Ageing Research Reviews 12 (2013) 90–102

Contents lists available at SciVerse ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Genes, physical fitness and ageing

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ARTICLE INFO

Article history:
Received 21 June 2012
Received in revised form 6 September 2012
Accepted 6 September 2012
Available online xxx

Keywords:
Ageing
Genes
Physical fitness
Genetic variation

ABSTRACT

Persons aged 80 years and older are the fastest growing segment of the population. As more individuals live longer, we should try to understand the mechanisms involved in healthy ageing and preserving functional independence in later life. In elderly people, functional independence is directly dependent on physical fitness, and ageing is inevitably associated with the declining functions of systems and organs (heart, lungs, blood vessels, skeletal muscles) that determine physical fitness. Thus, age-related diminished physical fitness contributes to the development of sarcopenia, frailty or disability, all of which severely deteriorate independent living and thus quality of life. Ageing is a complex process involving many variables that interact with one another, including – besides lifestyle factors or chronic diseases – genetics. Thus, several studies have examined the contribution of genetic endowment to a decline in physical fitness and subsequent loss of independence in later life. In this review, we compile information, including data from heritability, candidate-gene association, linkage and genome-wide association studies, on genetic factors that could influence physical fitness in the elderly.

1. Introduction

The number of persons aged ≥60 years worldwide is expected to nearly triple—from 760 million in 2010 to 2 billion (~22% of the total population) in 2050 (United-Nations, 2011). The oldest-old group (≥80 years, including centenarians) is the most rapidly expanding group among westerners (Robine and Paccaud, 2005; Waite, 2004). However, longevity comes at a price, including an eventual loss of functional independence (Christensen et al., 2008). In the elderly, functional independence is directly dependent on *physical fitness*, as explained below. Physical fitness has been recently defined as 'the ability to carry out daily tasks with vigour and alertness, without undue fatigue and with ample energy to enjoy [leisure] pursuits and to meet unforeseen emergencies' (Garber et al., 2011). Importantly, physical fitness is operationalized as several measurable health-related phenotypes including mainly cardiorespiratory fitness and muscle performance/function (Garber et al., 2011). With regards to this, old people commonly experience an age-associated decline in the systems and organs that determine the aforementioned physical fitness phenotypes (see below, Section 1.1).

It is important to understand how ageing and its interactions with lifestyle and genetic factors affect physical fitness. This paper reviews the available information on the genetic factors, including data from heritability, candidate-gene association, linkage and genome-wide association studies, that have been so far identified to influence physical fitness and physical fitness related phenotypes in the elderly.

1.1. Main physical fitness related phenotypes: definitions and ageing effects

Among the physiological changes associated with ageing, those affecting the cardiorespiratory and vascular system and skeletal muscles most affect physical fitness (Fig. 1).

1.1.1. Cardiorespiratory fitness

Maximal oxygen uptake (abbreviated $\dot{V}O_2$ max, and sometimes referred to as 'maximal aerobic capacity' or simply 'aerobic capacity' or 'aerobic endurance') is a main indicator of cardiorespiratory fitness. $\dot{V}O_2$ max is the product of multiplying maximal cardiac output by maximal arteriovenous oxygen difference (a-vO_2 diff), and is usually expressed in milliliters of O_2 consumed per kilogram of body weight per minute (ml kg^{-1} min^{-1}). This variable indicates the maximum capacity of the cardiorespiratory and vascular system to transport O_2 from the air to the working muscles, and of the latter to consume O_2 during dynamic exercise involving large muscles, e.g. running, very brisk-walking, bicycling. In a 6-year longitudinal study whose participants were of initial median age 70 years, $\dot{V}O_2$ max losses of 6.9 and 3.9 ml kg^{-1} min^{-1}/decade were estimated in men and women respectively (Hollenberg et al., 2006). In a similar study (participants aged 55–85 years), 10-year losses were 4.3 and 1.9 ml kg^{-1} min^{-1} in men and women (Stathokostas et al., 2004). The 7.9-year longitudinal Baltimore study reported

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http://dx.doi.org/10.1016/j.arr.2012.09.003

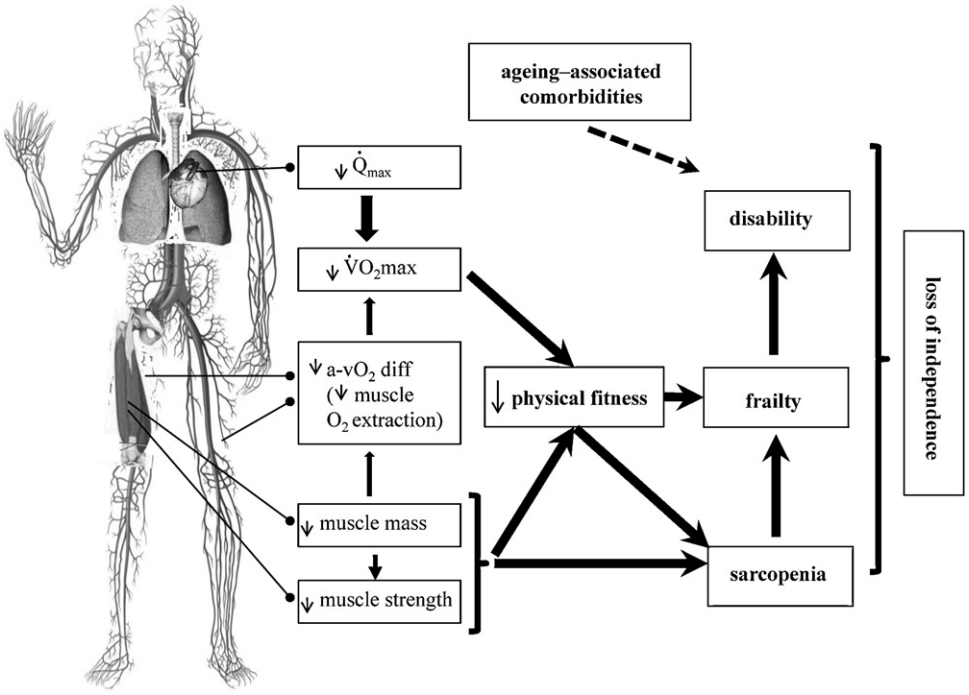

Fig. 1. Summary of the main factors that contribute to age-related declines in physical fitness and physical fitness related phenotypes, resulting in loss of independence. *Abbreviations*: a-vO_2 diff, arteriovenous oxygen difference; *Q*, cardiac output; $\dot{V}O_2$ max, maximal oxygen uptake (or maximal aerobic capacity). See text for recent definitions of sarcopenia, frailty and disability.

