review the association data between the important candidate genes of human longevity, including APOE and PON1, involved in lipoprotein metabolism, and TP53 and P21, involved in cell-cycle regulation (Table 1). These association studies provided examples of genetic influences on human longevity and differential survival.

2. Genetic association between the insulin/IGF-1 pathway and human longevity

Based on data from animal models, genes involved in the IIS pathway are known to affect lifespan and the aging processes (Lunetta et al., 2007; Cheng et al., 2005). To date, the characteristic of evolutionary conservation of the IIS pathway has been proven in diverse species, including C. elegans, S. cerevisiae, D. melanogaster, rodents, and humans (Wolkow et al., 2000; Lin et al., 2001; Bustamante et al., 2002). For example, mutation of daf-2 in C. elegans, encoding a receptor similar to insulin and IGF1R, resulted in almost doubling of the lifespan and a younger appearance, because of its downstream effect on the PI3-kinase/AKT/PDK kinase cascade (Herndon et al., 2002; Garigan et al., 2002). In Drosophila, reduced insulin production or insulin receptor increases lifespan understood, the underlying mechanisms involved in the aging process may include the insulin pathway, oxidative damage, DNA repair, tumor suppression, inflammatory processes, mitochondrial dysfunction, and apoptotic tissue degeneration (Carter et al., 2007; Kenyon and Murphy, 2006). Currently, there are more than 100 potential candidate genes that have been identified and analyzed for their possible association with human longevity in one or more sample collections (GenAge Database, 2010).

Of the longevity pathways, the insulin/insulin-like growth factor-1 (IGF-1) signaling (IIS) pathway is the first pathway shown to affect longevity in animals, and is also the most prominent and thus far best studied (Kenyon, 2005; Cohen and Dillin, 2008). This pathway involves a cascade of phosphorylation events (phosphatidylinositol 3-kinase (PI3K)/AKT/pyruvate dehydrogenase kinase (PDK)) that finally regulates the nuclear translocation and activity of FOXO (a forkhead transcription factor) protein (Fig. 1) (Christensen et al., 2006). Mutations that decrease the activity of the insulin/IGF-1 downstream cascade were found to extend the lifespan (Fig. 1) (Herndon et al., 2002). In addition to FOXO proteins, the inhibition of IIS signaling leading to a long life may go through other transcription factors, including HSF-1 (the heat-shock transcription factor) and SKN-1 (a Nrf-like xenobiotic-response factor (Lin et al., 1997; Brunet et al., 2004; Tullet et al., 2008)). These transcription factors regulate diverse downstream genes that affect the lifespan. For example, activation of daf-16/FOXO protein was found to increase the lifespan of different model organisms (Kenyon and Murphy, 2006; van Der Horst and Burgening, 2007; Russell and Kahn, 2007). In addition to longevity, the insulin/PI3K/AKT signaling pathway has been shown to regulate aging, stress resistance, and proteostasis (Cohen and Dillin, 2008).

Increasing evidence has revealed the genetic antecedents of human aging or longevity. Since the IIS pathway is an important, evolutionarily conserved, biological pathway that influences aging and longevity, many case/control association studies have been carried out on genotyping the candidate genes of this pathway. When searching for the genetic antecedents of human longevity, polymorphisms of FOXO3A (forkhead box O3A) showed the most notable association and have been replicated across different human populations. In this article we review the relevant data of genetic polymorphisms contributing to human longevity and describe the candidate genes potentially involved in the aging process. In particular, we focus on data from the case/control association studies of single nucleotide polymorphisms (SNPs) of candidate genes of the insulin/IGF-1 signaling pathway, including IGF1, IGF2, IGF1 receptor (IGF1R), insulin (INS), insulin receptor (INSR), insulin receptor substrate 1 (IRS1), AKT1, FOXO3A, and FOXO1A (Table 1). In addition, we also review the association data between the important candidate genes of human longevity, including APOE and PON1, involved in lipoprotein metabolism, and TP53 and P21, involved in cell-cycle regulation (Table 1). These association studies provided examples of genetic influences on human longevity and differential survival.

Fig. 1. Insulin/IGF1 signaling affects the lifespan. This pathway involves a cascade of phosphorylation events that ultimately regulate the translocation and activity of FOXO proteins, leading to a change in lifespan. In response to exogenous stimulation (e.g., diet) or growth hormone, the islet cells of the pancreas secrete insulin into the plasma, and liver cells produce IGF-1. Insulin/IGF-1 binds to the receptors, and activates a downstream signaling pathway containing IRS1 (insulin receptor substrate protein 1), PI3K, IP3, PDK1, and AKT. AKT is a kinase that can phosphorylate and inactivate FOXO transcription factors. Both the chronic dietary restriction and decreased concentration of growth hormone could downregulate the activity of these molecules involved in this signaling pathway, and lead to an up-regulated expression of FOXO proteins, resulting in transcriptional regulation and a prolonged lifespan.
### Table 1
Reviewed candidate genes for their possible association with human longevity.

