The genetics of muscle atrophy and growth: The impact and implications of polymorphisms in animals and humans

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Abstract

Much of the vast diversity we see in animals and people is governed by genetic loci that have quantitative effects of phenotype (quantitative trait loci; QTLs). Here we review the current knowledge of the genetics of atrophy and hypertrophy in both animal husbandry (meat quantity and quality), and humans (muscle size and performance). The selective breeding of animals for meat has apparently led to a few genetic loci with strong effects, with different loci in different animals. In humans, muscle quantitative trait loci (QTLs) appear to be more complex, with few “major” loci identified to date, although this is likely to change in the near future. We describe how the same phenotypic traits we see as positive, greater lean muscle mass in cattle or a better exercise results in humans, can also have negative “side effects” given specific environmental challenges. We also discuss the strength and limitations of single nucleotide polymorphisms (SNP) association studies; what the reader should look for and expect in a published study. Lastly we discuss the ethical and societal implications of this genetic information. As more and more research into the genetic loci that dictate phenotypic traits become available, the ethical implications of testing for these loci become increasingly important. As a society, most accept testing for genetic diseases or susceptibility, but do we as easily accept testing to determine one’s athletic potential to be an Olympic endurance runner, or quarterback on the high school football team. © 2005 Elsevier Ltd. All rights reserved.

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1. Introduction
Imagine retyping a 3 billion letter book millions and millions of times; even the best stenographer is likely that to make several typographical errors. Similarly, in the process of human development, spontaneous changes occur in the genome. While the vast majority are repaired quickly, rarely some slip through, and these changes may appear as either polymorphisms or disease causing mutations. There is no clear distinction between a “mutation” and “polymorphism”, some base changes that clearly destroy the function of the gene can show no obvious phenotype (e.g. alpha actinin 3), while single amino acid changes in some proteins can lead to a dramatic phenotype, even in the heterozygous state (e.g. the very common hyperkalemic periodic paralysis in Quarter Horses).

The identification of muscle quantitative trait loci (QTLs) is relatively well-evolved in animal husbandry, due to the economic importance of meat quantity and quality. Here, we regard atrophy and hypertrophy as similar processes, as they both may involve the AKT1 signaling pathway, with atrophy through downstream FOXO and atrogene signaling, and hypertrophy through mTOR signaling (Hoffman & Nader, 2004).

Indeed, some of the key QTLs identified to date in animal husbandry involve this pathway (e.g. IGF2) and this data will be reviewed below.

Studies of human QTLs for muscle atrophy/hypertrophy are less focused on quantity and quality, and more focused on performance, particularly in the context of aerobic and strength conditioning. Here, the great genetic diversity of human populations contrasts with the intensive line breeding of domesticated animals, leading to more complex genetics, and more difficult studies in human populations. However, QTL studies of humans for muscle phenotypes is becoming increasingly important as the incidence of type II diabetes skyrockets in all industrialized world populations. Muscle plays a key role in the progression to type II diabetes, including development of insulin resistance, determining the metabolic “set point”, and inactivity-driven remodeling. It is widely thought that the genetics underlying predispositions to body composition and type II diabetes is, in major part, the genetics of muscle. For example, a polymorphism in a muscle gene that results in the use of less energy in completing daily activities and less muscle mass is “advantageous” during periods of famine (muscle is metabolically expensive to maintain). However, this same QTL would be a liability when the individual must fight off predators (or neighbors).

The term polymorphism simply refers to something that occurs in different forms or different versions. While most commonly, polymorphisms are used to describe non-disease causing variants, the term itself can be applied anytime more than one version of a gene exists. Much of the genetic variation that underlies both disease susceptibility and differences in physical characteristics is driven by polymorphisms at genetic loci. These genetic differences can in turn have quantitative effects on phenotype. Much research has been devoted to the study of these polymorphisms, or quantitative trait loci (QTL), to define and measure their affect on phenotype variation. The investigation of QTLs to define a phenotype has been an uphill battle, with, in most cases, multiple QTLs contributing to a given phenotype. Additional confounding variables including environmental factors, gene/environment interactions and gene/gene interactions make the link between a phenotypic trait and a polymorphism difficult to elucidate.

