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Genes and the ageing muscle: a review on genetic association studies

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Abstract Western populations are living longer. Ageing decline in muscle mass and strength (i.e. sarcopenia) is becoming a growing public health problem, as it contributes to the decreased capacity for independent living. It is thus important to determine those genetic factors that interact with ageing and thus modulate functional capacity and skeletal muscle phenotypes in older people. It would be also clinically relevant to identify 'unfavourable' genotypes associated with accelerated sarcopenia. In this review, we summarized published information on the potential associations between some genetic polymorphisms and muscle phenotypes in older people. A special emphasis was placed on those candidate polymorphisms that have been more extensively studied, i.e. angiotensin-converting enzyme (*ACE*) gene I/D, α-actinin-3 (*ACTN3*) R577X, and myostatin (*MSTN*) K153R, among others. Although previous heritability studies have indicated that there is an important genetic contribution to individual variability in muscle phenotypes among old people, published data on specific gene variants are controversial. The *ACTN3* R577X polymorphism could influence muscle function in old women, yet there is controversy with regards to which allele (R or X) might play a 'favourable' role. Though more research is needed, up-to-date *MSTN* genotype is possibly the strongest candidate to explain variance among muscle phenotypes in the elderly. Future studies should take into account the association between muscle phenotypes in this population and complex gene–gene and gene–environment interactions.

Keywords Sarcopenia · Ageing · Genetic variation · Muscle phenotypes

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Introduction

Due to Western societies populations living longer, there is a demand to understand the ageing process and to explore the mechanisms associated with healthy ageing and preservation of functional independence at the end of life. In elderly people, functional capacity is directly dependent on muscular fitness as these persons experience age-associated declines in skeletal muscle mass and function, i.e. sarcopenia (Rosenberg 1997). Sarcopenia contributes to the decreased capacity for independent living associated with advanced age (Rexach et al. 2009) and imposes a significant economic burden. For instance, the estimated direct healthcare cost attributable to sarcopenia in the USA in 2000 was $18.5 billion, which represented about 1.5% of total healthcare expenditures for that year (Janssen et al. 2004). It is thus important to understand how ageing and the interaction of ageing with lifestyle

and genetic factors affect functional capacity and skeletal muscle phenotypes.

The influence of external factors, notably physical activity habits, on muscle phenotypes in the elderly has been investigated in depth (Daly et al. 2008; Liu and Latham 2011), yet the heritability of muscle strength is less well-known. There is, however, evidence supporting that the extreme plasticity of human skeletal muscle in response to several stimuli (particularly, exercise) is genetically regulated (Stewart and Rittweger 2006); thus, several genetic variations may explain, at least partly, individual variations in muscle strength and muscular fitness in the elderly, such as unfavourable genotypes potentially associated with accelerated sarcopenia.

In this review, we compiled available information, based on genetic association studies, on those polymorphisms that are candidates to be associated with muscle phenotypes in the elderly. Our literature search was primarily based on the journals available in MEDLINE, the National Library of Medicine's publication database covering the fields of life sciences, biomedicine, and health using a combination of key words (genetics, genotype, polymorphism, muscle mass, strength, muscular fitness, training, exercise, physical activity, physical or functional performance, older, elderly). Articles published since April 2011 are not included in this review. The literature search was limited to articles published in English.

Sarcopenia in the elderly: a common problem

The European Working Group on Sarcopenia in Older People recently recommended using the presence of both low muscle mass (criterion 1) and low muscle function (i.e. strength (criterion 2) or performance (criterion 3)) for the diagnosis of sarcopenia (Cruz-Jentoft et al. 2010). Thus, diagnosis requires documentation of criterion 1 plus documentation of either criterion 2 or criterion 3. As for cutoff values of muscle mass and function, Fielding et al. established that a diagnosis of sarcopenia is consistent with an objectively measured low muscle mass (e.g. appendicular mass relative to height^2 that is $\leq$7.23 kg m^{-2} in men and $\leq$5.67 kg m^{-2} in women) and a gait speed of less than 1 m s^{-1} (Fielding et al. 2011). On a myocellular level, sarcopenia is characterized by a reduction in muscle fibre number as well as fibre size, with specific type II muscle fibre atrophy (Lexell et al. 1983, 1988). Muscle mass usually reaches its peak at the age of 25–30 years and thereafter begins to decline (Lexell et al. 1988; Janssen et al. 2000). The decrease in muscle mass accelerates at the end of the fifth decade, when approximately 10% of the total muscle mass is usually lost; thus, at the age of 80 years, 40% of the muscle mass has disappeared on average (Lexell et al. 1988; Saini et al. 2009). The age-associated loss of muscle strength is more rapid than the parallel loss of muscle mass, suggesting a decline in muscle quality with ageing (Goodpaster et al. 2006). In sedentary people, muscle strength decreases by 1–3% per year after the third decade of life, and this rate of decrease can be higher after the eight decade (Connelly and Vandervoort 1997).

Sarcopenia contributes to the onset and progression of disability with advancing age (Hairi et al. 2010). Sarcopenia can induce muscle weakness and reduced ability to produce rapid force, which are considered to be two of the most common risk factors associated with falls and loss of functional independence in older adults (Taaffe and Marcus 2000; Buchman et al. 2007). Sarcopenia can be explained by several physiopathological factors including (a) progressive muscle denervation (Deschenes 2004; Saini et al. 2009); (b) alterations in muscle protein turnover, specifically manifested by difficulty to increase protein synthesis (Kumar et al. 2009); (c) malnutrition (Doherty 2003); (d) altered expression levels of anabolic hormones (Volpi et al. 2004); (e) increased levels of pro-inflammatory cytokines (Kamel 2003); (f) increased oxidative stress (Howard et al. 2007); (g) lower physical activity levels (Cesari and Pahor 2008) and (h) diminished number and function of satellite cells in skeletal muscles (Verdijk et al. 2007). Concerning the latter, satellite cells are the main contributor to muscle maintenance, growth and repair (Anderson and Wozniak 2004). Thus, a decline in the number of satellite cells (Kadi et al. 2004; Renault et al. 2002; Verdijk et al. 2007) or their inability to become active and proliferate in response to anabolic stimuli (Conboy et al. 2003; Conboy and Rando 2002) may contribute to the development of sarcopenia.

The prevalence of sarcopenia varies among studies depending on the race, age and sex of the studied samples, or the assessment tool (Abellan van Kan

2009). For instance, a recent report showed a prevalence of 42% in a cohort of 250 North American women aged 76–86 years (Frisoli et al. 2011). The lack of a standardized definition of sarcopenia until recently, at least in terms of cutoff points of muscle mass and function (Cruz-Jentoft et al. 2010; Fielding et al. 2011), has been an important recognized impediment to epidemiologic studies in the field.

Heritability studies

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). Heritability studies in humans have found overall genetic contributions of up to 66% for muscle mass (Abney et al. 2001) and 65% for muscle strength (Reed et al. 1991). The heritability of a given phenotype can be analysed in twin studies. Published research with older twins has reported that heritability can explain 22% to 52% of the variance in muscle strength, the latter been typically assessed with handgrip dynamometry (Arden and Spector 1997; Carmelli and Reed 2000; Frederiksen et al. 2002; Reed et al. 1991). The relative contribution of genetic and environmental effects to the individual variability in muscle strength changes over the ageing process. During a 10-year follow-up in male twins with a mean age of 63 years at baseline, the heritability of handgrip strength decreased from 35% to 22%, while the shared environmental effects increased from 39% to 45% (Carmelli and Reed 2000). Age-related diseases can also influence the heritability of muscle strength in the elderly. In a study of 1,757 Danish twins aged 45–96 years, Frederiksen et al. found that excluding individuals with chronic diseases (cardiopulmonary diseases, diabetes, stroke, cancer excluding skin cancer, osteoarthritis or osteoporosis) increased the heritability estimate from 52% to 62%, owing to a reduction in environmental variability (Frederiksen et al. 2002). Some data are also available on the heritability of muscle phenotypes in the lower extremities of old people. In research conducted on monozygotic and dizygotic female Finnish twin pairs aged 63–76 years, Tiainen and colleagues found that genetic effects accounted for 20–30% of the variance in handgrip strength, leg extensor power and maximal walking speed (Tiainen et al. 2004, 2005, 2008, 2009).

Muscle cross-sectional area (CSA) and lean body mass (LBM), which are close approximates of total body muscle mass, seem to be under a relatively strong genetic regulation across the human lifespan. Among boys and girls aged 10–14 years, genetic effects accounted for 87–95% of the variation in the circumference of the muscles of the upper and lower extremities (Loos et al. 1997). A heritability of more than 85% was observed for arm CSA among male twins aged 17–30 years (Thomis et al. 1997, 1998). Genetic effects accounted for 52–84% of the variation in LBM among older female twins, i.e. women averaging 45 years (Seeman et al. 1996) or ~53 years of age (Nguyen et al. 1998) and premenopausal women (Arden and Spector 1997). In a study by Schousboe et al., the heritability of LBM was 61% among female twins aged 18–67 years (Schousboe et al. 2004). Forbes et al. reported a heritability of 70% for LBM in twin pairs of the same sex over the age range of 7–85 years (Forbes et al. 1995).

On the other hand, the findings of several multivariate genetic studies suggest a shared pleiotropic gene action for the different muscle phenotypic characteristics (Thomis et al. 1997, 1998; Tiainen et al. 2004, 2005; De Mars et al. 2007). This would imply that different muscle phenotypes share the same chromosomal region with suggestive or significant evidence for linkage (De Mars et al. 2008).