| Gene names | Protein function | Populations/study locations | Genotype and phenotype data | Reference |
|------------|------------------|-----------------------------|-----------------------------|-----------|
| **AKT**    | IIS signaling    | Three cohorts enrolled Caucasian and African-American participants from the United States, including Study of Osteoporotic Fractures (SOF), Cardiovascular Health Study (CHS), and Ashkenazi Jewish Centenarians (AJC). | An intronic SNP (rs3803304) in AKT1 was identified to be significantly associated with lifespan. | Pawlikowska et al. (2009) |
| **APOE (Apolipoprotein E)** | Lipoprotein metabolism | A Swedish population which is composed of 407 healthy Swedish individuals, 244 men and 163 women, ages 17–86 years. | The e4 allele frequency correlated positively with LDL cholesterol, and decreased with increasing age, and was significantly lower in individuals >60 years of age. | Eggertsen et al. (1993) |
| **FOXO1A (forkhead box O1A)** | IIS signaling | 817 centenarians and younger individuals in Han Chinese. | Two intronic SNPs (rs2755209, rs2755213) showed a reduced minor allele frequency in the female centenarian group. | Li et al. (2009a) |
| **FOXO3A (forkhead box O3A)** | IIS signaling | 1762 German subjects, including 1031 unrelated centenarians/nonagenarians (age range 95–110 years; mean age 98.4 years) and 731 younger controls (age range 60–75 years, mean age 67.2 years). | Polymorphism of rs3800231 had a highly significant association with human longevity. | Flachsbart et al. (2009) |
| **GH1 (growth hormone 1)** | IIS signaling | A large cohort of Italians (age range 90–108 years). | Three SNPs (rs2253310, rs2802292, rs4946936) were found to have strong associations with longevity in sex-combined centenarians with an average age of 102 years. | Li et al. (2009a) |
| **IGF1 (insulin-like growth factor)** | IIS signaling | 1576 individuals (aged >85) from Dutch, or Leiden. | Female carriers of the intron 4 A allele had reduced height and mortality. | van Hemmst et al. (2005) |
| **IGF2 (insulin growth factor 2)** | IIS signaling | 1576 individuals (aged >85) from Dutch, or Leiden. | CA repeats (191 bp minor allele) seem to contribute most to female longevity. | van Hemmst et al. (2005) |
| **IGFIR (insulin-like growth factor 1 receptor)** | IIS signaling | 224 older (75 years) Jewish Jerusalem residents of Ashkenazi ethnicity and 441 younger subjects (22 years). | Increased A allele of RFLP marker (Apa I) was found in the older subjects. | Stessman et al. (2005) |
|           |                  | 496 Italian health subjects, including 278 young people (mean age 54.8 years; 76 males and 202 females) and 218 long-lived people (mean age 98.0 years; 56 males and 162 females). | Subjects carrying at least one A allele of codon 1013 had lower free IGF1 plasma levels, and were more represented among long-lived people than in young people. | Bonafè et al. (2003) |
Table 1 (Continued)

| Gene names                        | Protein function | Populations/study locations                                                                 | Genotype and phenotype data                                                                 | Reference              |
|-----------------------------------|------------------|----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|------------------------|
| INSR (insulin receptor)           | IIS signaling    | 122 Japanese semisupercentenarians (older than 105, mean age 106.8 years) and 122 healthy younger controls. | One INSR haplotype comprised of two intronic SNPs (rs3745548 and rs2252637) in linkage disequilibrium, and was more frequent in semisupercentenarians than in younger controls. | Kojima et al. (2004)   |
| IRS1 (insulin receptor substrate 1)| IIS signaling    | 1576 individuals (aged >85) from Dutch, or Leiden. 496 Italian health subjects, including 278 young people (mean age 54.8 years; 76 males and 202 females) and 218 long-lived people (mean age 98.0 years; 56 males and 162 females). | Arg allele of codon 972 seems to contribute to longevity in females. AA, GA, or GG genotype of codon 972 had identical levels of plasma IGF1, and had no association with longevity. | van Hemmst et al. (2005) |
| P21 (CDKN1A)                      | Cell-cycle inhibitor | 184 centenarians and 184 younger subjects in the Italian population.                                                                 | The rare alleles of two exon-derived SNPs (rs1801270, rs1059234), were significantly underrepresented among the centenarians. | Gravina et al. (2009)   |
| PON1 (Paraoxonase 1)              | Detoxication and lipoprotein metabolism | 308 centenarians and 579 controls enrolled from Italy. | The percentage of carriers of the B allele at codon 192 is higher in centenarians than in controls (0.539 versus 0.447). | Bonafè et al. (2002)   |
|                                   |                  | 256 healthy French Caucasian men (mean age 69.8 years). | Gln homozygotes of codon 192 were more frequent in aging than in Arg allele carriers. | Xie et al. (2003)       |
|                                   |                  | 100 healthy octogenarians and 200 adults of Sicilian. | Octogenerians had a higher percentage of (−107) CC genotype compared with controls, and displayed significant higher levels of PON1 activity. | Campo et al. (2004)     |
| TPS3 (tumor protein p53)          | Tumor suppressor | A community-based sample which was composed of up to 1345 Framingham Study participants from 330 families. Centenarians and younger controls from continental Italy and Sardinia. | One SNP, rs2374983 located near PON1 showed association with both age at death and morbidity-free survival at age 65. The carriers of P72 allele of rs1042522 were slightly increased in centenarians, though showing no statistic significance. | Lunetta et al. (2007)  |
|                                   |                  | 66 nonagenarians/centenarians and 150 young healthy volunteers enrolled from Northern Italy. | The absence of any TPS3 polymorphisms and of GSTT1 deletion, and the simultaneous presence of the three identified TPS3 polymorphisms and of GSTT1 deletion, were much more frequent in young subjects than in centenarians. | Bonafè et al. (1999a,b) |
|                                   |                  | 1226 people aged 85 years and over. | The carriers of the PP genotype of rs1042522 have a 41% increased survival. | van Hemmst et al. (2005) |

(Junger et al., 2003; Tatar et al., 2001). In addition, transgenic animal models and array-based analyses have also demonstrated the important role of components of insulin/IGF-1 signaling (including FOXO, IGF1 levels, as well as IGF1 receptor) in controlling longevity in mice (Holzenberger et al., 2003; Kappeler et al., 2008; Steger et al., 1993; Dozmrov et al., 2001).