QTLs have been studied in both animals and humans. The following sections describe some of the major trait loci studied in both groups and introduce the reality that, along with the positive traits so commonly studied, can come negative consequences and ethical dilemmas. Further sections serve to educate the reader on the SNP association studies so commonly seen in the literature today. Not all association studies are created equal and some guidelines about what to look for and what components make a well designed and well implemented study are given. Lastly, and most importantly, we discuss the ethical and moral issues that
necessarily co-evolve with increased study into non-disease genetic traits. As we learn more and more about the genetic loci underlying the traits we see as beneficial, we need to understand the circumstances under which those traits can be exploited.

2. QTLs in animal husbandry

Selective breeding has been occurring within animal species for thousands of years. Initially man with no knowledge of DNA or genetics, selected animals for breeding based on desired visual and functional traits. This resulted in domestic animal species with an overwhelming phenotypic diversity compared to non-domestic species (Andersson, 2001). With gains in scientific information and technology, selective breeding has become a molecular science field with powerful tools to unravel the phenotypic variety seen in domestic animals. Several major phenotypic traits, many involving body composition and muscle traits, have been well described in domestic animals.

One of the first muscle-related traits to be characterized at the molecular level was the Halothane locus in pigs (Andersson, 2001). At this locus, a single missense mutation (R614C) in the RYR1 gene has persisted due to selection for the beneficial effects of leanness and muscle hypertrophy associated with the heterozygous state (MacLennan & Phillips, 1992). Along with the beneficial musculature associated with the Halothane locus, it also causes susceptibility to halothane-induced malignant hyperthermia and rhabdomyolysis in homozygotes, a condition which, when triggered by stress, can cause muscle rigidity, high fever, cellular ion imbalances and death (Fujii et al., 1991; MacLennan & Phillips, 1992). Interestingly, a similar type of mutation is present in the human RYR1 gene where the condition is triggered by exposure to the same anesthetics (Fujii et al., 1991). This condition occurs in 1 in 15,000 anesthetized children and 1 in 50,000 anesthetized adults and can be fatal.

The Halothane locus is not the only variant that confers both positive and negative traits. The double muscling phenotype has been recognized in cattle for over 200 years (Grobet et al., 1997; Kambadur, Sharma, Smith, & Bass, 1997). This phenotype, seen primarily in Belgian Blue and Piedmontese cattle breeds, exhibits a >20% increase in skeletal muscle mass (a clear benefit to the cattle industry), and is due to one of several types of mutations observed in the myostatin encoding bovine MSTN gene. Both deletions and single-point missense mutations have been characterized, all of which cause a decrease in expression or a loss-of-function of the gene (Andersson, 2001). Along with the benefits of the phenotype, several problems are associated with the trait including, a reduction in stress tolerance, calf viability, and female fertility (Kambadur et al., 1997). Recently, a human child was observed with a loss-of-function myostatin mutation and a muscle hypertrophy phenotype similar to that seen in cattle (Schuelke et al., 2004). The muscle hypertrophy and a significantly increased strength have persisted to the child’s present age of 4.5 years with no observed health problems, but because myostatin is also expressed in the cardiac muscles, the child will be monitored to determine if cardiac function is affected (Schuelke et al., 2004).