Genotype–phenotype association studies

A large number of candidate genes have been studied to identify potential statistical associations with muscle-related phenotypes in a wide range of population groups of varying ages (Bray et al. 2009). Some of the studied genetic variations could be also associated with muscle phenotypes in the elderly. We included in our review all the genetic association studies in which the mean or minimum age range of the cohort (or at least of one study cohort in those reports with ≥2 cohorts) was ≥60 years. We also included some studies with large cohorts with a mean age (or minimum age range) <60 years, but in which subanalyses were performed in a subset of participants aged ≥60 years (Schrager et al. 2004; Roth

et al. 2001). We also included in our review two studies by Walsh et al. with large cohorts of a wide age range because the mean age of each study cohort was ≥60 years, as deduced from the information provided in the tables of these two papers (Walsh et al. 2007, 2008).

Summary of the functional significant polymorphisms studied in previous genotype–phenotype association reports

Angiotensin-converting enzyme gene I/D polymorphism The I/D polymorphism (rs1799752) of the human angiotensin-converting enzyme (*ACE*) gene is defined by the presence (insertion, I allele) or absence (deletion, D allele) of a 287-bp fragment in intron 16 (Rigat et al. 1990). The D and I alleles are usually associated with higher and lower ACE enzyme activity respectively (Danser et al. 1995; Tiret et al. 1992; Williams et al. 2005). The primary role of ACE in the renin–angiotensin system is to convert angiotensin I into angiotensin II (Rigat et al. 1990), which not only acts as a vasoconstrictor but also regulates smooth (Berk et al. 1989; Geisterfer et al. 1988) and cardiac muscle growth (Sadoshima et al. 1993; Ishigai et al. 1997). ACE inhibitors have been shown to inhibit hypertrophy in overloaded muscle, which also suggests a role for angiotensin II in skeletal muscle hypertrophy (Gordon et al. 2001; Westerkamp and Gordon 2005).

α-Actinin-3 gene α-Actinin-3 (ACTN3) is a structural protein that is the predominant component of the sarcomeric Z-discs, where it acts as a lattice structure that anchors actinin-containing thin filaments and stabilises the muscle contractile apparatus (Squire 1997). This protein is almost exclusively expressed in fast-twitch (type II) skeletal muscle fibres (Mills et al. 2001); thus, compared to the I type, α-actinin-3 may confer type II fibres with a higher capacity for the absorption/transmission of force at the Z line during rapid contractions (Squire 1997). The R577X polymorphism (rs1815739) of the gene (*ACTN3*) encoding α-actinin-3, which results from a C-to-T transition at position 1,747 in exon 16 that substitutes an arginine residue at codon 577 for a premature stop codon (North et al. 1999), may be associated with muscle phenotypes, particularly with the ability to produce powerful muscle contractions (MacArthur et al. 2007). The α-actinin-3-deficient XX genotype (with a frequency of ~18% among European Caucasians) is believed to preclude top-level athletic performance in 'pure' power and sprint sports (e.g. sprinting, jumping events), especially in women (Yang et al. 2003). In contrast, compared with the general population, the X allele tends to be overrepresented in those humans with an 'extreme endurance phenotype', i.e. elite endurance athletes (Lucia et al. 2006; Yang et al. 2003). Compared with the age-matched wild-type mouse, the ageing knockout (α-actinin-3-deficient) mouse shows greater loss of fast muscle force generation and male muscle mass, yet good maintenance of grip strength and increased oxidative metabolism and greater force recovery after fatigue (Seto et al. 2011).

Androgen receptor gene Androgen (total and free testosterone) concentrations decline progressively with advancing age because of defects at all levels of the hypothalamic–pituitary–testicular axis; low androgen levels have been associated with decreased skeletal muscle mass, muscle strength, physical function, bone mineral density, and fracture risk in older people (Bhasin and Storer 2009). The androgen receptor (*AR*) gene contains a polymorphic trinucleotide CAG microsatellite repeat sequence in exon 1 that modifies either the amount of AR protein inside the cell (GGNn, polyglycine) or its transcriptional activity (CAGn, polyglutamine).

Ciliary neurotrophic factor gene The ciliary neurotrophic factor (CNTF) is a member of the interleukin-6 family that exerts trophic effects on both neuronal (Sleeman et al. 2000) and muscle tissues (Guillet et al. 1999). Although CNTF synthesis is associated with peripheral nerves (Sendtner et al. 1992), a specific binding subunit of the CNTF receptor (CNTF receptor-α), abundantly expressed in skeletal muscle (Ip et al. 1993), is required for CNTF activity (Davis et al. 1993). In addition, CNTF levels decline with age, and exogenous CNTF administration in older rats increases muscular strength (Guillet et al. 1999). A G-to-A polymorphism (rs1800169) in the human *CNTF* gene that results in aberrant splicing was first identified by Takahashi et al. (1994).

Collagen type I alpha 1 gene Type I collagen is the major protein of bone and is composed of two alpha1

and one alpha2 chains, which are encoded by collagen type I alpha 1 (*COL1A1*) and *COL1A2* genes, respectively. Mutations in the coding regions of both genes give rise to different variants of *osteogenesis imperfecta*, an autosomal dominant disorder of the connective tissue that is characterized by a variable degree of bone fragility. Although Van Pottelbergh et al. (2001) found an association between a polymorphism in *COL1A1* and muscle phenotypes (see "Cross-sectional genetic association studies" section below), the mechanisms explaining such association remain to be elucidated. Because both bone and muscle tissue deteriorate with age and bone geometry is partly determined by muscle mass/strength, there might be a common genetic aetiology to sarcopenia and osteoporosis in the elderly, with some genetic variants contributing to both muscle and bone phenotypes (Karasik et al. 2009).

Follistatin and activin-type II receptor B genes *Follistatin* (*FST*) and activin-type II receptor B (*ACVR2B*) are two myostatin-related genes involved in the regulation and signalling of myostatin (see below for a detailed explanation on myostatin function).

Insulin-like growth factor genes Insulin-like growth factors (IGFs) are peptides that regulate the growth, differentiation and regeneration of cells (O'Dell and Day 1998). Insulin-like growth factor II (IGFII or IGF2) is one of the main determinants of foetal and post-natal growth (Rother and Accili 2000). It has also a proliferative action in adult muscle (Caroni et al. 1994), and the age-associated loss in muscle fibres may be related, at least partly, to a decline in the local production of IGFs like IGF2 (Sayer et al. 2002).

Interleukin-6 gene Interleukin-6 (IL6) is a multifunctional cytokine primarily involved in immune functions. Recent data also indicate a pivotal role of this protein in the processes of muscle repair and hypertrophy following exercise-induced damage (Serrano et al. 2008). A functional G/C polymorphism at position −174 [rs1800795] was described in the 5′ flanking region of the IL6 (*IL6*) gene (Fishman et al. 1998), with the G allele being associated with increased transcriptional response in vitro (Fishman et al. 1998) and in vivo conditions (Bennermo et al. 2004).

Myostatin gene The myostatin (*MSTN*; or growth differentiation factor 8) gene (Huygens et al. 2004) is receiving growing attention in the last years. The *MSTN* gene encodes myostatin, a skeletal muscle-specific secreted peptide that functions mainly to modulate myoblast proliferation and thus muscle mass and strength (McPherron et al. 1997). Variants of the *MSTN* gene are associated with muscle hypertrophy phenotypes in a range of mammalian species, most notably cattle (Grobet et al. 1997; McPherron and Lee 1997), dogs (Mosher et al. 2007) and mice (McPherron et al. 1997). The myostatin-null mouse model also provides insights into the physiological role of this protein. Old myostatin-deficient mice have minimal muscle atrophy compared to their wild-type controls (Siriett et al. 2006). It appears that myostatin also regulates the structure and function of tendon tissues, as the stiffness of tendons is 14 times higher in myostatin-deficient mice than in their wild-type controls (Mendias et al. 2008).

Myostatin inhibition, as well as variations in the *MSTN* gene, can have functional consequences in old humans. Systemic treatment with the myostatin inhibitor MYO-029 provides an adequate safety margin and can induce improvements in the muscle strength/function or muscle contractile properties of some adult patients with muscular dystrophies, supporting the bioactivity of myostatin inhibitors (Krivickas et al. 2009; Wagner et al. 2008). Because 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. Of the identified *MSTN* variations in humans, the Lys(K)153Arg(R) polymorphism located in exon 2 (rs1805086, 2,379A>G replacement) is one candidate to influence skeletal muscle phenotypes (Ferrell et al. 1999). The Lys(K)153Arg(R) amino acid replacement is found within the active mature peptide of the myostatin protein; it could theoretically influence proteolytic processing with its propeptide, or affinity to bind with the extracellular activin-type II receptor B. The latter results in intracellular activation of the SMAD pathway, through which myostatin induces myoblast proliferation (Thomas et al. 2000) and differentiation (Rios et al. 2002), and thus muscle mass growth (Kostek et al. 2009). The frequency of the mutant R allele is ~3–4% among Caucasians, with a frequency of mutant homozygotes (RR) below 1%

(Corsi et al. 2002; Ferrell et al. 1999; Kostek et al. 2009). Such low allelic frequency obviously limits the possibility of studying large groups of people carrying the R variant.