2.1. Variants of growth hormone 1 (GH1), growth hormone releasing hormone receptor (GHRHR), insulin-like growth factor (IGF1 and IGF2), IGF1 receptor and human longevity

van Hemmst et al. (2005) examined the relative impact on human lifespan of the separate variants in IIS pathway components, including growth hormone releasing hormone receptor, growth hormone 1, insulin-like growth factor (IGF1), insulin, and insulin receptor substrate 1. This study included two cohorts that enrolled a total of 1576 inhabitants (ages 85–103 years) of Leiden in the Netherlands. They reported that the relative mortality risks in females were lower for carriers of the three genetic variants (intron 4 A allele of the GH1 intronic SNP, CA repeat (191 bp minor allele) of the promoter of IGF1 and A/G SNP of IRS1 codon 972 Arg). All three variants reduce IIS activity. Of the three variants, the intron 4 A/T SNP of GH1 was significantly associated with female longevity (relative mortality risk = 0.8) (van Hemmst et al., 2005).

In addition, Bonafè et al. (2003) carried out a cohort study that enrolled a total of 496 healthy, Italian subjects, including 278 young people (76 males and 202 females; mean age 54.8 years) and 218 long-lived people (56 males and 162 females; mean age 98.0 years). They examined the association between polymorphic variants of IGF1R (insulin-like growth factor 1 receptor; G/A, codon 1013), PI3KCB (phosphoinositol 3-kinase; T/C, −359 bp; A/G, −303 bp), IRS1 (insulin receptor substrate 1; G/A polymorphism, codon 972), and FOXO1A (T/C, +97347 bp), and IGF1 response and human longevity. They reported that lower free IGF1 plasma levels were more frequently found in individuals carrying at least an A allele at IGF1R (AG and AA genotypes) than in GG genotype subjects (Bonafè et al., 2003). In addition, there were more AG and AA genotype subjects among long-lived than among young people.
Activation of AKT (RAC-alpha serine/threonine-protein kinase, also designated as PKB or RacPK) has been reported to promote proliferation and survival of mammalian cells (Brunet et al., 2001). Miyauchi et al. (2004) showed that AKT activity increases along with cellular senescence and that inhibition of AKT extends the lifespan of primary cultured human endothelial cells. In addition, inhibition of forkhead transcription factor FOXO3A by AKT was reported to be essential for the growth arrest of the primary cultured human cells to occur (Miyauchi et al., 2004).

Variants of AKT have been linked to human longevity (Pawlikowska et al., 2009). Pawlikowska et al. (2009) studied the association of common genetic variations in the IIS pathway with human longevity in three cohorts, including the Study of Osteoporotic Fractures (SOF), the Cardiovascular Health Study (CHS), and the Ashkenazi Jewish Centenarians (AJC). The cohort of SOF originally enrolled 9704 Caucasian women aged 65 years and older from the United States, the CHS cohort included a total of 5885 Caucasian and African-American participants from the United States, and the AJC cohort recruited 383 cases (74.8% females; mean age 97.7 years, age range 95–108 years), and 363 controls (57% females; mean age 79.5 years, age range 43–94 years) (Pawlikowska et al., 2009). They found that FOXO3A variants with human longevity (De Luca et al., 2001). In contrast to the non-relevance finding of IGF2 for human lifespan, studies of body mass index (BMI), metabolic actions, and obesity showed that subjects with Apa I GG genotype of IGF2 had increasing levels of fasting plasma insulin and oral glucose tolerance test than individuals with AA or AG under the condition of caloric surplus (O’Dell et al., 1997). Furthermore, a consistent result was reported, since increased A allele frequency and the AA genotype of IGF2 Apa I RFLP marker were found in 224 older (75 years) Jewish (Ashkenazi ethnicity) residents of Jerusalem compared to the control group of 44 younger subjects (22 years) (Stessman et al., 2005). Large samples and independent populations are required to validate the genetic association data.

2.2. Variants of insulin, insulin receptor, and insulin receptor substrate 1 and human longevity

Kojima et al. enrolled 122 Japanese semisupercentenarians (older than 105 years, mean age 106.8 years) and 122 healthy younger controls, and they examined the polymorphic variations of six genes involved in insulin/IGF-1 signaling, including FOXO1A, insulin receptor, IRS1, PIK3CB, PIK3CG, and PPARC1A. They reported that one INSR haplotype, which comprised of two intronic SNPs (rs3745548 and rs2252637) in linkage disequilibrium, was more frequent in semisupercentenarians than in younger controls (Kojima et al., 2004). The same study also showed that the allele frequencies of two exonic SNPs (rs1801123 and rs1801278) in insulin receptor substrate 1 gene had no difference between centenarians and controls, implying that IRS1 has no effect on lifespan (Kojima et al., 2004). A consistent result was reported by Bonafé et al. (2003), who examined G/A polymorphism (codon 972) of IRS1 gene in long-lived Italians, and they showed that the carriers with AA, GA, or GG genotype of IRS1 gene had identical levels of plasma IGF1, and there was no association with longevity. By comparison, van Hemmst et al. (2005) reported that the Arg allele of codon 972 of IRS1 was associated with a lower mortality risk and might be involved in female longevity.