A super-muscular phenotype is seen in Quarter horses and Appaloosas due to a point mutation (F1419L) in the equine sodium channel gene. This mutation leads to the disease hyperkalaemic periodic paralysis (HYPP) (Rudolph et al., 1992). The mutation was (and still is) selected “for” by halter class breeders, due to the high success of the heterozygotes in the show ring. The beneficial trait of well defined and large musculature also holds the liability of a high risk for attacks of paralysis and death. About 10% of affected horses have been reported to die from attacks, and this leads to controversial issues in registration, breeding, and insurance coverage. All horses exhibiting HYPP have traced their lineage to one award winning sire, and that one sire has contributed disproportionately to the genetic make up of the 3 million registered Quarter horses (Rudolph et al., 1992). Along with the physical benefits and drawbacks the HYPP phenotype raises significant ethical concerns, specifically that of genetic discrimination. While the American Quarter Horse Society has embraced HYPP positive horses, the Appaloosa Horse Club of Canada1 will not accept HYPP positive horses unless they are unable to reproduce (http://www.appaloosa.ca). In addition,

most major equine insurance companies require the disclosure of HYPP status on applications for insurance (http://www.equine-ins.com/Mortality%20Application.pdf; http://www.eqgroup.com/Pdf/MortalityApp.PDF) whereby insurance will not be granted without disclosure. HYPP is also seen in humans where it is characterized by attacks of muscle weakness and paralysis and caused by a single mutation in the adult skeletal muscle sodium channel gene (Zhou, Speir, Beech, & Hoffman, 1994), but appears to be due to random mutation, rather than any beneficial traits. Some other loci with important effects on body composition and muscle include the G3072A mutation of the IGF2 locus (Jeon et al., 1999; Van Laere et al., 2003), the R200Q mutation of the PRKAG3 locus (Milan et al., 2000), both in pigs, and the single point mutation at the CLPG locus in sheep (Cockett et al., 1994; Freking et al., 2002). All three exhibit beneficial muscle traits. Increases in muscle mass at the expense of fat deposition are associated with the IGF2 mutation (Nezer et al., 1999) and a ∼70% increase in the glycogen content of muscle is associated with the PRKAG3 mutation (Milan et al., 2000). The mutation at the CLPG locus is associated with the callipyge phenotype exhibiting substantial muscle hypertrophy (Freking et al., 2002).

These examples of QTLs characterized in animals show that traits have been modified over time through selective breeding for beneficial phenotypes. It also shows that with those beneficial traits typically are associated with negative traits as well. The future of phenotypic selection of breeding animals will undoubtedly include more research to define other QTLs exhibiting beneficial traits; and will include breeding not solely on visual traits, but on the genes each animal has. While negative consequences of selective breeding in animals are detrimental to those industries that rely on those domestic animals, similar negative consequences in humans poses a much greater problem. If beneficial QTLs in humans are exploited, one could imagine that the negative “side effects” of muscle QTLs could become increasingly prominent health concerns.

3 The Equestrian Group, A Division of Allen Financial Insurance Group: http://www.eqgroup.com/Pdf/MortalityApp.PDF

3. Human polymorphisms

The same human thought process that drives selective breeding in animal husbandry has implications for human reproduction. We all choose our partners based on specific characteristics, height, eye color, religion, etc. Through our cognitive and sometimes seemingly superficial selectivity we are fulfilling the basic rules of evolution, the drive to get our gametes into the next generation in the best possible shape. In order to achieve this goal we select based on evolutionary benefit; who has the “best” genes? At first this may seem like an easy question: the strongest, fastest, and most disease resistant, the higher the benefits. However, beneficial traits in one environmental context often become liabilities in another. For instance, in 19th century Europe in the midst of a cholera epidemic, what better genetic selection than an individual who appears to be resistant? However, we now know that the individuals, who were resistant to cholera, were so because they were carriers for cystic fibrosis, the most common recessive hereditary disease in Caucasians (Bramanti, Hummel, Chiarelli, & Herrmann, 2003).

While clear cut examples of the balance between good and bad exist (resistance to cholera and cystic fibrosis; resistance to malaria and sickle cell anemia (Feng, Smith, McKenize, & Levin, 2004)) the “evolutionary/environmental rationale” of most other polymorphisms is far from clear.