$\dot{V}O_2$ max losses of 5%/decade in young adults, and 20%/decade in middle-old (60–69 years) and old-old (≥70 years) individuals (Fleg et al., 2005). Thus, although there are differences between studies, it seems that a $\dot{V}O_2$ max decline ≥4–5 ml kg^{-1} min^{-1}/decade continues into later life (Shephard, 2009).

Reduced maximal cardiac output [=maximal stroke volume × maximum heart rate (HRmax)] is the main contributor to this age-related decline in $\dot{V}O_2$ max. HRmax usually decreases by 3–5%/decade, independently of fitness level or sex (Eskurza et al., 2002; Hawkins et al., 2001), and the relative contribution of this HRmax drop to reduced maximal cardiac output with ageing ranges from 40 to 100% (Hagberg et al., 1985; Ogawa et al., 1992; Stratton et al., 1994). Older adults also show lower stroke volumes during maximal exercise (Hagberg et al., 1985; Ogawa et al., 1992; Stratton et al., 1994). A maximal a-vO_2 diff decrease with ageing (∼−3%/decade) (Hossack and Bruce, 1982; Ogawa et al., 1992) partially contributes to age-reductions in $\dot{V}O_2$ max (Rivera et al., 1989; Wiebe et al., 1999) and reflects less O_2 utilization by skeletal muscles owing to: decreased muscle mass and increased fat (Proctor and Joyner, 1997; Toth et al., 1994), increased peripheral resistance (Lakatta and Levy, 2003), reduced muscle capillary density (Coggan et al., 1992), endothelial dysfunction (Schrage et al., 2007), changes in skeletal muscle microcirculation (Degens, 1998), and reduced muscle oxidative capacity (Conley et al., 2000).

1.1.2. Muscle performance/function

Muscle mass (i.e. the amount of body mass that is made of skeletal muscle tissue) usually peaks at 25–30 years and thereafter begins to decline (Janssen et al., 2000; Lexell et al., 1988). This decline speeds up at the end of the fifth decade, when approximately 10% of total muscle mass is usually lost, such that by 80 years, 40% of muscle mass on average has disappeared (Lexell et al., 1988; Saini et al., 2009). Both a low muscle mass (criterion 1) and low muscle function [i.e. strength (criterion 2) or performance (criterion 3)] are necessary for a diagnosis of *sarcopenia* (Cruz-Jentoft et al., 2010), with the following recently established cut-offs (Fielding et al., 2011): appendicular mass/height^2 ≤7.23 kg m^{-2} (men) and ≤5.67 kg m^{-2} (women) for muscle mass; and gait speed <1 m s^{-1} for muscle function. Factors explaining sarcopenia include: gradual muscle denervation (Deschenes, 2004; Saini et al., 2009); diminished satellite cell numbers/functions (Verdijk et al., 2007); impaired muscle protein turnover, reduced protein synthesis (Kumar et al., 2009); malnutrition (Doherty, 2003); lower anabolic hormone levels (Volpi et al., 2004); increased pro-inflammatory cytokines (Kamel, 2003); greater oxidative stress (Howard et al., 2007); and lower physical activity levels (Cesari and Pahor, 2008). The prevalence of sarcopenia is difficult to determine, mostly because of practical difficulties in assessing muscle mass (von Haehling et al., 2010) and between-study differences in participants' ethnic origin, age or sex (Abellan van Kan, 2009). On average, 5–13% and 11–50% of people aged 60–70 years and ≥80 years respectively suffer sarcopenia (Baumgartner et al., 1998; Frisoli et al., 2011; Janssen, 2006; Janssen et al., 2002; Lauretani et al., 2003; Rolland et al., 2003). Higher prevalences (68%) have been reported in male nursing home residents ≥70 years (Landi et al., 2012).

1.1.3. Frailty and disability

A consequence of the aforementioned effects of ageing on cardiorespiratory fitness and muscle performance/function, alone or in combination with comorbidities, is the *frailty syndrome* (Heuberger, 2011). Although there is no clear consensus, frailty can be defined as 'unintentional weight and muscle loss, exhaustion, and declines in grip strength, gait speed, and activity' (Fried et al., 2001). A main outcome of frailty is *disability* (Sternberg et al., 2011), i.e. 'difficulty or dependency in carrying out activities necessary for independent living, including roles, tasks needed for self-care and household chores, and other activities important for a person's quality of life' (Fried et al., 2004).

Thus, in this review we will report the results of those studies in elderly people which analyzed one or more of the abovementioned phenotypes that determine physical fitness, i.e. mainly $\dot{V}O_2$ max,

cardiac output, stroke volume, HR, a-vO_2 diff, peripheral resistance, indicators of muscle performance/function including muscle mass (e.g. muscle cross sectional area, muscle volume, body composition) and strength (e.g. results of dynamic/isometric strength tests, or walking speed in the oldest cohorts) sarcopenia, frailty, or disability.

1.2. Genetic studies are important for the non-geneticist: basic concepts and main research approaches

Human genetic studies analyze the influence of our *genotype* (our genetic makeup) on our *phenotype* (observable characteristics). Hair or eye color, how strong a person's muscles are or $\dot{V}O_2$ max are examples of phenotypes (sometimes also called *phenotype traits* or simply *traits*). Most phenotypes traits, such as those studied in this review, are not *Mendelian*, i.e. they are *complex* traits, and their heritance is based on the combined influence of multiple genes, environment, and gene-environment interactions. As such, to study the genetic influence on a given phenotype is a difficult task. Rare variations in gene structure (<1% of population) are known as *mutations*; whereas more frequent ones (≥1%) are called *polymorphisms*. The different forms that a particular polymorphism may take are called *alleles*, e.g. the angiotensin-converting enzyme (*ACE*) gene has two common alleles, *Insertion* (I) and *Deletion* (D), with three possible allele combinations or genotypes, II, ID or DD. The location of a particular allele within a chromosome is called a *locus*. Alleles that occur more frequently in the population are called *wild-type* or *major* alleles, whereas the less common alleles are known as *minor* or *variant* alleles. The different types of polymorphisms include: (i) the presence/absence of an entire stretch of DNA (*insertion/deletion* polymorphisms, such as the aforementioned *ACE* I/D polymorphism), (ii) DNA duplication, called *copy number variation*; (iii) *repeating patterns* of DNA that vary in the number of repeats (200–300 base pair (bp) stretches repeated a few to hundreds of times); and (iii) a single-bp change, called a *single-nucleotide polymorphism* (SNP), which are the most common type of polymorphism, with 12 million SNPs already identified (International HapMap Consortium, 2005; Frazer et al., 2007; Sachidanandam et al., 2001). Some SNPs affect parts of a gene (exons) that code for the gene-product (protein), leading or not to a change in the amino-acid sequence of the resultant protein, whereas other SNPs occur in non-coding chromosome areas but may still influence gene function, e.g. by controlling the amount of protein produced (Attia et al., 2009). Owing to the high number of SNPs, the most common nomenclature system assigns a number with the prefix "rs" (for 'reference SNP'), e.g. rs805086. Since they are responsible for most genetic variations in humans and are relatively easy and cheap to detect, SNPs have been the main focus of research into gene–disease associations. The basic idea is relatively simple. For instance, if the variant allele of a SNP is more frequent in old men with accelerated sarcopenia compared to similarly aged men with better muscle mass/function, then we can say that this SNP is *associated* with sarcopenia in the elderly. Thus, in the same way that variation in an environmental or lifestyle factor is linked to an outcome in traditional epidemiologic studies, genetic variation can be associated with an outcome (or phenotype). Some alleles form *haplotypes* i.e. they tend to occur together on the same chromosome and are therefore inherited together. Thus, some genetic studies also include haplotype analyses.