2.3. AKT variants and human longevity

FOXO transcription factors mediate crucial cellular processes at the interface, orchestrating programs of gene expression that regulate apoptosis, cell-cycle progression, and oxidative-stress resistance/tolerance. FOXO activates transcription of FasL and Bim-1 (Bcl-2 family) to initiate apoptosis (Dijkers et al., 2000). Alternatively, FOXO factors promote cell-cycle arrest by upregulating p27kip1 to induce G1 arrest or GADD45 to induce G2 arrest (Tran et al., 2002; Dijkers et al., 2000; Kops et al., 2002a). OtherFOXO target genes have been shown to play roles in glucose metabolism by activating G6Pase and PEPCK (Puigserver et al., 2003), cellular differentiation and muscle atrophy by promoting catalase and MnSOD, as well as stimulating AgRP and NPY to regulate energy homeostasis (Ramawamy et al., 2002). FOXO may control different patterns of gene expression based on the intensity of the stimulus, e.g., activating stress-resistance genes under mild conditions but pro-apoptotic genes with increas-
In 2009, Flachsbart et al. (2009) further replicated the same association of FOXO3A SNPs with longevity using an extensive collection of 1762 German subjects, including 1031 unrelated centenarians/nonagenarians (age range 95–110 years; mean age 98.4 years) and 731 younger controls (age range 60–75 years, mean age 67.2 years). They performed genotyping on 16 known polymorphisms of the FOXO3A gene and identified four SNPs (rs6911407, rs9400239, rs3800231, and rs479744) showing a nominal association with the entire long-lived German individual sample, and 11 SNPs (rs6911407, rs768023, rs2802288, rs2802290, rs13220810, rs7762395, rs9400239, rs3800231, rs1268170, rs473268, and rs479744) having a significant association with attaining exceptional old age of the 388 centenarians (mean age 101.6 years) (Flachsbart et al., 2009). In particular, obtained from an allele-based case–control comparison, the top-ranking SNP, rs3800231, of FOXO3A had a highly significant (p < 0.0005) OR of 1.42 (CI: 1.18–1.70). They reported that the genetic association of longevity with FOXO3A was stronger in centenarians than in nonagenarians and affected both genders. These data confirmed the association between genetic variation in the FOXO3A gene and human longevity. However, the three top-ranking SNPs (rs3800231, rs7762395, and rs768023) did not present a statistically robust replication result, and only showed a trend for the association with longevity in the French sample consisting of 535 centenarians (mean age 103.8 years) (Flachsbart et al., 2009).

Li et al. (2009a) examined six tagging SNPs from FOXO3A and FOXO1A in 1817 centenarians and younger individuals in Han Chinese. Three (rs2255310, rs2802292, and rs4946936) of the six selected SNPs were found to have strong associations with longevity in sex–combined centenarians with an average age of 102 years in this Han Chinese population. In addition, the GTC haplotype of the three SNPs of FOXO3A presented with a lower frequency in centenarians than in controls (age around 47 years), which further demonstrated the FOXO3A haplotype association with longevity (Li et al., 2009a). These data suggested that FOXO1A was more closely associated with female longevity.

From analysis in a large cohort of Italians (age range 90–108 years), FOXO3A was validated to be associated with lifespan (Anselmi et al., 2009). One SNP of the FOXO3A gene, rs2802292, was postulated to play a beneficial role in lifespan by increasing FOXO3A expression and then enhancing the downstream targets. A gender difference was also found in the association with rs2802288, which showed linkage disequilibrium with rs2802292, presenting allelic association in males, but not in females (Anselmi et al., 2009).

Pawlikowska et al. (2009) reported that two intronic SNPs (rs1935949 and rs4946935) in FOXO3A were significantly associated with female lifespan (rs1935949, OR = 1.35, adjusted p = 0.0093). In addition, they also found that SNP rs4946935 of FOXO3A was associated with death caused by cardiovascular, non-cardiovascular, or non-cancer diseases in the cohort of the Cardiovascular Health Study (Pawlikowska et al., 2009). Only rs1935949 of FOXO3A was associated with cancer deaths in a cohort of elderly Caucasian women from the Study of Osteoporotic Fractures (Pawlikowska et al., 2009).

Lunetta et al. (2007) conducted a genome-wide association study using the Affymetrix 100K SNP GeneChip for longevity in a community-based sample that was composed of up to 1345 Framingham Study participants from 330 families. In the analysis of selected candidate genes, SNP associations were identified for age at death in or near the following genes: FOXO1A, GAPDH, KL, LEPR, PON1, PSEN1, SOD2, and WRN. Top-ranked SNP associations included rs6910534 (p = 0.00003) near FOXO3A and rs3751591 (p = 0.00006) in CYT19A1. Though none of the SNP genetic associations achieved genome-wide significance, these data may serve as a resource for replication as more genes and biologic pathways are
proposed as contributing to longevity and healthy aging (Lunetta et al., 2007).