Vitamin D receptor genotype Although there is some recent controversy with regards to its actual expression in skeletal muscle fibres (Wang and DeLuca 2011), the vitamin D receptor (VDR) is thought to play an important role in calcium homeostasis and skeletal muscle function. Vitamin D deficiency can cause a myopathy of varying severity, and clinical studies have indicated that vitamin D status is positively associated with muscle strength and physical performance and inversely associated with risk of falling; in vitamin D-deficient older adults, vitamin D supplementation has been shown to improve tests of muscle function, reduce falls and possibly impact on muscle fibre composition and morphology (Ceglia 2008). Molecular mechanisms of VDR action on muscle tissue include activation of signal transduction pathways in skeletal muscle cells through which vitamin D regulates contractility and myogenesis (Wang and DeLuca 2011).

Cross-sectional genetic association studies

The information on cross-sectional studies is detailed in Table 1. These studies reported the association of one or more polymorphisms with muscle phenotypes in old people at a single time point. Most studied subjects were sedentary. Some cross-sectional analyses were part of large studies including both cross-sectional and longitudinal designs, with the results of the latter being reported in the next section (see "Longitudinal genetic association studies").

The *ACE* I/D polymorphism is arguably the most widely studied genetic variation with regards to physical fitness phenotypes in humans, with controversial results (Bray et al. 2009). Published findings are also controversial in older people, starting with the possible association between this polymorphism and muscle mass. Some studies reported a positive association between the D allele and the following phenotypes: muscle mass in healthy inactive old men and women (Charbonneau et al. 2008), lean mass (as well as handgrip force) in advanced cancer patients (Vigano et al. 2009) or appendicular fat free fat (FFM) in old women (Lima et al. 2011). In contrast, McCauley et al. found no association with whole body and thigh lean mass in old Caucasians (McCauley et al. 2010).

Between-studies differences also exist for the potential association between *ACE* I/D genotypes and muscle strength and muscle fitness. Yoshihara and co-workers studied the relationship of the *ACE* I/D variation with muscle and fitness phenotypes in old Japanese men and women who did not require special care for their daily activities (Yoshihara et al. 2009). They found the *ACE* I/D polymorphism to be associated with handgrip strength and 10-m maximum walking speed, but not with leg muscle extensor strength. We recently reported no association between *ACE* genotypes and handgrip strength, leg muscle strength and walking ability in Caucasian (Spanish) nonagenarians (Bustamante-Ara et al. 2010). Frederiksen et al. found no association between the *ACE* I/D polymorphism and baseline levels of muscle strength, walking speed or body composition in elderly Danes (Frederiksen et al. 2003a). The same group found no association between *ACE* genotypes and the baseline levels of self-reported physical performance in a large cohort of old Danish twins (Frederiksen et al. 2003b).

Published data on *ACTN3* genotypes and specific muscle phenotypes in old people are also controversial. When present, the effect of *ACTN3* genotypes in ageing muscle seems to be more marked in women. Our group found no association between *ACTN3* genotype and functional capacity and muscle phenotypes (included leg muscle strength, sit–stand test and 1-mile walk test) in old Caucasian women (San Juan et al. 2006). This preliminary finding was overall corroborated in other studies. Delmonico et al. found no association of the *ACTN3* R577X polymorphism with muscle strength (knee extensor) and physical performance (short physical performance battery score, and 400-m walk time) in a large cohort of old men and women (Delmonico et al. 2008). McCauley et al. reported no association between this polymorphism and knee extension muscle strength or indices of muscularity (whole body or thigh non-skeletal lean mass) in old Caucasian men (McCauley et al. 2010). Recently, we observed no major influence of *ACTN3* genotypes on muscle phenotypes (leg and grip strength, walking and stair climbing ability) in nonagenarians (mostly women) (Bustamante-Ara et al. 2010). Lima et al. found no effect of the *ACTN3* R577X variation in quadriceps

Table 1 Summary of cross-sectional studies on different genes and muscle phenotypes in old people

Reference	Ethnic and demographic data of cohorts	Muscle phenotypes studied	Polymorphisms studied	Main results	Authors' main conclusions
ACE					
Charbonneau et al. (2008)	65% Whites and 35% Blacks North Americans *n*=225 (86 men and 139 women) Age 50–85 years (mean 62 years)	Muscle strength (1RM knee extensor) Body composition (FFM, FM, % body fat, quadriceps MV)	*ACE* I/D (rs1799752)	*ACE* genotype was significantly associated with total FFM and body weight, with higher values in DD genotype carriers (both $P<0.05$) DD genotype carriers exhibited significantly greater quadriceps MV compared with II genotype carriers ($P<0.05$)	*ACE* I/D genotype is associated with differences in MV
Frederiksen et al. (2003a)	Caucasians (Danish) *N*=203 (73 men and 130 women) Age ≥65 years	Muscle strength (handgrip strength, shoulder strength) Body composition (FM, FFM) Physical performance (30- and 10-m maximal walking speed test, self-reported functioning [Katz index, ADL strength score, SF-36 physical function score])	*ACE* I/D (rs1799752)	There was no association between the *ACE* I/D polymorphism and levels of muscle strength, walking speed or body composition in elderly Danes	The authors could not detect any association between the *ACE* genotype and the level of physical performance
Frederiksen et al. (2003b)	Caucasians (Danish) *n*=684 twins (234 men and 450 women) Mean age 78.2±4.4 years	Physical performance (self-reported physical abilities from 26 items)	*ACE* I/D (rs1799752)	There was no significant association between *ACE* genotypes and the levels of self-reported physical performance	*ACE* genotypes do not influence physical performance
Giaccaglia et al. (2008)	75% White/Caucasian, 22% Black/African-American and 3% Native American, Asian/Pacific Islander and Hispanic *n*=213 (63 men and 150 women) Age ≥60 years Subjects were obese (BMI≥28 kg m^{-2})	Muscle strength (concentric knee extensor isokinetic strength at 30° s^{-1}) Physical performance (6-min walk distance, self-reported FAST functional performance inventory)	*ACE* I/D (rs1799752)	There were no associations between *ACE* genotypes and measures of muscle strength or physical performance	Muscle strength and physical performance do not depend on *ACE* genotype
Vigano et al. (2009)	Caucasians (North Americans) *n*=172 (101 men and 71 women) Mean age 65.0±12.5 years Subjects were advanced cancer patients	Muscle strength (handgrip strength) Body composition (total FM, % body fat, LBM, appendicular lean mass)	*ACE* I/D (rs1799752)	Subjects with the ID genotype had significantly lower total FM than DD individuals. Handgrip strength percentiles were significantly higher in DD subjects compared with their II peers	*ACE* genotypes seem to be primarily associated with differences in body composition and muscle strength in advanced cancer patients
Yoshihara et al. (2009)	Japanese *n*=431 (228 men and 203 women) Age=76 years	Muscle strength (handgrip strength, isometric knee extensor strength) Physical performance (maximal stepping rate for 10 s, one-leg standing time with open eyes, 10-m maximum walking speed)	*ACE* I/D (rs1799752)	The *ACE* I/D polymorphism was positively associated with handgrip strength and 10-m maximum walking speed	There was a significant relationship between *ACE* I/D genotype and physical performance
ACTN3					
Delmonico et al. (2007)	Ethnic origin not specified	Muscular strength (1RM knee extensor)	*ACTN3* R577X (rs1815739)	In women, but not in men, absolute and relative peak power was higher	

Table 1 (continued)

Reference	Ethnic and demographic data of cohorts	Muscle phenotypes studied	Polymorphisms studied	Main results	Authors' main conclusions
	n=157 (71 men and 86 women)	Muscle power (knee extensor concentric peak power, peak movement velocity)		in the XX genotype group than in the RR and RX groups (P<0.05)	Peak power was significantly greater in XX women than in RR or RX women
	Age 50–85 years [mean 65± 8 years (men), 64±9 years (women)]	Body composition (FFM, %body fat, quadriceps MV)			
Delmonico et al. (2008)	White North Americans n=1,367 (726 men and 641 women) Age range 70–79 years	Muscle strength (isokinetic knee extensor muscle torque at 60° s^{-1}) Muscle mass (mid-thigh CSA, muscle quality) Body composition (FFM, FM, %body fat) Physical performance [SPPB (5-chair stand test, 4-m walk test, and 3 balance tests), persistent lower extremity limitation (self-reported difficulty walking one quarter mile or climbing 10 steps without resting at two consecutive 6-month intervals)] Physical activity (caloric expenditure in the past week for self-reported walking, climbing stairs, and exercise)	*ACTN3* R577X (rs1815739)	In men, there was a significant difference between the three genotype groups only for physical activity (P=0.020) There were no differences in women	*ACTN3* R577X polymorphism does not appear to have a strong effect on muscular phenotypes
Judson et al. (2011)	Two cohorts of Caucasians (Scottish) n=4,163 postmenopausal women (NOSOS: n=1,245; APOSS: n=2,918) Mean age (NOSOS 69.6±5.5; APOSS 54.8±2.2)	Falls (self-reported) in the last year	*ACTN3* R577X (rs1815739)	Carriage of 577X (one or two copies) was significantly associated with a 33% (10–61%) increased risk of falling	The X allele of the *ACTN3* R577X genotype represents a genetic risk factor for falling in older females
San Juan et al. (2006)	Caucasians (Spanish) n=23 women Age range 61–80 years	Muscle strength (1RM leg press) Body composition (%body fat) Physical performance (sit stand test, 1-mile walk test)	*ACTN3* R577X (rs1815739)	XX homozygotes did not present significantly differences from RX + RR group in widely accepted indices of health status performance during functional tests (sit–stand test, 1-mile walk test or maximal muscle strength)	Complete deficiency of α-actinin-3 (i.e. XX genotype) does not affect functional capacity or maximal muscle strength in elderly women
Walsh et al. (2008)	North American whites	Muscle strength (knee extensor shortening and lengthening peak torque at 30 and 180° s^{-1})	*ACTN3* R577X (rs1815739)	XX women displayed lower knee extension shortening and lengthening peak torque (P<0.05) and displayed lower levels of both total FFM and lower limb FFM	The absence of α-actinin-3 protein (i.e. XX genotype) influences knee extensor peak torque and FFM in women, but not in men