Heritability describes the extent to which differences in a phenotype are explained by genetic differences in a certain population at a certain time (Plomin et al., 2001). Knowing the heritability of a phenotype is important to define the biological mechanism underlying the phenotype (Visscher et al., 2008). *Candidate gene association studies* assess the association of one or more specific genetic variants with outcomes or phenotypes of interest; genetic variants to be tested are selected according to their features, e.g. known or postulated biology or function (Attia et al., 2009). The results of genetic association studies can be very useful. Besides providing new insights into pathways involved in disease or disease-related phenotypes and identify new therapeutic targets (e.g. myostatin-inhibitors to increase muscle mass—see below), the most likely short-term clinical application of this genetic information is to enhance risk stratification, by providing individuals with information about their disease risk or prognosis, e.g. risk of developing sarcopenia, or sarcopenia-induced disability (Attia et al., 2009). The entire bp sequence of the 25,000 genes that constitute the human genome is ~99% identical in different people (Lander et al., 2001), yet the human genome contains 3.3 billion bp; as such, there are still more than 12 million potential variations between the genomes of two different persons of the same age, sex, or exercise habits that may partly explain inter-individual differences in phenotype traits such as those indicative of physical fitness, e.g. $\dot{V}O_2$ max, muscle performance/function (International HapMap Consortium, 2005; Frazer et al., 2007; Sachidanandam et al., 2001).

Most published studies have used a candidate gene approach based on the rationale that a single gene (or a few genes) plays an important role in a given disease or disease-related phenotype. However, the more 'agnostic' approach of *genome-wide association* (GWA) studies has also proved fruitful. GWA studies examine the 'association of genetic variation with outcomes or phenotypes of interest by analyzing 100,000 to millions SNPs across the entire genome without any previous hypotheses about potential mechanisms' (Attia et al., 2009). These two types of study are not mutually exclusive: thus GWA studies serve to identify candidate genes for gene association studies. Both approaches can be used on relatives in *genetic linkage* studies, in which the presence or absence of certain variant alleles in family members with or without a disease or phenotype is analyzed (Attia et al., 2009). Notwithstanding, the results of linkage studies are interpreted in an entirely different manner to population-based (gene-association or GWA) studies (Dawn Teare and Barrett, 2005; Risch, 1997).

2. Method

2.1. Literature search

A three-step literature search was conducted: (1) identifying physical fitness phenotypes, (2) searching for heritability, candidate-gene association, linkage and genome-wide association studies (3) expansion by cross-referencing. The following databases were searched: MEDLINE and the National Library of Medicine. For step 1, keywords used were: 'muscle mass', 'strength', 'muscular fitness', 'cardiorespiratory fitness', 'aerobic endurance', 'physical fitness', 'sarcopenia', 'frailty', 'disability', 'exercise', 'physical activity', 'physical or functional performance'. For step 2, the search was expanded to include the terms: 'genetics', 'genotype', 'polymorphism'. To enable inclusion of all relevant studies, reference lists of relevant articles were cross- referenced and hand searched while applying the above criteria systematically.

2.2. Inclusion criteria

The following inclusion criteria were required: (a) studies published in a peer-reviewed journal (b) studies written in the English language (c) the mean or minimum age of the study cohort (or at least of one sub-cohort) was ≥60 years, (d) at least one of the main identified physical fitness phenotypes (e.g., muscle mass, muscle strength, $\dot{V}O_2$ max, sarcopenia, frailty or disability) was objectively measured (i.e. not self-reported or estimated). For those candidate-gene association studies including cohorts of old (mean

or minimum age ≥60 years) and also younger individuals (maximum age <60 years) and analyzing the different cohorts separately, we also reported the results obtained in the younger people. Indeed, comparing the genetic influence on physical fitness phenotypes in young vs. old people is of interest to understand how genetic factors interact with ageing and these phenotypes. Candidate–gene association studies also had to meet at least 3 of the 5 validity criteria proposed by Attia et al. (2009).

A total of 73 studies were identified in the literature using the aforementioned search terms and criteria. (Of these, only 2 studies analyzed separately the influence of the same genetic factors on physical fitness phenotypes in cohorts of young and old people). Although we have cited all of them to provide the reader with all the available information, a quality criterion that is particularly important to ensure the external validity of a gene–candidate association study is the replication of the findings in at least one different, independent cohort (Attia et al., 2009). Only 4 gene–candidate association studies (summarized in supplementary tables) met this important criterion of external validity.

3. Heritability studies

Sarcopenia-related phenotypes are highly heritable, with genetic contributions reported of up to ∼65–66% for muscle mass (Abney et al., 2001) and strength (Reed et al., 1991), 52–80% for lean body mass (LBM) (Deng et al., 2001; Hsu et al., 2005), 70–90% for muscle size (Huygens et al., 2004b) and 45–65% for fat free mass (FFM) (Abney et al., 2001). Studies conducted on elderly twins have established that heritability can explain 22–52% of variance in muscle strength (Arden and Spector, 1997; Carmelli and Reed, 2000; Frederiksen et al., 2002; Reed et al., 1991). In sedentary individuals, the heritability of $\dot{V}O_2$ max can be as high as 50% (Bouchard et al., 1998). A genetic influence was found in frailty variability among 3719 individuals aged ≥75 years (Dato et al., 2012), yet with considerable between-sex differences: in men, frailty status was more genetic-dependent whereas in women environmental factors were more important. A more modest extent of physical fitness heritability (determined through a validated physical ability score) was described in Danish twins (≥70 years); the heritability of overall muscle strength amounting to ∼10% in men and ∼30% in women (Christensen et al., 2003).