As the association of FOXO3A has been observed in genetically diverse groups of European and Asian descent, these results point to FOXO3A playing an important role in controlling human longevity in many different ethnic populations.

2.5. Genetic association of FOXO1A with longevity

FOXO1A (forkhead box O1A) gene variants have also been linked to longevity in Chinese and American cohorts (Lunetta et al., 2007; Li et al., 2009a). Li et al. (2009a) reported that FOXO1A had a strong association with longevity in Han Chinese female centenarians. There were two intronic SNPs (rs2755209 and rs2755213) of FOXO1A that showed a reduced minor allele frequency (MAF) in the female centenarian group, when compared with a younger group (Li et al., 2009a). The decreased frequency of the MAF (i.e., T allele) of rs2755209 and rs2755213 is associated with increased longevity, and the adjusted p value for multiple comparison by the Bonferroni correction was from 9.0 \times 10^{-4} to 3 \times 10^{-6} (Li et al., 2009a).

In addition, using a genome-wide association study, Lunetta et al. (2007) reported that the top 30 SNPs associated with age at death included two SNPs intronic to FOXO1A, rs10507486 (p = 0.0001) and rs4943794 (p = 0.0002).

3. Other genes participating in human longevity

In addition to the genes involved in IIS signaling, there are other lifespan-related genes that have been connected to human longevity as described below.

3.1. Apolipoprotein E (APOE) variants

Abundant evidence has linked cholesterol metabolism and the occurrence of late-onset Alzheimer’s disease. Apolipoprotein E, involved in lipid metabolism, is known to be related to susceptibility to age-related diseases, as well as being a proposed risk factor for coronary heart disease and Alzheimer’s disease (Kolovou et al., 2004, 2002). The APOE gene encodes a ligand for low-density lipoprotein (LDL) receptor. Protein isoforms of APOE are produced from several common polymorphic forms, APOE e2, e3, and e4, which interact differently with specific lipoprotein receptors, ultimately altering circulating cholesterol levels. High, low, and intermediate levels of LDL cholesterol have been reported to be associated with APOE e4, APOE e2, and APOE e3, respectively. The APOE e4 allele which promotes premature atherosclerosis, has also been identified as a biomarker for an increased risk of Alzheimer’s disease. Since coronary heart disease and Alzheimer’s disease are common diseases in the elderly, increasing genetic association studies revealed that APOE is an important genetic antecedent of human longevity (Christensen et al., 2006; GenAge Database, 2010; Wilson et al., 1996; Rubinsztein and Easton, 1999; Smith, 2002).

In fact, the polymorphisms in the APOE gene are the first and most replicated genetic associations with the human longevity phenotype and age-related diseases (Christensen et al., 2006; GenAge Database, 2010; Wilson et al., 1996; Rubinsztein and Easton, 1999; Smith, 2002). Eggertsen et al. (1993) first studied the association between APOE isoforms and age in a Swedish population composed of 407 healthy Swedish individuals, 244 men and 163 women, ranging in age from 17 to 86 years. They found that the e4 allele frequency correlated positively with LDL cholesterol and decreased with increasing age, and it was significantly lower in individuals >60 years of age (14.7%) (Eggertsen et al., 1993). Following this line, Schächter et al. (1994) validated the genetic associations of APOE with human longevity by carrying out case–control studies of populations of centenarians (n = 338) and adults aged 20–70 years. They reported that the e4 allele of APOE was significantly less frequent in centenarians than in controls (p < 0.001), while the frequency of the e2 allele was significantly increased (p < 0.01) (Schächter et al., 1994). In addition, they also first identified that the D allele of ACE (encoding Angiotensin I-Converting Enzyme) gene is more frequent in centenarians, with a significant increase of the homozygous genotype (p < 0.01) (Schächter et al., 1994).

Until now, at least 17 studies have examined the relationship between APOE variants and human longevity and/or survival in old age, and 11 of 17 reported a statistically significant association between APOE and longevity (GenAge Database, 2010). The decrease of the APOE e4 allele at older ages correlated with its pathogenetic role in Alzheimer’s disease, hypertension, and dyslipidemia (Christensen et al., 2006; GenAge Database, 2010). By comparison, an increased frequency of the APOE e2 allele at older ages has been validated in different populations, and it also showed a negative correlation with myocardial infarction (Kolovou et al., 2002; Louhija et al., 1994; Blanche et al., 2001; Frisoni et al., 2001; Seripa et al., 2006). In addition, polymorphisms of other apolipoproteins (e.g., APOA4, APOB, APOC3) have also been reported in different populations, which showed a statistically significant association with human longevity (Pepe et al., 1998; De Benedictis et al., 1997; Anisimov et al., 2001). Nowadays, variants of APOE and other apolipoproteins, as well as the plasma concentrations of lipids and lipoproteins, are established risk factors for age-related diseases and human longevity (Kolovou and Anagnostopoulou, 2007).