Table 1 (continued)

Reference	Ethnic and demographic data of cohorts	Muscle phenotypes studied	Polymorphisms studied	Main results	Authors' main conclusions
				($P<0.05$) compared with RX + RR women	
	n=848 adults (454 men and 394 women) Age range 22–90 years (estimated mean age≥60 years, as deduced from the information provided in Table 1 of the paper, although not specifically stated in the text)	Body composition (total FM, total FFM, total leg FFM)		No genotype-related differences were observed in men	
Zempo et al. (2010)	Japanese	Muscle mass (thigh muscle CSA)	*ACTN3* R577X (rs1815739)	No differences in physical activity were observed among the genotypes	The *ACTN3* R577X polymorphism influences muscle mass in older Japanese women
	n=109 postmenopausal women Age 50–78 years (mean=64.1± 6.0 years)	Daily physical activity (uniaxial accelerometer)		The XX genotype showed lower thigh muscle CSA compared with RR and RX genotypes	
ACE and *ACTN3*					
Bustamante-Ara et al. 2010	Caucasians (Spanish)	Muscle strength (handgrip strength, 1RM leg press)	*ACE* I/D (rs1799752)	Mean values of the study phenotypes did not significantly differ (all $P>0.05$) across *ACE* genotypes	*ACE* I/D and *ACTN3* R577X genotypes, whether analysed separately or in combination do not significantly influence muscle phenotypes in nonagenarians
	n=41 (33 women and 8 men) Age range 90–97 years	Physical performance (8-m walk test, 4-step stairs test)	*ACTN3* R577X (rs1815739)	The analyses of the combined effects between genotypes (*ACE* DD and *ACTN3* RR/RX vs. *ACE* II/ID and *ACTN3* XX) did not yield any significant difference	
Lima et al. (2011)	Brazilians	Muscle strength (knee extensor isokinetic peak torque at 60° s^{-1})	*ACE* I/D (rs1799752)	*ACE* DD individuals presented higher appendicular FFM compared to I allele carriers ($P<0.05$); *ACTN3* X allele carriers presented higher relative FFM than RR subjects ($P<0.05$). Mean values of muscle strength did not significantly differ (all $P>0.05$) across *ACE* or *ACTN3* genotypes	The findings do not support a pivotal role for *ACE* I/D or *ACTN3* R577X in determining muscle strength in older women, but suggest a modest role in FFM determination, and this observation was found to be stronger when these genes were examined together
	n=246 women Mean age 66.7±5.5 years	Body composition (total FFM, appendicular FFM) Physical activity (International Physical Activity Questionnaire)	*ACTN3* R577X (rs1815739)		
McCauley et al. (2010)	Caucasians (British)	Muscle strength (isometric and isokinetic strength at 30 and 240° s^{-1})	*ACE* I/D (rs1799752)	Whole body and thigh non-skeletal lean mass were independent of *ACE* genotypes	*ACE* and *ACTN3* genotypes were not associated with muscle function or muscularity phenotypes in older Caucasian men
	n=100 men	Body composition (whole body non-skeletal lean mass, thigh lean mass)	*ACTN3* R577X (rs1815739)	Absolute and relative high velocity strength and the time course of an evoked twitch were not associated with *ACE* genotype	
	Age range 60–70 years	Contractile properties (time-to-peak tension, half-relaxation time, peak rate of force development)		No differences existed between *ACTN3* genotypes for the studied muscle phenotypes	
AR					
Kenny et al. (2005)	North Americans	Muscle strength (grip strength, leg press strength)	*AR* CAG microsatellite repeat	No significant correlations with CAG repeat length and muscle	No association was found between CAG repeat length

Table 1 (continued)

Reference	Ethnic and demographic data of cohorts	Muscle phenotypes studied	Polymorphisms studied	Main results	Authors' main conclusions
	n=91 men	Physical performance (Established Population for Epidemiologic Studies of the Elderly battery (including gait speed, chair stand and balance tests))		strength, physical activity or physical performance were observed	of the *AR* and physical function in older men with osteoporosis and normal controls
	Age >65 years 42 subjects had a history of femoral fracture, 33 suffered osteoporosis and 16 were normal	Physical activity (Physical Activity Scale for the Elderly questionnaire)			
Lapauw et al. (2007)	Ethnic origin not specified n=159 men living in Belgium Age range 75–89 years	Body composition (FM, FFM, relative skeletal muscle index)	*AR* CAG microsatellite repeat	*AR* gene CAG repeat length was not directly related to body composition, either with or without adjustment for confounding variables. However, exploration of effect modification showed that CAG repeat length modulated the relation between testosterone and body composition	The testosterone effects on both FFM and FM were modulated by the length of the CAG repeat polymorphism of the *AR* gene
Walsh et al. (2005)	Two independent cohorts of Caucasians (BLSA and STORM study)	Muscle strength (BLSA: isokinetic concentric and eccentric knee extensor peak torque at 0.52 and 3.14 rad s^{-1}. STORM: handgrip strength, and knee extensor isometric strength)	*AR* CAG microsatellite repeat	Men with greater CAG repeat number exhibited significantly greater total FFM than those with fewer CAG repeats in both cohorts (P<0.05). Similar results were observed for total FFM normalized to height	The *AR* CAG repeat polymorphism was associated with FFM in men
	n=496 [BLSA: n=202 (112 men and 90 women); STORM: n=294 men]	Body composition (BLSA: total body fat, FFM and relative FFM; STORM: appendicular and total FFM normalized to height)		No significant differences were observed in muscle strength between *AR* repeat groups (P>0.05)	
	Age range: BLSA 19–90 years; STORM 55–93 years (estimated mean age ~73 years, as deduced from the information provided in Table 1 of the paper, although not specifically stated in the text)	Physical activity (BLSA: self-reported time spent in 97 activities; STORM: Modified Paffenbarger scale)			
CNTF					
Arking et al. (2006)	North American Caucasians	Muscle strength (handgrip strength, knee extension and hip flexion strength)	*CNTF* (rs948562, rs1800169, rs550942, rs4319530)	The rs1800169 null allele fully explained the association between this haplotype and handgrip strength under a recessive model, with individuals homozygous for the null allele exhibiting a 3.80-kg lower handgrip strength	Individuals homozygous for the *CNTF* null allele had significantly lower handgrip strength but did not exhibit overt frailty
	n=363 women Age range 70–79 years	Frailty syndrome (presence of three or more of five frailty indicators, i.e. weakness, slowness, weight		No association was observed between the *CNTF* null allele and frailty	

Table 1 (continued)

Reference	Ethnic and demographic data of cohorts	Muscle phenotypes studied	Polymorphisms studied	Main results	Authors' main conclusions
		loss, low physical activity, exhaustion)			
Roth et al. (2001)	83% Caucasians, 13% African-American and 4% other ethnic origins	Muscle strength (isometric torque knee extensor, concentric and eccentric isokinetic peak torque for the knee extensors and knee flexors at $30°\cdot s^{-1}$ and $180°\cdot s^{-1}$)	*CNTF* (rs1800169)	Individuals heterozygous for the *CNTF* null (A) allele exhibited significantly higher muscle quality and concentric peak torque of the knee extensors and flexors, than GG homozygotes ($P<0.05$)	GA individuals exhibit significantly greater muscular strength and muscle quality at relatively fast contraction speeds than GG individuals (a result which also applies for people aged 60 years and over)
	n=494 (250 men and 244 women) Age 20–90 years	Muscle quality (knee extensor) Body composition (total body mass, FFM)		The genotype effect was more profound in people over 60 years, with GA individuals exhibiting an 11% greater peak torque than their GG peers	
COL1A1					
Van Pottelbergh et al. (2001)	Caucasians (Belgians) n=273 men Age range 71–86 years	Muscle strength (handgrip strength, isometric biceps strength) Body composition (%FM, %LBM) Physical performance (5-chair stand test)	*COL1A1* (rs1800012)	Presence of the s allele was associated with lower handgrip (P=0.03) and biceps strength (P=0.04) at the dominant arm, with the difference between extreme genotype groups amounting to 21% and 30% respectively	The *COL1A1* Sp1 polymorphism was associated with forearm and upper limb muscle strength in elderly men
FST and *ACVR2*					
Walsh et al. (2007)	North American Caucasians	Muscle strength (quadriceps isokinetic peak torque at $30°\cdot s^{-1}$ and $180°\cdot s^{-1}$)	*ACVR2B* (rs2268757)	Women, but not men, carriers of *ACVR2B* Hap Group 1 exhibited significantly less quadriceps muscle strength than women homozygous for Hap Group 2	Haplotype structure at the *ACVR2B* and *FST* loci may contribute to inter-individual variation in skeletal muscle mass and strength, although these data indicate sex-specific relationships
	n=593 (315 men and 278 women) Age 19–90 years (estimated mean age≥60 years, as deduced from the information provided in Table 1 of the paper, although not specifically stated in the text)	Body composition (Total FM, soft tissue FFM, total leg fat and FFM)	*FST* (rs3797297, rs3756498, rs12152850, rs12153205)	Male, but not women, carriers of *FST* Hap Group 3 exhibited significantly less total leg FFM than non-carriers	
IGF2					
Sayer et al. (2002)	Caucasians (English) n=693 (397 men and 296 women) Age 64–74 years (mean 67.5 years) Subjects had historical records of birth weight	Muscular strength (handgrip strength)	*IGF2 ApaI* (820G>A, (rs680))	*IGF2* genotype and birth weight were both significant predictors of adult handgrip strength in men, but not in women	*IGF2 ApaI* genotype and birth weight were independent predictors of handgrip strength in men with both variables exerting additive effects, but not in women
Schrager et al. (2004)	Cohort 1: North American Caucasians. Cohort 2: 83% Caucasians, 13%	Cohort 1: muscle strength (handgrip strength, arm sustained power)	*IGF2 ApaI* (820G>A (rs680))	Although the results were not corroborated in cohort 1, *IGF2* genotypes influenced muscle mass	The results from cohort 2 support the hypothesis that variation within *IGF2* gene