4. Candidate–gene association studies

The reader is referred to Fig. 2 for a diagram showing the main functions of the genes described below, to Table 1 for a list of candidate genes and their abbreviations, and to supplementary tables for the detailed results of gene–candidate association studies in the field. As discussed later (Section 6), to note is that differences among studies in population characteristics (sample size, age, gender, health state, ethnic/geographic origin) and phenotype assessment largely explain the heterogeneity of the results published in the literature and preclude drawing solid conclusions at present.

4.1. ACE I/D polymorphism

The D and I alleles of the *ACE* I/D polymorphism have been linked to a higher and lower ACE enzyme activity respectively (Danser et al., 1995; Tiret et al., 1992; Williams et al., 2005). The role of ACE in the renin–angiotensin–aldosterone system (RAAS) is to convert angiotensin I (AngI) into AngII (Rigat et al., 1990), which, besides working as a potent vasoconstrictor (thereby increasing cardiac after-load), also stimulates smooth (Berk et al., 1989; Geisterfer et al., 1988), cardiac (Ishigai et al., 1997; Sadoshima et al., 1993), and skeletal muscle growth (Gordon et al., 2001; Westerkamp and Gordon, 2005). Studies conducted mainly on sexagenarians have reported a positive association between the D-allele and muscle mass (Charbonneau et al., 2008), LBM (Vigano et al., 2009), and appendicular FFM (Lima et al., 2011), while others have observed no association with whole-body or thigh non-skeletal LBM (McCauley et al., 2010), or thigh-muscle cross-sectional area (CSA) (Garatachea et al., 2012). Controversy also exists concerning the link between I/D genotypes and physical fitness phenotypes.

Table 1
Gene candidates under investigation for their association with physical fitness-related phenotypes in old people.

Abbreviation	Gene
ACE	angiotensin-converting enzyme
ACTN3	α-actinin-3
ACVR	activin-type receptor B
ADR	adrenergic receptor
AGT	angiotensinogen
AMPD1	AMP deaminase (skeletal-muscle isoform)
ApoE	apolipoprotein E
AR	androgen receptor
BTRC	beta-transducin repeat containing
CASP8	caspase 8
CNTF	ciliary neurotrophic factor
CNTFR	ciliary neurotrophic factor receptor
COL1A1	collagen type I alpha 1
CREBBP	CREB-binding protein
FST	follistatin
GR	glucocorticoid receptor
IGF	insulin-like growth factor
IL6	interleukin-6
KAT2B	lysine acetyltransferase 2B
MSTN	myostatin
MTR	5-methyltetrahydrofolate-homocysteine methyltransferase
NOS3	nitric oxide synthase 3
TERT	telomerase reverse transcriptase
TRHR	thyrotropin-releasing hormone receptor
UCP	uncoupling protein
VDR	vitamin D receptor
V1aR	vasopressin 1a receptor

The *ACE* I/D polymorphism was associated with: handgrip-strength in advanced cancer patients (Vigano et al., 2009), handgrip-strength and 10 m maximum walking speed in Japanese men and women (Yoshihara et al., 2009), and several hemodynamic variables (e.g. HR) recorded during submaximal exercise in postmenopausal women (Hagberg et al., 2002). No association was detected between *ACE* genotypes and muscle strength or ability to cope with activities of daily living (ADLs, according to Barthel index) in octogenarians (Garatachea et al., 2012), handgrip-strength, leg-muscle strength, and functional mobility (walk-stair tests) in nonagenarians (Bustamante-Ara et al., 2010), and muscle strength in chronic heart failure patients (Williams et al., 2011).

The association between *ACE* I/D polymorphism and physical fitness phenotype responses to specific exercise training programs has also been addressed. Obese DD homozygotes showed greater gains in knee-extensor strength than II-allele homozygotes, after an 18-month walking and light resistance training (RT) program (Giaccaglia et al., 2008) and, in women who performed *quadriceps* RT for 24 weeks, FFM increased after training only in the I-allele carriers (Lima et al., 2011). However, other authors observed no link between the *ACE* I/D polymorphism and muscle volume adaptation to RT (Charbonneau et al., 2008), muscle strength (30 s sit–stand test) and endurance (3 min-walk test) responses to a brisk-walking program (Okamoto et al., 2010), or the training response of muscle strength/endurance and $\dot{V}O_2$ max in chronic heart failure patients (though an association was found for peak power output during cycle-ergometry) (Williams et al., 2011). When examining data in elderly Danes ($n = 203$), Frederiksen et al. found no association between the *ACE* I/D polymorphism and baseline levels or time

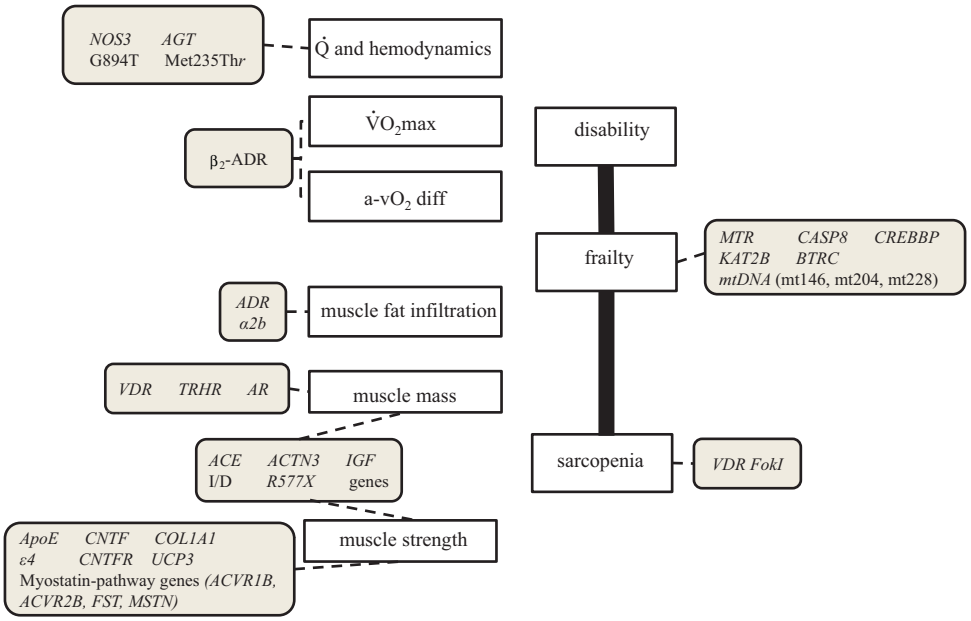

Fig. 2. Summary of the main possible functions (still remaining confirmation and thus marked with dash lines) of candidate genes.

changes (whether induced by training or not) in muscle strength, walking speed or body composition (Frederiksen et al., 2003a). In a 2-year longitudinal study performed in elderly twins, *ACE* genotypes could not be correlated with baseline levels or changes in self-reported physical fitness (Frederiksen et al., 2003b).