3.2. Paraoxonase 1 (PON1) variants

PON1, a paraoxonase, also has the enzyme activity of arylesterase, or esterase, which hydrolyzes liperoxides, toxic oxon metabolites, aromatic esters, and aromatic and aliphatic lactones (Draganov et al., 2005). PON1 is synthesized in the liver and secreted into the blood, where it is associated exclusively with high density lipoproteins (HDLs) and is considered to be a protective factor against oxidative modification of LDL and may therefore play an important role in the prevention of the atherosclerotic process (Draganov et al., 2005). Two polymorphisms of PON1 have been extensively studied: L55M (a leucine (L allele) to methionine (M allele) substitution at codon 55), and Q192R (a glutamine (A allele) to arginine (B allele) substitution at codon 192). Due to its detoxification function and HDL binding ability, PON1 has been tested for genetic association with many disorders and validated in the susceptibility to organophosphate poisoning (Cherry et al., 2002), coronary artery disease (Serrato and Marian, 1995), coronary artery spasm (Itô et al., 2002), and exudative age-related macular degeneration (Ikeda et al., 2001).

An association between PON1 and human longevity has been studied in different human populations. Bonafé et al. (2002) examined the two polymorphisms, L55M and Q192R, in 308 centenarians and 579 controls in Italy. They found that the percentage of carriers of the B allele (Arg) at codon 192 was higher in centenarians than in controls (0.539 versus 0.447), though this was due to an increase of people carrying M alleles at codon 55 (Bonafé et al., 2002). They proposed that genetic variability at PON1 locus may affect survival at extremely advanced age (Bonafé et al., 2002). Xia et al. (2003) examined polymorphism at codon 192 (Gln/His) in 256 healthy, French, Caucasian men (mean age 69.8 years) and reported that Gln homozygotes were more frequent in aging than in Arg allele carriers. By comparison, the data of studies on Sicilians suggested that there is no association between human longevity and the L55M and Q192R genotype distributions, yet octogenarians had a higher percentage of (−107) CC genotype compared with controls, and displayed significantly higher levels of PON1 activity (Campos et al., 2004). In addition, in a genome-wide association
study, Lunetta et al. (2007) identified several SNPs associated with both age at death and morbidity-free survival at age 65 years, which include one SNP, rs2374983, located near PON1. Since the association between PON1 variants and human longevity was not replicated in all studies, a reasonable assumption to explain these differences was the possibility of population-specific effects (Rea et al., 2004; Lescai et al., 2009; Caliebe et al., 2010).

3.3. TP53 (tumor protein p53) variants

TP53, which encodes the tumor suppressor protein p53, could act as a transcription factor. In response to diverse cellular stresses, P53 regulates target genes that induce cell-cycle arrest, apoptosis, senescence, DNA repair, and changes in metabolism (Toledo and Wahl, 2006; Bourdon, 2007; Vousden and Lane, 2007). In addition, p53 appears to induce apoptosis through nontranscriptional cytoplasmic processes. Numerous posttranslational modifications modulate p53 activity, most notably phosphorylation and acetylation. Activity of p53 is ubiquitously lost in human cancer either by mutation of the p53 gene itself or by loss of cell signaling upstream or downstream of p53 (Toledo and Wahl, 2006; Bourdon, 2007; Vousden and Lane, 2007). The p53/p21-dependent pathway was reported to be involved in the senescence-like arrest of cell growth by constitutive activation of Akt (Miyauchi et al., 2004).

More than 40 allelic variants of TP53 gene have been reported (http://www.ncbi.nlm.nih.gov/omim/191170?report=Variants). Among them, one SNP, rs1042522, which is able to substitute residue 72 of p53 protein (P72 R), is one of the most studied variants. The Pro72-to-Arg polymorphism occurs in the proline-rich domain of p53, which is necessary for the protein to fully induce apoptosis. R72 allele was reported to have up to a 15-fold increased apoptotic ability compared with P72, in both the inducible cell lines and cells with endogenous p53 homozygous for each variant (Dumont et al., 2003). In fact, P72R is caused by polymorphism rather than mutation (Ara et al., 1990). Allelic analysis of patients with HPV-associated tumors revealed a striking overrepresentation of homozygous R72 p53 compared with the normal population, indicating that individuals homozygous for R72 are about seven times more susceptible to tumorigenesis than heterozygotes (Storey et al., 1998). Later, many studies assessed the function of P72R as well as the association between P72R allele and cancer risk, and they suggested that these two alleles have different biologic properties in their ability to bind components of the transcriptional machinery, leading to different risks for cancer development (Thomas et al., 1999; Marin et al., 2000; Jones et al., 2004; Bougeard et al., 2006).

Since longevity may depend on a balance between tumor suppression and tissue renewal mechanisms, genetic variation in TP53 gene has been tested in different populations (Campisi, 2003; Pim and Banks, 2004; Gaspari et al., 2003; van Heemst et al., 2005; Bonafé et al., 1999a, b; Bojesen and Nordestgaard, 2008). Bonafé et al. (1999a, b) studied P53 codon 72 polymorphism and longevity by enrolling centenarians from continental Italy and Sardinia. They reported that no significant difference was detected between centenarians and young controls, though P72 allele carriers were slightly increased in centenarians (Bonafé et al., 1999a, b). Gaspari et al. (2003) examined the germline TP53 mutations in 66 nonagenarians/centenarians and 150 young healthy volunteers enrolled from Northern Italy. They reported that the absence of any TP53 polymorphisms and of GSTT1 deletion, and the simultaneous presence of the three identified TP53 polymorphisms and of GSTT1 deletion, were much more frequent in young subjects than in centenarians (41.5% versus 26.9% and 8.8% versus 3.8%, respectively). In addition, van Heemst et al. used a meta-analysis and showed that carriers of the TP53 codon 72 PP genotype have an increased cancer risk compared with RR genotype carriers (p<0.05). In addition, they carried out a prospective study of 1226 people aged 85 years and over and showed that carriers of the PP genotype have a 41% greater survival (p=0.032) (van Heemst et al., 2005). These studies suggested that codon 72 variation in the human TP53 gene affects cancer mortality, as well as old age survival.