Table 1 (continued)

Reference	Ethnic and demographic data of cohorts	Muscle phenotypes studied	Polymorphisms studied	Main results	Authors' main conclusions
	African-American and 4% other ethnic origins n=94 men (cohort 1) and 485 subjects (246 men and 239 women) (cohort 2) Age range 22–80 (cohort 1) and 20–94 (cohort 2) years	Cohort 2: muscle strength (isokinetic peak torque) and body composition (total body FFM)		and function at age 65 years, with the AA genotype exerting a negative effect on the isokinetic arm strength in men and on the total body FFM and isokinetic arm and leg strength of women	affects muscle mass and muscle function in later life
IL6					
Walston et al. (2005)	Caucasians (Italians) and African-Americans n=729 women Age 70–79 years	Muscle strength (grip, hip and knee strength) Physical performance (frailty that consisted of 5 screening criteria: slow walking speed, weight loss, fatigue, low activity levels and weak grip strength)	*IL6* (rs2067074, rs2073990, rs2106549, rs1404008, rs1880243, rs3087221, rs1800795, rs2069832, rs1554606, rs1839699, rs2177473, rs4722172, rs1524103)	No clinically significant relationships were observed between *IL-6* genotypes and serum IL-6 levels, muscle strength or physical performance	The findings suggest that other aetiologies of age-related increases in serum IL-6 such as disease states and declines in sex steroid levels may play a more important role than *IL6* gene variations
MSTN					
Corsi et al. (2002)	Caucasians (Italian) n=450 (189 men and 261 women) Age 22–96 years (mean 69.5 years)	Average of the isometric strength assessed in 8 muscle groups (not specified) by a handheld dynamometer	*MSTN* A55T (rs1805065), *MSTN* K153R (rs1805086)	The presence of a 153R allele was associated with lower muscle strength (P=0.05), although the difference was not significant after adjusting by age (P=0.09)	The R allele may be associated with accelerated sarcopenia
Gonzalez-Freire et al. (2010)	Caucasians (Spanish)	Muscle strength (1RM leg press)	*MSTN* A55T (rs1805065), *MSTN* E164K (rs35781413), *MSTN* I225T, *MSTN* K153R (rs1805086), *MSTN* P198A	Overall, in KR women muscle phenotype values (1RM leg press and estimated muscle mass) were low-to-normal compared to the whole group (~25th–50th percentile), and their functional capacity (Barthel and Tinetti tests) was normal	Heterozygosity for the *MSTN* K153R polymorphism do not seem to exert a negative influence on the muscle phenotypes of women who are at the end of the human lifespan, yet homozygosity might do so
	n=41 (33 women and 8 men) Age 90–97 years	Muscle mass (estimated muscle mass) Physical performance (Tinetti test, Barthel index)		In the woman bearing the very rare RR genotype, values of muscle mass and functional capacity were below the 25th percentile	
Seibert et al. (2001)	81.1% Caucasians, 18.8% African-American and 0.2% Asian or Hispanic n=286 women Age range 70–79 years	Muscle strength (overall strength: sum of the strongest measures of hip, knee and grip strength)	*MSTN K153R* (rs1805086)	African-American women with the R allele achieved lower muscle strength than their wild-type (KK) peers	These data suggested association of the R allele with lower strength in high-functioning older women, which should be corroborated in larger cohorts
VDR					
Bahat et al. (2010)	Ethnic origin not specified	Muscle strength (isokinetic peak torque of the knee flexors and extensors at 60° s^{-1})	*VDR BsmI* (rs1544410), *VDR FokI* (rs2228570), *VDR Taq1* (rs731236)	Knee extensor strength was higher in *BsmI* BB homozygotic men than in the *BsmI* Bb/bb	The *VDR BsmI* polymorphism is associated with muscular strength in elderly men

Table 1 (continued)

Reference	Ethnic and demographic data of cohorts	Muscle phenotypes studied	Polymorphisms studied	Main results	Authors' main conclusions
	n=120 men living in Istanbul Age >65 years	Muscle mass (body muscle mass)		group. No significant association was found with *TaqI* and *FokI* haplotypes	
Barr et al. (2010)	Two independent cohorts of Caucasians (APOSS and OPUS study) *n*=7,493 postmenopausal women (APOSS: *n*=5,119; OPUS: *n*=2,374)	Muscle strength (OPUS: hand grip) Physical performance (OPUS: balance (walk along a 5-m line marked on the floor without moving off the line), muscle power (ground reaction force along stand up quickly), rising from chair with and without arms)	APOSS: *VDR ApaI* (rs7975232), *VDR BsmI* (rs1544410), *VDR Cdx2* (*rs11568820*), *VDR FokI* (rs2228570), *VDR Taq1* (rs731236)	Carriers of the 'B' allele (*BsmI*) showed an increased risk for falls *BsmI*, but no *FokI*, polymorphisms were associated with balance and muscle power measurements	These results showed an association between the *Bsm1* polymorphism and risk of falling that may explain some of the excess fracture risk associated with *VDR* in previous studies
	Mean age 54.3±2.3 years (APOSS), 66.9±7.0. years (OPUS)	Falls reported in the last year (APOSS and OPUS)	OPUS: *VDR BsmI* (rs1544410), *VDR FokI* (rs2228570)		
Geusens et al. (1997)	Caucasians *n*=501 women Age >70 years	Muscle strength (handgrip and quadriceps strength)	*VDR BsmI* (rs1544410)	A significant association between the *VDR* genotypes and quadriceps and handgrip strength was observed. In non-obese women, a 23% difference in quadriceps strength ($P<0.01$) and 7% in handgrip strength ($P>0.05$) was observed between the bb and BB genotype. After correction for confounding factors and bone mineral density, this association was significant for quadriceps and handgrip strength	There was an association between the *VDR BsmI* variation and muscle strength in elderly non-obese women
Hopkinson et al. (2008)	Caucasians *n*=211 (107 patients with stable COPD (70 men and 37 women) and 104 healthy (46 men and 58 women)) Mean age 61.8±8.5 years (control group), 63.5±9.5 years (COPD patients)	Muscle strength (quadriceps strength, handgrip strength only in control group) Body composition (FFM)	*VDR BsmI* (rs1544410), *VDR FokI* (rs2228570) *ACE* I/D (rs1799752)	Both patients and control subjects who were homozygous for the C allele of the *FokI* polymorphism had less quadriceps strength than did those with ≥1 T allele ($P\leq0.01$). The *BsmI* b allele was associated with greater quadriceps strength in patients but had no effect in healthy control subjects. The effect of *BsmI* on quadriceps strength was least apparent in patients with the *ACE* II genotype ($P<0.01$)	The *FokI VDR* polymorphism is associated with skeletal muscle strength in both COPD patients and control subjects, whereas the *BsmI* polymorphism is associated with strength only in patients
Moreno Lima et al. (2007)	Brazilians *n*=191 women Mean age 67.9±5.2 years	Body composition (FFM, appendicular FFM) Physical activity level (International Physical Activity Questionnaire)	*VDR ApaI* (rs7975232). *VDR BsmI* (rs1544410), *VDR Cdx2* (*rs11568820*), *VDR FokI* (rs10735810), *VDR Taq1* (rs731236)	No relationship between *VDR* allelic variations and FFM was observed	Data indicated no genotype association between studied *VDR* polymorphisms and FFM in old Brazilian women

Table 1 (continued)

Reference	Ethnic and demographic data of cohorts	Muscle phenotypes studied	Polymorphisms studied	Main results	Authors' main conclusions
Onder et al. (2008)	Caucasians (Italians) *n*=259 (87 men and 172 women) Age ≥80 years (mean 85.0±4.5 years)	Falls occurring within 90 days of assessment	*VDR BsmI* (rs1544410), *VDR FokI* (rs2228570)	Compared with participants with the *BsmI* BB genotype, those with the bb genotype had a significantly lower odds ratio for falls (0.14, 95% CI, 0.03–0.66). Rate of falls did not differ significantly across *FokI* genotypes ($P>0.05$)	The *VDR* bb genotype of the *BsmI* gene is associated with a reduced rate of falls compared with the BB genotype, whereas no such effect was shown for the *FokI* polymorphism
Roth et al. (2004)	Caucasians *n*=302 men Age range 58–93 years (estimated mean age ~73 years, as deduced from the information provided in Table 1 of the paper, although not specifically stated in the text)	Muscle strength (muscle quadriceps strength) Body composition (FFM, appendicular FFM, relative appendicular FFM, lower FFM) Sarcopenia (defined as appendicular FFM <7.26 $kg \cdot m^{-2}$)	*VDR BsmI* (rs1544410), *VDR FokI* (rs2228570)	The *FokI* polymorphism was significantly associated with total FFM, appendicular FFM and relative appendicular FFM ($P<0.05$), although the *BsmI* polymorphism was not associated with FFM. FF homozygotes had 2.17-fold higher risk for sarcopenia compared to men with 1 or more f alleles	*FokI* polymorphism was significantly associated with FFM and sarcopenia in older Caucasian men
Vandevyver et al. (1999)	Caucasians *n*=270 postmenopausal women Age ≥70 years (mean 75±5 years)	Muscle strength (quadriceps isometric strength)	*VDR BsmI* (rs1544410)	Quadriceps strength was associated with *VDR* polymorphism, resulting in a difference in quadriceps strength of 25% between the bb and BB haplotype ($P<0.01$) No differences were found in grip strength	Data indicated significant effects of *VDR* genotype on quadriceps strength in elderly women