4.2. Angiotensinogen (AGT) gene

Another important RAAS gene is *AGT*, which encodes angiotensinogen, a circulating protein produced by the liver that is cleaved by renin to yield Ang I. A common *AGT* polymorphism, T-for-C substitution at nucleotide 704 causing a methionine-to-threonine substitution at codon 235 (Met235Thr, rs699), was associated with cardiovascular responses to dynamic exercise (HR, systolic blood pressure, and a-vO_2 diff) in postmenopausal women (McCole et al., 2002).

4.3. α-Actinin-3 (ACTN3) gene

α-Actinin-3 is a sarcomere protein almost exclusively expressed in fast, glycolytic type II skeletal-muscle fibers where it is used to produce powerful contractions (MacArthur and North, 2004, 2007). A polymorphism (R577X, rs1815739) identified in its gene (*ACTN3*) causes replacement of an arginine (R) residue by a premature stop-codon (X) at amino-acid 577 (North et al., 1999). Approximately 18% of the world-population is homozygous for this stop-codon (i.e. has the XX genotype) and is thus completely deficient in the protein (MacArthur and North, 2007; Yang et al., 2003). However, compared to age-matched wild-type mice, ACTN3-knock-out (α-actinin-3 deficient) mice showed a greater loss of fast muscle force generation and male muscle mass, yet good maintenance of grip strength, increased oxidative metabolism and greater force recovery after fatigue (Seto et al., 2011). Although the R- and X-alleles seem to favor performance in 'power' (jumping, throwing, sprinting) and endurance athletic events respectively (Yang et al., 2003), the association between *ACTN3* genotypes and physical fitness in old people remains unclear, including the putative roles of the R- and X-alleles.

Brazilian women who were X-allele carriers showed a higher relative FFM than RR women (Lima et al., 2011), whereas Japanese XX women had lower thigh-muscle CSA compared to the other genotypes (Zempo et al., 2010). Other studies on aged Caucasians found no association between the *ACTN3* R577X polymorphism and muscularity indices in men (McCauley et al., 2010), mid-thigh CSA in old men and women at baseline or after 5 years (Delmonico et al., 2008), or thigh-muscle CSA in octogenarians (Garatachea et al., 2012). The XX genotype was associated with higher knee-extensor concentric peak power compared to RR/RX genotypes, especially in women (Delmonico et al., 2007). However, in another cohort of women, the XX genotype was related to lower peak torque in knee-extensor muscles (Walsh et al., 2008). Genotype XX men showed a significantly greater adjusted 5-year increase in 400 m-walk time compared to their RR/RX peers whereas in women, the XX genotype was linked to a ~35% greater risk of lower extremity limitation compared to RR (Delmonico et al., 2008). Several authors have detected no relationship between *ACTN3* genotypes and physical fitness phenotypes, i.e. *quadriceps* strength in Brazilian women (Lima et al., 2011), one-repetition maximum (1RM) leg press, sit-stand test and 1-mile walk test in women aged 61–80 years (San Juan et al., 2006), muscle strength and ability to cope with ADLs (Barthel index) in octogenarians (Garatachea et al., 2012), leg and handgrip strength, walking and stair climbing in nonagenarians (Bustamante-Ara et al., 2010), or muscle function (absolute/relative isokinetic strength during knee-extension and *quadriceps* muscle twitch-response) in Caucasian men (McCauley et al., 2010).

The putative effects of *ACTN3* genotypes (whether beneficial or not) may also differ between baseline and post-training. At baseline, XX women had higher absolute and relative peak power values compared to RR/RX genotypes with no differences existing in men, whereas after 10 weeks of knee-extensor RT, RR women showed significantly greater training improvements in relative peak power than their XX counterparts (Delmonico et al., 2007). Lima et al. found no *ACTN3* genotype effect on *quadriceps* strength after 24 weeks of RT in women (Lima et al., 2011).

4.4. β-Adrenergic receptors' genes

β-Adrenergic receptors (β-ADR) are members of a family of G protein-coupled receptors stimulated by naturally occurring catecholamines. In humans, three β-ADRs have been identified:

β_1-ADR, β_2-ADR and β_3-ADR. Two common genetic variations at the β_2-ADR (Gln27Glu, rs1042714) and β_3-ADR (Trp64Arg, rs4994) gene loci were linked to physical fitness-related phenotypes during treadmill exercise in old women; $\dot{V}O_2$ max being lower in the β_2-ADR Glu/Glu group than the other genotypes, and higher in β_3-ADR Trp/Arg women than in their β_3-ADR Trp/Trp peers, and the β_2-ADR Gln/Gln group having a greater a-vO_2 diff than their Glu/Glu counterparts (McCole et al., 2004). In another study, β_2-ADR Gln27Glu and the inhibitory adrenergic receptor (ADRα2b)gene Glu^9 polymorphism influenced mid-thigh muscle fat infiltration in old men (a phenotype associated with low muscle strength, poor leg function and limited mobility in elderly persons); intra-muscle fat accumulation being reduced after RT in participants carrying the mutant alleles Glu27 and Glu^9 compared to non-carriers (Yao et al., 2007).

4.5. Skeletal-muscle AMP deaminase (AMPD1) gene

Young adults, especially TT homozygotes, featuring the C34T mutation (rs17602729) [also termed Gln(Q)12Ter(X)] in the gene (*AMPD1*) encoding skeletal-muscle AMP deaminase, an important regulator of energy metabolism during exercise (Gross, 1997), can exhibit easy fatigability, cramps, as well as an increased severity of coexisting neuromuscular disorders (Sabina, 2000). However, the T-allele was not related to endurance ($\dot{V}O_2$ max, 1-mile walk test) or muscle performance (sit-stand test) in a study with old women (Perez et al., 2006).