3.4. Genetic association of p21 (CDKN1A) with longevity

P21 (encoded by CDKN1A, also known as Cip1 and Waf1) is a cell-cycle inhibitor, and is known to be up-regulated during DNA damage pathways, such as telomere shortening which limits the proliferative lifespan of human cells (Tary-Adkins et al., 2006). Choudhury et al. (2007) reported that deletion of p21 prolongs the lifespan of telomerase-deficient mice with dysfunctional telomeres. And, the deletion of P21 improved the stem cell function of hematolymphopoiesis and the maintenance of intestinal epithelia without rescuing telomere function (Choudhury et al., 2007). Moreover, in these mice, apoptotic responses remained intact, and P21 deletion did not accelerate chromosomal instability or cancer formation (Choudhury et al., 2007).

P21 is considered as a crucial mediator for integrating the mechanism of the stress response to aging (Dudek and Johnson, 1994). Some evidence has suggested that the effects of P21 induction on gene expression in senescent cells may contribute to the pathogenesis of cancer and age-related diseases (Chang et al., 2000). It has been revealed to act as an inhibitor of P53-dependent cell-cycle arrest after DNA damage (el-Deiry et al., 1994). In addition, P21 has been reported to upregulate multiple genes related to not only senescence but also age-related diseases, including atherosclerosis, Alzheimer’s disease, amyloidosis, and arthritis (Chang et al., 2000). Current available data suggest that P21 may play a linking role for different age-related diseases (Seki et al., 1998). In addition, evidence has shown that P21 induces the expression of the main component of Alzheimer’s amyloid plaques, β-amyloid peptide, and increases serum levels of amyloid A, leading to the deposition of inflammatory protein SAA, which has been found to be related to the development of amyloidosis, atherosclerosis, osteoarthritis, and rheumatoid arthritis (Jensen and Whitehead, 1998). P21 also has been reported to induce the expression of t-TGase (tissue transglutaminase), which has been described as a pleiotropic mediator involved in cell differentiation, carcinogenesis, apoptosis, and aging (Jensen and Whitehead, 1998). Furthermore, the induction of CTGF (connective tissue growth factor) and galectin-3 by P21 has been implicated in atherosclerosis (Nachigal et al., 1998). Increased expression of P21-inducible proteins, such as cathepsin B, PAI-1 (plasminogen activator inhibitor-1), fibronectin, N-acetylgalactosamine-6-sulfate sulfatase, and Mac2-BP (Mac-2 binding protein) has also been found to be involved in osteoarthritis and/or rheumatoid arthritis (Seki et al., 1998; Cerinic et al., 1998). The specific effects of P21 on regulating gene expression and the elucidation of P21-mediated mechanisms provide new approaches to the prevention of different aging-related diseases that are associated with human longevity.

Since P21 has been implicated in several age-related diseases, the possible relationships between longevity and P21 (CDKN1A) variants have been explored in an Italian population (Gravina et al., 2009). Although a cluster of minor alleles in the region of P21 promoter (between –4547 and –3489 bp) had no effects on P53 responsiveness, rare alleles of two exon-derived SNPs (rs1801270 and rs1059234) showed a significant difference between a long-lived population and younger controls in the Italian population. One of these two SNPs, rs1801270, changes the sequence of amino acid codon 31 of P21 from Ser to Arg, and rs1059234 leads to a C to T transition at the 20th nucleotide downstream of the stop codon in the 3’ untranslated region. In addition, a six-SNP haplotype (GGGCCG) comprising rs1801270 and rs1059234 is more prevalent in cen-
tenarians than in control populations. These two relevant SNPs have been reported to be associated with squamous cell carcinoma, breast cancer, and sarcoma. The amino acid change at codon 31 of P21 may abolish the phosphorylation of P21 at Ser 31, which may cause cell-cycle arrest or induce the transcription of genes implicated in age-related diseases. Furthermore, the stability or translational efficiency of P21 mRNA may be affected by the polymorphism of rs1059234 in the 3′ untranslated region (Gravina et al., 2009).

3.5. Genes of the electron transport chain (ETC) participating in the aging process

Mitochondria have been connected to the aging process for over 50 years. The inner membrane embedding the ETC produces reactive oxygen species (ROS) that are responsible for cell damage and premature apoptosis, and are involved in the aging process and longevity (Lambert and Brand, 2009). Mitochondrial DNA encodes cytochrome b (CYTB) protein, which is located centrally in complex III (cytochrome bc1 complex) of the ETC. The I7T polymorphism of the CYTB gene substitutes residue 7 (threonine) of the protein for an isoleucine. CYTB I7T of mitochondrial haplogroup H has been reported to be associated with prolonged longevity in humans (Beckstead et al., 2009). This association may be explained by the role of CYTB in promoting the replenishing ability of water to the Q, binding site and diminishing the time ubisemiquinone stays at the Q, site, which results in reduced ROS production (Beckstead et al., 2009).