See text for gene and polymorphism abbreviations

1RM one-repetition maximum, *ADL* activity of daily living, *APOSS* Aberdeen Prospective Osteoporosis Screening Study, *BLSA* Baltimore Longitudinal Study of Aging, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *CSA* cross-sectional area, *FAST* Fitness Arthritis and Seniors Trial, *FFM* fat-free mass, *FM* fat mass, *LBM* lean body mass, *MV* muscle volume, *NOSOS* North of Scotland Osteoporosis Study, *OPUS* Osteoporosis and Ultrasound Study, *SF-36* short-form 36-item questionnaire, *SPPB* Short Physical Performance Battery, *STORM* Study of Osteoporotic Risk in Men

strength (using isokinetics) at baseline in Brazilian old women (Lima et al. 2011).

In contrast, others found an association between the *ACTN3* R577X variation and muscle phenotypes in old people, yet with controversial results with regards to which allele (R or X) has a favourable or unfavourable effect. Delmonico and co-workers found that the XX genotype was associated with higher knee extensor concentric peak power compared with RR/RX genotypes, especially in old women (Delmonico et al. 2007), whereas in old women from another cohort the XX genotype was associated with lower peak torque in knee extensor muscles (Walsh et al. 2008). In women, the XX genotype was associated with a greater risk of incident lower extremity limitation compared to RR.

Findings on *ACTN3* genotypes and muscle mass are also controversial. Delmonico et al. found no association between the *ACTN3* R577X polymorphism and mid-thigh CSA in older men and women (Delmonico et al. 2008). McCauley et al. found no association with indices of muscularity (whole body or thigh non-skeletal lean mass) in older Caucasian men (McCauley et al. 2010). In contrast, in the aforementioned study by Lima et al. women who were X allele carriers presented higher relative FFM at baseline compared with RR women (Lima et al. 2011). Zempo et al. (2010) showed that Japanese women with the XX genotype had lower thigh muscle CSA compared with RR and RX genotypes. Finally, in a recent study by Judson et al., carriage of the X allele (one or two copies) was significantly associated with increased risk of falling (Judson et al. 2011).

The *AR* CAG repeat polymorphism was associated with (FFM) in men of two independent North American cohorts, with men bearing greater CAG repeat number exhibiting significantly higher total FFM than those with fewer CAG repeats (Walsh et al. 2005). However, other studies reported no association of CAG repeat length with body composition (Lapauw et al. 2007) or with physical performance in old men (Kenny et al. 2005).

Roth et al. found an association between the A null allele of the *CNTF* rs1800169 and quadriceps muscle strength in a large cohort of individuals with a wide age range, with higher values in GA individuals compared with the wild-type (GG) genotype (Roth et al. 2001). This genotype effect was more profound in people over 60 years. Arking et al. (2006) studied eight polymorphisms at the *CNTF* locus, including the G-to-A polymorphism (rs1800169) variation, in old Caucasian women. The authors performed haplotype analysis, with the rs1800169 null allele fully explaining haplotype association with handgrip strength under a recessive model; AA individuals exhibited significantly lower handgrip strength. A comparable (not significant) trend was observed for hip flexion and knee extension strength (both assessed with a handheld isometric dynamometer). There was, however, no significant association between the *CNTF* null allele and frailty syndrome.

A study designed to examine the association of the *COL1A1* Sp1 binding site polymorphism (rs1800012) with indices of muscle strength found that mean handgrip and biceps strength were lower in the unfavourable ss group compared with the SS group, whereas no differences were noted for lower limb strength (Van Pottelbergh et al. 2001). Walsh et al. studied the associations of both *FST* and *ACVR2B* with skeletal muscle-related phenotypes in men and women (Walsh et al. 2007). *FST* and *ACVR2B* were genotyped to determine respective haplotype groupings based on HapMap data. Women carriers of *ACVR2B* haplogroup 1 exhibited significantly less quadriceps muscle strength than women homozygous for haplogroup 2, while men carriers of *FST* haplogroup 3 exhibited significantly less total leg FFM than non-carriers. The authors concluded that *ACVR2B* and *FST* haplogroups may contribute to inter-individual variation in skeletal muscle mass and strength, although genotype–phenotype associations seem to be sex specific.

Sayer et al. studied old men and women who had historical records of birth weight to determine whether the *IGF2* 820G>A (*ApaI*, rs680) polymorphism explains the link between size at birth and grip strength in later life (Sayer et al. 2002). Their results indicated that *IGF2 ApaI* genotype and birth weight were independent predictors of grip strength in men with both variables exerting additive effects, but not in women. Schrager et al. reported that *IGF2 ApaI* genotypes influenced muscle mass and function at age 65 years, with the AA genotype exerting a negative effect on the isokinetic arm strength of men and on the total body FFM and isokinetic arm and leg strength of women (Schrager et al. 2004); however, these results were only corroborated in one of two studied North American cohorts. On the other hand,

although elevated levels of IL6 can be associated with the development of disability, frailty and mortality in older adults, Walston et al. found no significant relationship between *IL6* 174 G/C genotypes and serum IL6 levels, grip, knee or hip strength, or frailty in old women (Walston et al. 2005).

Despite controversy existing with regards to adults (Kostek et al. 2009), the *MSTN* K153R polymorphism is likely associated with muscle phenotypes in old people, with the infrequent mutant R allele possibly exerting a negative influence (Ferrell et al. 1999; Huygens et al. 2004; Seibert et al. 2001). In a cohort of old African-American women, Seibert et al. reported lower muscle strength in those who carried the variant 153R allele (Seibert et al. 2001). Similar findings were reported by Corsi et al. for the isometric strength assessed in eight muscle groups in Italian Caucasians (Corsi et al. 2002). We recently reported that the muscle mass and function (especially gait and balance ability, as assessed with the Tinetti scale, and capacity for performing daily life activities independently, as assessed with the Barthel score) of a very old woman (age 96 years) with the very rare *MSTN* 153RR genotype was in the lowest 25th sex- and age-specific percentile (Gonzalez-Freire et al. 2010). In the same study, the muscle strength and mass of KR women were low to normal (~25th–50th percentile) compared to the wild-type (KK) genotype, yet their functional capacity (Barthel and Tinetti tests) was normal. Corsi et al. also found a Caucasian person (assumed age <80 years) with the rare RR genotype, yet with no specification on individual phenotype data (Corsi et al. 2002).

Some studies showed a beneficial effect of the b allele of the *VDR BsmI* polymorphism (rs1544410) in the muscle function of older people. Two studies found an association between *VDR BsmI* genotypes and muscle strength in postmenopausal women (Vandevyver et al. 1999) and in healthy (non-obese) old women (Geusens et al. 1997), with bb individuals exhibiting significantly higher quadriceps strength than those with the BB genotype, yet this association was not corroborated in obese old women (Geusens et al. 1997). Hopkinson et al. (2008) reported that the b allele of the *BsmI* polymorphism was associated with greater quadriceps strength in patients with chronic obstructive disease, but had no effect in healthy controls. Both patients and controls that were homozygous for the C allele of the *VDR FokI* polymorphism (rs2228570) had less quadriceps strength than those with one or more T alleles. In a study of Italian nonagenarians (men and women), the *BsmI* bb genotype was associated with a reduced rate of falls compared with the BB genotype, whereas no effect was shown for the *FokI* polymorphism (Onder et al. 2008). Barr et al. analysed five polymorphisms of the *VDR* gene [*Cdx2* (rs11568820), *FokI*, *BsmI*, *TaqI* (rs731236) and *Apa1* (rs7975232)] in postmenopausal women and showed that carriers of the *BsmI* B allele had an increased risk for falls (Barr et al. 2010). The *BsmI* polymorphism was also associated with balance and muscle power. In contrast, Bahat et al. (2010) reported a beneficial effect associated with the *BsmI* B allele, with BB homozygotic old men showing higher knee extensor muscle strength compared with the Bb/bb group. However, no association existed between *BsmI* genotypes and muscle mass, and *VDR TaqI* and *FokI* polymorphisms were not associated with muscle phenotypes.

There is also controversy with regards to the potential association between *VDR* genotypes and muscle mass in the elderly. Moreno Lima et al. (2007) found no genotype association between *VDR* polymorphisms (*ApaI*, *Cdx2*, *BsmI*, *FokI* and *TaqI*) and FFM in old Brazilian women. Similar findings were obtained by Bahat et al. (2010), who showed no effect of *BsmI*, *TaqI* and *FokI* genotypes on the muscular mass of old men. In contrast, Roth et al. (2004) found higher risk for sarcopenia in FF homozygotes for the *FokI* polymorphism compared to men with one or more f alleles. No significant effect was, however, noted for the *BsmI* polymorphism.