4.6. Apolipoprotein E (ApoE) gene

The *ApoE* gene polymorphism is related to significant lipoprotein profile modifications, as well as to the incidence of several diseases, including cardiovascular and Alzheimer's disease or vascular dementia, and could also be involved in the ageing selection process. Although it has been also proposed as a 'frailty gene', no association has been reported with frailty (Rockwood et al., 2008), or longevity and disability (Bader et al., 1998). Controversy also exists regarding the association of *ApoE* genotypes and physical fitness in old people. Thus, the ε4 allele has been linked to more (Albert et al., 1995) but also to less disability during ADLs (Kulminski et al., 2008), while other studies report no association (Bader et al., 1998; Gustafson et al., 2012). Three studies have suggested that the presence of the ε4 allele is a risk factor for more rapid functional decline with ageing (Buchman et al., 2009; Melzer et al., 2005; Snejdrlova et al., 2011), whereas others have detected no association with lower extremity function (Carmelli et al., 2000), self-reported functional capacity in men (Blazer et al., 2001), handgrip-strength (Deary et al., 2006), or aerobic capacity expressed as 6 min-walking performance (Deary et al., 2006) or $\dot{V}O_2$ max (Etnier et al., 2007).

4.7. Androgen receptor (AR) gene

Androgen (total and free testosterone) concentrations decline progressively with age, and low androgen levels have been linked to skeletal-muscle mass loss and physical fitness in old people (Bhasin and Storer, 2009) and could thus contribute to the development of sarcopenia and frailty (Travison et al., 2010). The *AR* gene contains a polymorphic trinucleotide CAG microsatellite repeat sequence that modifies either the amount of AR protein inside the cell (GGNn, polyglycine) or its transcriptional activity (CAGn, polyglutamine). North-American men bearing a greater number of CAG repeats exhibited higher total FFM than those with fewer CAG repeats (Walsh et al., 2005), but other studies detected no correlation between CAG-repeat length and body composition in community-dwelling men (Lapauw et al., 2007) or physical fitness in North-American men (Kenny et al., 2005). In older Caucasian men, body composition and muscularity measures (% body fat, FFM, thigh lean mass) were not different across CAG-repeat length genotypes (Folland et al., 2012).

4.8. Ciliary neutrophic factor (CNTF) gene

The ciliary neurotrophic factor (CNTF) exerts trophic effects on neuronal (Sleeman et al., 2000) and muscle tissues (Guillet et al., 1999). Roth et al. found an association between the A-allele of the G-to-A polymorphism (rs1800169) in the *CNTF* gene and muscular strength; old (>60 years) GA individuals exhibiting an 11% greater peak torque than their GG peers (Roth et al., 2001). In another study conducted in women (70–79 years), AA individuals homozygous for the rs1800169 polymorphism showed lower handgrip-strength, but no link to frailty syndrome was detected (Arking et al., 2006). After a 3-month low-intensity RT program, CC genotype older Japanese people improved their 32-meter walking-performance more than CT/TT genotypes (Murakami et al., 2009). On the other hand, C1703 T (rs3808871) and T1069A (rs2070802) polymorphisms of the CNTF receptor (*CNTFR*) gene have been associated with muscle strength, with the presence of a T allele of the C1703 T variation resulting in overall higher levels of muscle force production than the presence of a C allele in both old (60–78 years) and middle-aged men (45–49 years) but not in old (60–80 years) or middle-aged women (38–44 years), and with carriage of the T allele of the T1069A variation leading to overall higher muscle force in old and middle-aged women, but not in men of either age (De Mars et al., 2007).

4.9. Collagen type I genes

Type I collagen, the main bone protein, consists of two alpha1 and one alpha2 chains encoded by *COL1A1* and *COL1A2* genes respectively. The Sp1 binding site polymorphism in *COL1A1* has been associated with hand-grip and biceps strength in men aged $\geq$70 years (Van Pottelbergh et al., 2001). The mechanisms for this association remain unclear. However, both bone and muscle deteriorate with age, and since bone geometry is partly determined by muscle mass/strength, there might be a common genetic etiology to sarcopenia and osteoporosis, whereby some genetic variants contribute to both muscle and bone phenotypes (Karasik et al., 2009).

4.10. Follistatin (FST) and activin-type I and II receptor B (ACVR1B and ACVR2B) genes

FST and *ACVR1B* and *ACVR2B* genes participate in myostatin regulation and signaling (see below, Section 4.14). In a study in old men (60–78 years) designed to replicate the findings of a larger study through combined linkage and family-based association, the rs2854464 SNP in *ACVR1B* was related to knee muscle strength (Windelinckx et al., 2011). In another report, women carriers of *ACVR2B* Haplotype Group 1 showed less *quadriceps* muscle strength than women homozygous for Haplotype Group 2, whereas no association was observed in men (Walsh et al., 2007). Male carriers of *FST* Haplotype Group 3 exhibited less total leg FFM than non-carriers, but no link was found in women.

4.11. Glucocortoicoid receptor (GR) gene

Cortisol levels increase with age and hypercortisolism causes muscle weakness. Although the ER22/23EK polymorphism of the *GR* gene has been associated with relative glucocorticoid resistance, a healthier metabolic condition, and better survival in old people (Manenschijn et al., 2009), other studies have noted no association with mean appendicular skeletal-muscle mass and

handgrip-strength (Peeters et al., 2008), or with 2-year changes in Barthel scale (Mora et al., 2012).

4.12. Insulin-like growth factors genes

Insulin-like growth factors (IGFs) are peptides that regulate cell growth, differentiation and regeneration (O'Dell and Day, 1998). Age-related skeletal muscle fiber loss may be partly related to diminished local IGF production (Sayer et al., 2002). The *IGF1* gene cytosine adenine (CA)-repeat polymorphism was found to affect knee-extensor peak power at baseline in old adults, but not in response to RT (Sood et al., 2012), whereas Hand et al. correlated this polymorphism with RT-induced changes in muscle strength and volume (Hand et al., 2007). Black old women (70–79 years) with the CC genotype of the *IGF1* C1245 T (rs35767) polymorphism had lower total muscle mass than their TT counterparts, while white CC women showed reduced muscle function compared with white TT women (Kostek et al., 2010). Yet these results were not replicated in the same study with a cohort of young women (mean age ~25 years). This polymorphism was also associated with functional state in Spanish elderly subjects (Mora et al., 2011). Two studies have analyzed the influence of gene *IGF2* on muscle mass and strength in old people (Sayer et al., 2002; Schrager et al., 2004): in one, *IGF2* 820G > A (*ApaI*, rs680) genotypes emerged as independent predictors of handgrip-strength in men, but not in women (Sayer et al., 2002), and in a study by Schrager et al. performed at ~2-year intervals in two Caucasian cohorts, *IGF2* genotypes were found to affect muscle mass and function at age 65 years, the AA genotype exerting a negative effect on arm strength in men, and on total body FFM and arm and leg strength in women (Schrager et al., 2004). However, the results were not corroborated in one cohort. Moreover, a recent multi-cohort study (Alfred et al., 2012) found no evidence for associations between two polymorphisms of IGF genes (*IGF1* rs35767and *IGF2* rs7127900) and grip strength, timed get up and go/walks and timed chair rises after adjusting for age and sex.