3.6. Suspected and possible genes of uncertain association in longevity

Some other gene variants have also been proposed to be involved in the aging process, such as genes related to infectious diseases or pathogen recognition (Vasto et al., 2007). Dendritic cell-specific intracellular adhesion molecular-3-grabbing nonintegrin (DC-SIGN), also known as CD209 (cluster of differentiation 209), is a protein encoded by the CD209 gene (Mitchell et al., 2001; Boilly-Larouche et al., 2007). DC-SIGN is a C-type lectin receptor, expressed by macrophages and dendritic cells. DC-SIGN related (DC-SIGNR) protein is a type II transmembrane protein. The neck region of DC-SIGNR is composed of a highly conserved 23-amino-acid repeat and a C-terminal extracellular C-type carbohydrate recognition domain (CRD). Length variations of the neck region of DC-SIGNR have been reported to be associated with different susceptibilities to various infectious diseases, including HIV, HCV, and SARS (severe acute respiratory syndrome). Therefore, the variants on CRD of DC-SIGNR are proposed to crucially affect pathogen-binding properties (Mitchell et al., 2001; Boilly-Larouche et al., 2007). Though it has been proposed that the immune-related genes may influence the aging process through immunosenescence (Pawelec and Larbi, 2008), a study performed in peri-centenarians in a Han Chinese population did not find an association between DC-SIGNR and longevity (Li et al., 2009b).

Because of their role in the control of ROS, genetic variants of cellular antioxidant enzymes in the pathway of oxidative stress have been studied in a Japanese cohort. It was reported that, in Japanese men, but not women, glutathione peroxidase 1 (GPX1) polymorphism Pro198Leu variant was associated with the prevalence of metabolic syndrome. This study also suggested that gender differences might be important in causing diversity in the human lifespan (Kuzuya et al., 2008). In addition, other genetic polymorphisms, such as SOD2–9 T/C or MTHFR 677C/T, have been studied. They have been demonstrated to have positive modulation roles in the longevity of Ashkenazi males (Stessman et al., 2005). However, no association was found for longevity phenotype in a Jordanian population (Khabour et al., 2009), nor in an Italian population (De Benedictis et al., 2009).

4. Improvements and future directions

As reviewed in this article, genetic studies have uncovered part of the mystery of the human lifespan. However, to date, the genetic components known to influence human aging and longevity are scarce. Only few repetitions have been observed across human populations, and for most of them, it is difficult to replicate the results due to the small number of enrolled subjects. Further precise assessment of genetic contributions will rely on two main kinds of researches: (1) case/control association studies that examine the difference in genetic polymorphisms between centenarians/nonagenarians (case) and the general population (control) subjects; and (2) wet-laboratory analyses of genetic and biochemical mechanisms that may contribute to human aging and longevity.

Case/control association studies are often hampered by small sample size, lack of precise phenotyping, variation of ethnic population stratification, and the limitations of budget/technique platform/methods of statistics applied in genome-wide association studies (GWAS) or candidate gene approaches, among others. Although several genetic variations have been identified and have been shown to be associated with human longevity, the limited available data further emphasizes the following points: (1) a well-characterized and large sample size is important for a robust replication, (2) a genome-wide association study comprehensively searching for longevity associated genes is lacking, and (3) validation of a consistent association of longevity polymorphisms in different human populations is necessary. Regarding sample collection in a case/control study, a large, homogeneous, long-lived population with well-characterized aging phenotypes is required for genetic longevity research. In particular, the age of the cases is of utmost importance, and a sample of centenarians is thought to be more valuable than one including octogenarians and nonagenarians. This idea is supported by the stronger association of FOXO3A polymorphisms with centenarians than with nonagenarians or all long-lived individuals in a German sample (Flachsbar et al., 2009). Finally, replications of genetic polymorphism associations in different populations with larger quantities and various study approaches will validate the genes controlling human longevity.

Considering the robust findings in model organisms of aging, candidate longevity genes may also include the genes involved in several biological mechanisms, such as the insulin pathway, oxidative damage, DNA repair, tumor suppression, inflammatory processes, mitochondrial dysfunction, and apoptotic tissue degeneration (Carter et al., 2007; Kenyon and Murphy, 2006). Furthermore, wet-laboratory analyses for the functional role of polymorphisms identified from genetic associations are also required to address the biological mechanisms of human longevity. Taking FOXO3A as an example, in addition to the validation of genetic associations across different populations, FOXO3A protein has been shown to control insulin sensitivity and influence coronary heart disease, type 2 diabetes, and longevity (Brunet et al., 2004; Tran et al., 2002; Puisieux et al., 2003). The multiple functions of FOXO3A also suggest that it could be a “master regulator” in the IIS pathway, and its genetic polymorphisms may modulate a broad array of downstream targets that could exhibit larger effects on lifespan extension (van Der Horst and Burgerting, 2007; Dillin et al., 2002).

Gaining knowledge about genetic control of the mechanisms of human longevity may result in the design of better treatment methods for age-related diseases, predict susceptibility to mortality, and offer the opportunity to prevent disease, delay the aging process, and ultimately, prolong human lifespan. As expected for polygenic traits like human aging and longevity, multiple genetic factors may contribute to the phenotype, and each of them may
have only a rather modest effect. This is correlated to the increasing reports of genetic antecedents contributing to human longevity. Greater effort should be devoted to validating the functional role of these associated genes in determining healthy human aging. Understanding the genetic contribution to human longevity will ultimately enable expansion of the human lifespan and quality of life improvement.

Conflict of interest

The authors declare no conflicts of interest.

Role of funding source

None.

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