Longitudinal genetic association studies

The information on longitudinal studies is detailed in Table 2. These studies reported phenotype assessment at two or more time points. Many, but not all, of these studies assessed the effects of an exercise training intervention.

Frederiksen et al. (2003a) found no association between the *ACE* I/D polymorphism and time changes (whether induced by training or not) of muscle strength, walking speed or body composition in elderly Danes. In a 2-year longitudinal study on a large cohort of twins, the same group found no association between *ACE* genotypes and the time changes in self-reported physical performance

(Frederiksen et al. 2003b). Individual physical activity levels might influence the possible interaction between the *ACE* I/D polymorphism and muscle phenotypes. Kritchevsky et al. (2005) studied the interaction between *ACE* I/D genotype, high levels of physical activity and functional decline over time (mean follow-up of ~4 years) in a large cohort of well-functioning community-dwelling old men. Physically active participants (i.e. those reporting expending ≥1,000 kcal week^{-1} in exercise, walking and stair climbing) were less likely to develop mobility limitation regardless of genotype, but physical activity levels interacted significantly with the *ACE* genotype. In the inactive group, the *ACE* genotype was not associated with mobility limitation, whereas among active subjects, those who had the II genotype were more likely to develop mobility limitation compared with the rest of genotypes.

Some studies have analysed the association between the *ACE* I/D variation and muscle responsiveness to specific exercise training programmes. Charbonneau et al. (2008) found no association between the *ACE* I/D polymorphism and the muscle volume adaptation to resistance training (RT). In contrast, in a study with obese old people, Giaccaglia et al. (2008) found greater gains in knee extensor strength in DD homozygotes compared with II homozygotes after 18 months of walking and light RT. However, no genotype association was found with the muscle volume adaptation in response to RT. Lima et al. (2011) recently reported that, among old Brazilian women who performed quadriceps RT during 24 weeks, FFM was increased after training only in the I allele carriers.

There are controversies and sex differences with regards to the putative effects over time of *ACTN3* R577X genotypes on muscle phenotypes. In a 5-year follow-up study, Delmonico et al. (2008) found that XX men had higher increase in 400-m walk time compared with RR or RX men. In contrast, XX women had a greater risk of incident persistent lower extremity limitation compared to RR women. The same group examined knee extensor concentric peak power after ~10 weeks of unilateral knee extensor RT in older men and women (Delmonico et al. 2007). In men, absolutes changes in peak power after training approached a significantly higher value in the XX group, whereas women with the RR genotype showed significantly greater training improvements in relative peak power than their XX counterparts. However, Lima et al. (2011) reported no significant association between *ACTN3* genotypes and RT adaptations. Finally, a recent report showed that carriage of the X allele (one or two copies) was significantly associated with increased risk of falling over time (Judson et al. 2011).

Schrager et al. (2004) studied the influence of *IGF2 ApaI* genotypes on total body FFM, muscle strength and sustained power repeatedly at ~2-year intervals in two North American cohorts of men and women of different ethnic origin (Caucasian and African-American, respectively). The results did not support the hypothesis that A/A individuals have greater rates of age-associated decline in muscle phenotypes than G/G individuals. In fact, G/G men demonstrated an unexpected greater rate of loss in FFM compared with A/A men. No significant genotype effect was noted in women.

Some preliminary findings might suggest a possible role for the *MSTN* K153R polymorphism in the muscle volume response to RT, yet definitive data in old people are missing. Ivey et al. (2000) found a trend towards a genotype effect on the muscle volume response to RT, such that women of varying ages (23–73 years) with the KR genotype exhibited a higher increase in trained leg muscle volume after 9 weeks of RT than their age and sex-matched peers with the KK genotype.

Research gaps in the field and recommendations

Between-studies differences in several methodological aspects might explain, at least partly, the controversy existing in the field. Besides disparities in the choice of candidate polymorphisms, there are also differences among studies in age of the participants and in the tests for muscle mass and muscle strength/function assessment. For instance, 1-repetition maximum (1RM) strength tests or the 1-mile walk test are often used in healthy sexagenarians or septuagenarians, whereas more debilitated or older cohorts (typically, nonagenarians) are better assessed with tests of ambulation ability. Thus, although a meta-analysis would have provided a more accurate perspective that the type of review we performed here, we believe such type of systematic review cannot be performed at present due to heterogeneity among studies.

Table 2 Summary of longitudinal studies on different genes and muscle phenotypes in old people

Reference	Design	Ethnic and demographic data of cohorts	Muscle phenotypes studied	Polymorphisms studied	Main results	Authors' main conclusions
ACE						
Charbonneau et al. (2008)	Interventional 10-week of unilateral knee extensor RT	65% Whites and 35% Blacks North Americans n=225 (86 men and 139 women) Age 50–85 years (mean 62 years)	Muscle strength (1RM knee extensor) Body composition (FFM, FM, %body fat, quadriceps MV)	*ACE* I/D (rs1799752)	There was no association of the *ACE* I/D genotype with the response of either 1RM knee extensor or quadriceps MV to RT in either men or women	*ACE* I/D genotype is not associated with the muscle hypertrophic response to RT
Frederiksen et al. (2003a)	4 interventional studies (8-month exercise programme in the studies of healthy people and 12-week in the studies of frail elderly people)	Caucasians (Danish) n=203 (73 men and 130 women) Age ≥65 years	Muscle strength (handgrip strength, shoulder abduction strength) Body composition (FM, FFM) Physical performance [30- and 10-m maximal walking speed test, self-reported functioning (Katz index, ADL strength score, SF-36 physical function score)]	*ACE* I/D (rs1799752)	No association was found between the *ACE* genotype and level of physical performance, or response to training or change after a control period	Late in life, *ACE* genotype is not associated with the change of physical functioning
Frederiksen et al. (2003b)	2-year follow-up (from 1997 to 1999)	Caucasians (Danish) n=547 twins (men and women) Age ≥68 years	Muscle strength (handgrip strength) Physical performance (5-chair stand test, self-reported physical abilities)	*ACE* I/D (rs1799752)	Longitudinal changes in physical performance did not depend on *ACE* genotype	There were no substantial effects of *ACE* genotype on physical performance, or rate of change in performance among the elderly
Giaccaglia et al. (2008)	Interventional 18-month exercise training (walking and light weight lifting)	75% White/Caucasians, 22% Black/African-American and 3% Native American, Asian/Pacific Islander and Hispanic n=213 (63 men and 150 women) Age ≥60 years Subjects were obese (BMI≥28 kg m^{-2})	Muscle strength (concentric knee extensor isokinetic strength at 30° s^{-1}) Physical performance (6-min walk distance, self-reported FAST)	*ACE* I/D (rs1799752)	Individuals with the DD genotype showed greater gains in knee extensor strength compared to II individuals after exercise training (P<0.05) After exercise training, improvement in physical disability score and 6-min walk distance were not different between genotype groups	Changes in muscle strength with exercise training in older individuals may be dependent on *ACE* genotypes
Kritchevsky et al. (2005)	4.1-year follow-up on average	Whites and Blacks n=2,966 (1,439 men and 1,527 women) Age 70–79 years	Muscle strength (maximal and mean isokinetic strength of the knee extensors at 60° s^{-1}) Muscle mass (thigh muscle CSA) Body composition (BMI, total FM) Physical performance (interviewer administered physical activity questionnaire, mobility limitation (self-reported of any difficulty	*ACE* I/D (rs1799752)	Physical activity levels interacted significantly with the *ACE* genotype. In the inactive group, the *ACE* genotype was not associated with mobility limitation; whereas among active subjects (participants who expended >1,000 kcal $week^{-1}$ in any exercise activity) those who had the II genotype were more likely to develop mobility	Among older physically active individuals, those with the *ACE* DD or ID genotypes were less likely to develop mobility limitation than those with the II genotype

Table 2 (continued)

Reference	Design	Ethnic and demographic data of cohorts	Muscle phenotypes studied	Polymorphisms studied	Main results	Authors' main conclusions
			either walking a quarter mile or going up 10 steps without resting due to health or a physical problem on 2 consecutive interviews administered 6 months apart))		limitation compared with the rest of genotypes	
ACTN3						
Delmonico et al. (2007)	Interventional 10-week RT	Ethnic origin not specified	Muscle strength (1RM knee extensor)	*ACTN3* R577X (rs1815739)	In men, absolute peak power change with RT tended to be significantly higher in the RR group than in the XX group (P=0.07)	*ACTN3* R577X polymorphism influences the response of quadriceps muscle power to RT in older adults
		n=157 (71 men and 86 women)	Muscle power (knee extensor concentric peak power, peak movement velocity)		In women, relative peak power change with RT in the RR group was higher than in the XX group (P=0.02)	
		Age 50–85 years [mean 65±8 years (men), 64±9 years (women)]	Body composition (FFM, %body fat, quadriceps MV)			
Delmonico et al. (2008)	5-year follow-up	White North Americans	Muscle strength (isokinetic knee extensor muscle torque at 60° s^{-1})	*ACTN3* R577X (rs1815739)	XX men had a significantly greater adjusted 5-year increase in 400-m walk time compared to RR and RX men (P=0.03)	Declines in certain measures of physical performance could be mediated by the *ACTN3* polymorphism in older white adults, although this polymorphism does not appear to have a strong effect on skeletal muscle
			Muscle mass (mid-thigh CSA, muscle quality)			
			Body composition (FFM, FM, %body fat)			
			Physical performance: SPPB (5-chair stand test, 4-m walk test and 3 balance tests), persistent lower extremity limitation (self-reported difficulty walking one quarter mile or climbing 10 steps without resting at two consecutive 6-month intervals)		XX women had a ~35% greater risk of incident persistent lower extremity limitation compared to RR women	
		n=995 (529 men and 466 women)	Physical activity (caloric expenditure in the past week at baseline for self-reported walking, climbing stairs and exercise)			
		Age range 70–79 years				
Judson et al. (2011)	Follow-up (NOSOS: from 2001–2003 to 2004; APOSS: from 1998–2000 to 2002)	Two cohorts of Caucasians (Scottish)	Falls (self-reported) in the last year	*ACTN3* R577X (rs1815739)	The effect of the X allele on falling in the previous year was evident for the follow-up falls assessment	*ACTN3* R577X genotype is an important genetic risk factor for falling in older females
		n=4,163 postmenopausal women (NOSOS: n=1,245; APOSS: n=2,918)				
		Mean age (NOSOS 69.6±5.5; APOSS 54.8±2.2)				
ACE and ACTN3						