4.13. Interleukin-6 (IL6) gene

Interleukin-6 (IL6) is a multifunctional cytokine primarily involved in immune functions. However, recent data also ascribe a pivotal role to IL6 in muscle repair and hypertrophy following exercise-induced damage (Serrano et al., 2008). A functional G/C polymorphism at position -174 (rs1800795) has been described in the *IL6* gene (Fishman et al., 1998), the G allele enhancing the transcriptional response (Bennermo et al., 2004; Fishman et al., 1998). Although elevated levels of IL6 have been linked to disability, frailty, and mortality in older adults, Walston et al. (2005) found no association between *IL6* genotypes and serum IL6, handgrip, knee and hip strength, or frailty in older women, and no relationship was detected between *IL6* genotypes and muscle strength in Brazilian women despite an observed genotype effect on serum IL6 (Pereira et al., 2011).

4.14. Myostatin gene

The myostatin (*MSTN* or growth differentiation factor 8, *GDF8*) gene (Huygens et al., 2004a) encodes myostatin, a skeletal muscle-specific secreted peptide that essentially modulates myoblast proliferation and thus muscle mass/strength (McPherron et al., 1997). Old *MSTN*- knock-out (myostatin-deficient) mice show minimal muscle atrophy compared to wild-type controls (Siriett et al., 2006). Of the *MSTN* variations identified in humans, the Lys(K)153Arg(R) polymorphism (rs1805086) is thought to influence skeletal-muscle phenotypes in old people, the rare variant R-allele possibly exerting a negative influence (Ferrell et al., 1999; Huygens et al., 2004a; Seibert et al., 2001). Reduced overall muscle strength (several muscle groups) has been reported in old African-American women (Seibert et al., 2001) and Italian Caucasians of both sexes carrying the R-allele (Corsi et al., 2002). The muscle mass and function (gait and balance) and ability to cope with ADLs (Barthel score) of a 96-year-old woman with the very rare RR genotype was in the lowest 25th sex- and age-specific percentile (Gonzalez-Freire et al., 2010). In the same study, the 1RM leg press and muscle mass of KR nonagenarian women was low-to-normal (~25th–50th percentile) compared to peers with the wild-type (KK) genotype. Some findings also suggest a possible role for the *MSTN* K153R polymorphism in the muscle volume response to RT (Ivey et al., 2000), yet definitive data for old people are lacking. Genetic studies on the *MSTN* gene have provided the rationale for therapeutic trials on myostatin-inhibitors, such as MYO-029; the latter has an adequate safety margin and is able to improve the muscle strength/function or muscle contractile properties in some patients with muscular dystrophy (Krivickas et al., 2009; Wagner et al., 2008). Given this type of treatment could also stimulate muscle growth in healthy humans (Wagner et al., 2008), it would be interesting to determine its effect in ageing people.

4.15. Mitochondrial DNA (mtDNA)

Mitochondrial DNA (mtDNA) codes for 13 of the 83 polypeptides involved in the respiratory chain. mtDNA is more prone to oxidative damage than nuclear DNA owing to a lack of histone-mediated protection, and the build-up of somatic mtDNA mutations over a lifespan is one of the main features of age-related loss of mitochondrial function (Wallace et al., 2003). Since mtDNA variations could influence individual susceptibility to mtDNA damage, they could also affect human longevity (Eynon et al., 2011), as well as cause a functional decline and vulnerability to disease in later life. Moore et al. (2010) identified three mtDNA SNPs associated with frailty: mt146, mt204, and mt228. These data were later corroborated in a larger cohort, in which the mt204 C allele was associated with a greater likelihood of frailty and lower handgrip-strength in later life.

4.16. Mitochondrial uncoupling protein (UCPs) genes

Five UCPs have been identified in humans to play an important role in the regulation of reactive oxygen species (ROS) formation in mitochondria (Cannon et al., 2006). UCP3 is mainly expressed in skeletal muscle where it regulates fatty acid metabolism, redox state, and ROS formation (Echtay, 2007). Polymorphism rs1800849 in the *UCP3* gene was related to handgrip-strength in elderly Italians, with carriers of the T-allele showing greater strength than the other genotypes (Crocco et al., 2011).

4.17. Endothelial nitric oxide synthase (NOS3) gene

The *NOS3* gene encoding endothelial nitric oxide synthase (eNOS) has been proposed as a candidate to explain individual variability in several health-related phenotypes, owing to the key role of nitric oxide (NO) in regulating vascular tone (Cooke et al., 1991; Quyyumi et al., 1995). The T-allele of the Glu298Asp (G894 T) polymorphism (rs1799983) leads to reduced eNOS activity and basal NO production (Wang et al., 2000; Yoshimura et al., 1998). In postmenopausal women, the T-allele was associated with a higher stroke volume and lower HR during submaximal dynamic exercise (Hand et al., 2006).

4.18. Telomerase reverse transcriptase (TERT) gene

Several age- and disease-related traits have been associated with shorter telomeres, the structures that protect the ends of chromosomes. A common polymorphism (rs401681) near the *TERT* gene, which is involved in telomere maintenance that is linked to cancer risk, could not be associated with physical fitness phenotypes (handgrip-strength, timed up-rises, timed chair-rises) in 9 UK cohorts (5 of which met the age criteria for this review) (Alfred et al., 2011).

4.19. Vitamin D receptor (VDR) gene

Although there is some controversy regarding its expression in skeletal-muscle fibers (Wang and DeLuca, 2011), the vitamin D receptor (VDR) is thought to play an important role in skeletal-muscle function, through activation of signal transduction pathways that regulate contractility and myogenesis (Wang and DeLuca, 2011). The b-allele of the *VDR BsmI* polymorphism (rs1544410) was found to exert a beneficial effect on muscle strength (Geusens et al., 1997; Hopkinson et al., 2008), muscle boundary length (Murakami et al., 2009), balance (Barr et al., 2010) and fall risk (Barr et al., 2010; Onder et al., 2008) in some studies. In contrast, Bahat et al. reported a desirable effect of the *BsmI* B-allele, BB homozygous men (>65 years) showing higher knee-extensor muscle strength compared to the Bb/bb group (Bahat et al., 2010). People with the CC genotype of the *VDR FokI* polymorphism (rs2228570) had reduced *quadriceps* strength relative to T-allele carriers (Hopkinson et al., 2008), but this polymorphism was not associated with fall risk in nonagenarians (Onder et al., 2008). The potential link between *VDR* genotypes and muscle mass in the elderly has also been disputed, with two studies reporting no association (Bahat et al., 2010; Moreno Lima et al., 2007), and one reporting the risk of sarcopenia (defined as appendicular FFM $<7.26\,kg\,m^{-2}$) to be 2.17-fold higher in men homozygous for the *FokI* polymorphism (FF) compared to their peers with one or more f-alleles (Roth et al., 2004).