Table 2 (continued)

Reference	Design	Ethnic and demographic data of cohorts	Muscle phenotypes studied	Polymorphisms studied	Main results	Authors' main conclusions
Lima et al. (2011)	Interventional 24-week RT	Brazilians *n*=246 women Mean age 66.7±5.5 years	Muscle strength (knee extensor isokinetic peak torque at 60° s^{-1}) Body composition (total FFM, appendicular FFM) Physical activity (International Physical Activity Questionnaire)	*ACE* I/D (rs1799752), *ACTN3* R577X (rs1815739)	No significant interaction was observed between *ACTN3* and RT adaptations In response to RT, I allele carriers significantly increased FFM and a significant training × genotype interaction was noted	*ACE* I/D or *ACTN3* R577X have an important role in determining muscle strength in adaptation to a RT programme
IGF2						
Schrager et al. (2004)	Longitudinal [12.7-year (cohort 1) and 4.5-year follow-up on average (cohort 2)]	Cohort 1: North American Caucasians. Cohort 2: 83% Caucasians, 13% African-American and 4% other ethnic origins *n*=94 men (cohort 1) and 485 subjects (246 men and 239 women) (cohort 2) Age range 22–80 (cohort 1) and 20–94 (cohort 2) years	Cohort 1: muscle strength (handgrip strength, arm sustained power) Cohort 2: muscle strength (isokinetic peak torque) and body composition (total body FFM)	*IGF2 ApaI* (820G>A (rs680))	G/G men showed an unexpected greater rate of loss in FFM compared with A/A men No genotype effect was noted in women	Overall, the *IGF2 ApaI* variation did not affect age changes in muscle phenotypes
MSTN						
Ivey et al. (2000)	Interventional 9-week unilateral knee extension RT and 31 week of detraining	Caucasians (North American) *n*=45 (11 young men, 11 young women, 12 older men and 11 older women) Age: mean age of 25±3 (young men, range 21–29 years), 26±2 (young women, range 23–28 years), 69±3 (older men, range 65–75) and 68±2 (older women, range 65–73 years) years	Muscle mass (quadriceps MV and CSA) Body composition (FFM, %body fat)	*MSTN* K153R (rs1805086)	When all subjects (men and women) were grouped according to *MSTN* genotype, MV response to RT or detraining was not significantly different between genotype groups A trend was noted, only in women, for a genotype effect on the MV response to RT, such that women heterozygous for the rare R allele exhibited a 68% higher increase in trained leg MV with RT than women without the variant (P=0.056)	Though *MSTN* genotypes may not explain gender differences in the hypertrophic response to RT, they might play a role in women

See text for gene and polymorphism abbreviations

1RM one-repetition maximum, *ADL* activity of daily living, *APOSS* Aberdeen Prospective Osteoporosis Screening Study, *BMI* body mass index, *CSA* cross-sectional area, *FAST* Fitness Arthritis and Seniors Trial, *FFM* fat-free mass, *FM* fat mass, *MV* muscle volume, *NOSOS* North of Scotland Osteoporosis Study, *RT* resistance training, *SF-36* short-form 36-item questionnaire, *SPPB* Short Physical Performance Battery

There is a clear need to improve as much as possible the methodology of research examining the association between specific genetic variants and muscle phenotypes in old people. Future studies should adhere to the recent guidelines for 'Strengthening the Reporting of Genetic Association' (STREGA) studies (Little et al. 2009). The STREGA Statement was built on the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) Statement and provides additions to 12 of the 22 items on the STROBE checklist. The additions concern population stratification, genotyping errors, modelling haplotype variation, Hardy–Weinberg equilibrium, replication, selection of participants, rationale for choice of genes and variants, treatment effects in studying quantitative traits, statistical methods, relatedness, reporting of descriptive and outcome data and the volume of data issues that are important to consider in genetic association studies. Many genetic association studies performed in the last decade did obviously not adhere to STREGA guidelines and thus are difficult to compare with future studies that might follow these guidelines.

On the other hand, the current knowledge on genetic factors associated with human muscle phenotypes comes mainly from Caucasian cohorts. It is necessary to replicate previously reported associations between genetic polymorphisms and muscle phenotypes in other cohorts of different ethnic origin. An additional potential gap to be kept in mind when interpreting the literature in the field is that studies reporting no genetic association (i.e. 'negative results') are less 'attractive' and thus less likely to be published than others showing 'statistical significance' ('positive results').

Most reports in the field have used a candidate gene approach based on the rationale that a single gene (or a few genes) plays an important function in muscle phenotypes (e.g. *ACTN3* is crucial for muscles' ability to produce 'power'). However, the more 'agnostic approach' provided by 'genome-wide association' (GWA) studies may also add valuable information. This type of studies evaluates the association of genetic variation with outcomes or traits of interest by using 100,000 to 1 million or more markers across the genome without any previous hypotheses about potential mechanisms (Attia et al. 2009). In a recent GWA study, Liu et al. tested 379,319 single nucleotide polymorphisms (SNPs) in a cohort of US unrelated whites (n=492 men and 481 women) with a mean age of 50 years (Liu et al. 2009). They found that two SNPs, rs16892496 and rs7832552 within the thyrotropin-releasing hormone receptor (*TRHR*) gene were significantly associated with LBM. Subjects carrying unfavourable genotypes at rs16892496 and rs7832552 had, on average, 2.70 and 2.55 kg lower LBM, respectively, compared to those with alternative genotypes. The results were replicated in (a) another cohort of unrelated US whites (659 men, 829 women, mean age of 63 and 61 years, respectively), (b) Chinese unrelated subjects (1,437 men, 1,518 women, mean age of 30 and 35 years) and (c) 593 nuclear families comprising 1,972 US whites (mean age of men and women of 53 and 47 years, respectively). Thus, their findings support the *TRHR* gene as an important gene for LBM variation. GWA studies and simpler genotype–phenotype association studies focusing on just one or few polymorphisms (as the ones we extensively reviewed in this paper) are not mutually exclusive. More GWA as the one by Liu et al. (2009) are needed in older people (a) to interrogate traditional candidates that are thought to play an influence on muscle phenotypes and (b) to propose new candidate genes. The latter inevitably implies replication and more detailed analyses in genotype–phenotype association studies, e.g. recent findings on the *TRHR* gene should be replicated in association studies focusing on this gene and its putative influence on the baseline and training response of well-defined muscle phenotypes in old people.

Studies investigating gene expression analysis are also recommended, in order to better understand the molecular mechanisms underlying the potential association between a given polymorphism and muscle phenotypes at advanced age. Nonetheless, ideally this would require collecting skeletal muscle biopsies, which might not be easily feasible in the elderly. The relevant information that can be obtained with gene expression studies is best exemplified by a recent study on the RNA expression of 17,881 genes at the skeletal muscle level in a cohort of healthy Pima Indians (age range 18–50 years) (Mason et al. 2011). Using exon array expression chips, the authors found *ACTN3* to be one of the only eight genes that showed bimodal expression. Both modes were at levels indicative of transcript abundance, with the distinct separation in expression levels being nearly

completely explained by rs509556, which is in perfect linkage disequilibrium with the *ACTN3* R577X polymorphism. Thus, future expression studies in the elderly might also help providing new insights into the genetic associations of important disease phenotypes in this population. For instance, the authors of the aforementioned study found that insulin sensitivity was higher in those individuals with the low mode of *ACTN3* expression (Mason et al. 2011).

Conclusions

In summary, although previous heritability studies have indicated that there is an important genetic contribution to the individual variability in muscle phenotypes among old people published data on specific gene variants are controversial. To date, no solid evidence exists supporting the existing of an 'unfavourable' genotype, e.g. associated with accelerated sarcopenia or loss of independence. Although the *ACTN3* R577X polymorphism is the only structural gene for which a clear genotype effect has been shown in human muscle phenotypes, especially for athletic women, there is controversy with regards to which allele (R or X) plays a potential 'favourable' role in old people. The *MSTN* K153R variation is possibly the strongest candidate to explain variance among muscle phenotypes in the elderly, yet more research is still needed with large cohorts owing to the very low population frequency of the 'unfavourable' 153R allele.

Age declines in muscle phenotypes are likely polygenic traits and thus not reducible to specific polymorphisms. Future studies should take into account the association between muscle phenotypes in older people and (a) complex gene–gene interactions, including those interactions between genetic variants that might not influence muscle phenotypes *individually*, and (b) the interaction between genes and environmental/external factors, particularly physical activity.

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