4.20. Vasopressin V1a receptor (V1aR) gene

Although the vasopressin V1a receptor (V1aR) has metabolic and cardiovascular effects related to physical fitness phenotypes, notably lipid metabolism modulation, Masuki et al. (2010) detected no association between the rs1042615 polymorphism in the *V1aR* gene and the $\dot{V}O_2$ max response to a 5-month walking training program in old people.

4.21. Other genes

To address the hypothesis that variations in genes related to inflammation and muscle maintenance are associated with frailty, Ho et al. (2011) performed the most comprehensive candidate-gene study in the field, including 1,354 SNPs across 134 genes, in women aged 70 – 79 years. These authors were able to associate with frailty, several SNPs located in genes involved mainly in apoptosis- and transcription regulation-related pathways [5-methyltetrahydrofolate-homocysteine methyltransferase (*MTR*), caspase 8 (*CASP8*), CREB-binding protein (*CREBBP*), lysine acetyltransferase 2B (*KAT2B*), and beta-transducin repeat containing (*BTRC*)].

5. Linkage and GWA studies

In the first genome-wide linkage investigation into several physical fitness-related phenotypes in older people (Finnish female twins aged 66–75 years), Tiainen et al. found suggestive linkage for walking speed on chromosome 13q22.1, muscle strength on chromosome 15q14, 2, muscle power on chromosome 8q24.23, and muscle CSA on chromosomes 9q34.32 and 20q13.31 (Tiainen et al., 2008). In two cohorts of the Framingham Heart Study (men and women of mean age ≥60 years), Karasik et al. (2009) identified chromosome regions potentially linked to leg lean mass and femoral bone geometry, including 12p12.3–12p13.2 and 14q21.3–22.1.

In a recent GWA study examining 379,319 SNPs in a cohort of US unrelated whites (492 men, 481 women, mean age 50 years) (Liu et al., 2009), the authors associated with LBM two SNPs within the thyrotropin-releasing hormone receptor (*TRHR*) gene, rs16892496 and rs7832552. Individuals carrying 'unfavorable' rs16892496 and rs7832552 genotypes showed lower LBM respectively, compared to the other genotypes. These results were confirmed in other cohorts, including unrelated old US whites (659 men, 829 women, mean age 63 and 61 years respectively). Thus, their findings indicate *TRHR* is an important gene for LBM variation.

There is a need for more GWA studies in older people, mainly to propose new candidate genes for more detailed association studies.

6. Discussion

The controversy existing in the field is likely the consequence of differences among the different study cohorts such as participant age, sex or ethnic/geographic origin and mainly, sample size. The sample size for detecting associations between disease or health related phenotypes (as those reviewed here) and SNP markers is known to be highly affected by factors such as allele frequency, degree of linkage disequilibrium (i.e. a measure of association between alleles at different loci), inheritance models (e.g. additive vs. dominant), or the effect size of the genetic variants (e.g. odds ratio). Nevertheless, it could be estimated that, for instance, testing a single SNP would require ~250 cases to obtain a statistical power of 80% (Hong and Park, 2012). With regards to this, only 38 studies reviewed here included more than 250 cases.

Differences in the tests used to assess physical fitness phenotypes are further possible confounding factors. For instance, 1RM strength tests or the 1-mile walk test can be used in healthy sexagenarians or septuagenarians, whereas more debilitated or older cohorts are better assessed using ambulation tests. Furthermore, a main confounder and limitation in the field lies on the very limited number of studies ($n = 4$) that have corroborated their main findings on the same phenotypes using an independent replication cohort of old people. Thus, although a comprehensive meta-analysis would provide an accurate perspective of the question addressed here, this is not yet recommended due to heterogeneity among studies. To standardize research in the field, future studies should adhere to the recent guidelines for 'STrengthening the REporting of Genetic Association' studies (STREGA) (Little et al., 2009), built on the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE). Besides the need for reported associations to be externally validated with replication cohorts, functional studies examining gene expression are also recommended for understanding the molecular mechanisms underlying potential links between a given polymorphism and physical fitness phenotypes in advanced ages. However, this will require tissue biopsies (i.e. skeletal-muscle) in old people, which is not always feasible. Finally, we believe that, in order to understand how genetic factors interfere with ageing and physical fitness, ideally the same cohort should be followed over decades to assess if the interaction between the same genetic variants and physical fitness phenotypes changes as a result of the ageing process.

7. Conclusions

Studies assessing the contribution of genetic makeup to age-related diminished physical fitness and subsequent loss of independence are of broad interest owing to our ever-increasing longevity and accompanying health problems. For instance, the estimated direct healthcare cost attributable to sarcopenia in the United States in 2000 was US$ 18.5 billion, representing some 1.5% of the entire healthcare budget for that year (Janssen et al., 2004). Heritability studies have identified an important genetic component of physical fitness-related phenotypes among old people. Published data on specific gene variants are however relatively recent and controversial. As such, no solid evidence currently exists supporting an 'unfavorable' genotype associated, for example, with accelerated sarcopenia or frailty. Among many candidates (most of which probably remain to be identified), variations in the *MSTN* gene and genes involved in the myostatin signaling pathway (e.g. *ACVR1B*) warrant further, in-depth research due their important role in muscle mass modulation. Future studies should consider that physical fitness is the result of complex interactions among several organ (heart, lung, muscle) functions. Accordingly, physical fitness is a *polygenic* phenotype, not reducible to specific polymorphisms. Thus, the question that needs to be resolved in the foreseeable future is: how do multiple genes interact with each other and environmental factors to determine healthy ageing allowing for an independent, active lifestyle up until the end of life?

Acknowledgements

We thank Ana Burton for her lingustic assistance. Research in the field by the authors is supported by the *Fondo de Investigaciones Sanitarias* (grant # FIS PI09-00194).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arr.2012.09.003.

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