The angiotensin I converting enzyme (ACE) gene insertion/deletion polymorphism (defined as the presence, insertion, or absence, deletion, of a 287 base pair fragment) has been the topic of significant study and debate over the years. Homozygosity for the I allele has been associated with elite endurance performance, enhanced metabolic efficiency, and positive changes in body morphology (Gayagay et al., 1998; Montgomery et al., 1998, 1999) and not (Rankinen et al., 2000), while the presence of the D allele in either the heterozygous or homozygous state has been associated with increased strength as a result of exercise (Folland et al., 2000) and not (Frederiksen, Bathum, Worm, Christensen, & Puggaard, 2003). While there is persistent debate regarding the exercise related benefits of the ACE insertion/deletion polymorphism, potential disease associations have begun to surface. It has been suggested that the D allele of the ACE gene confers an increased risk of cardiovascular disease.
(Soubrier, Nadaud, & Williams, 1994) however several larger follow up studies have ruled out any association between ACE and myocardial infarction (Arca et al., 1998; Ferrieres et al., 1999; Keavney et al., 2000; Fig. 1).

Myostatin (GDF-8) is a muscle specific negative regulator of muscle growth (McPherson, Lawler, & Lee, 1997) and a member of the transforming growth factor B family, and, as described in text above, causes double muscling in cattle and mice. In 2004, Schuelke and colleagues described a child who was born, after a normal pregnancy, with both increased muscle mass and increased strength. This individual showed a quadriceps cross-sectional area 7.2 SD above the mean for age and sex matched controls and the ability to hold two 3 kg dumbbells in “horizontal suspension with arms extended” age the age of 4.3 years. The child showed a splice site mutation in the myostatin gene (at IVS1 + 5), and this mutation prevented the production of the myostatin protein. As suggested by McNally (2004), other less dramatic changes in the myostatin gene (or heterozygosity for the splice site mutation) may confer enhanced athletic prowess in a less conspicuous manner. However, the child’s mutation has not been found in any other individuals, and is therefore not a polymorphism driving normal human variation. Furthermore, genetic association studies with myostatin polymorphisms have consistently failed to demonstrate any statistically significant relationship with any human muscle trait (Ferrell et al., 1999; Ivey et al., 2000; Thomis et al., 2004).

Alpha actinin 3 is one protein in a family of proteins that bind to actin at the Z-line and act to anchor actin filaments (Beggs et al., 1992). Unlike its isoform alpha actinin 2, which is expressed in all skeletal muscle, alpha actinin 3 is expressed only in type 2 muscle fibers (North & Beggs, 1996). Research into the gene that codes for alpha actinin 3 revealed a common nonsense mutation (R577X) found in the homozygous state in approximately 18% of the world’s population (Mills et al., 2001). The frequency of this genetic alteration

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**Fig. 1. Single nucleotide polymorphisms associated with muscle phenotypes.** Figure showing function (red) of single nucleotide polymorphisms and published associations (blue) with muscle phenotypes: ACE (angiotensin 1 converting enzyme), GDF-8 (myostatin), ACTN3 (alpha actinin 3), IL-15R (interleukin-15 receptor), CNTF (ciliary neurotrophic factor), VDR (vitamin D receptor). Figure adapted from http://home.aclab.nieus.edu/~robocop/human_body.jpg and http://www.sirstin.net/~jjg/hum/amuscle.html.
clearly excluded it as a disease-causing change, however it has still had a substantial impact in the realm of functional genetics in muscle North et al. (1999). Yang et al. (2003) conducted a study of elite Australian Athletes from the Australian Institute of Sport and found that sprinters (both male and female) were homozygous for the R577X genotype significantly less often than a control population ($p < 0.01$). Alternatively, endurance athletes were found to be homozygous for the R577X allele more often than controls. These findings were further supported by Clarkson et al. (2005) who found that women who were homozygous for the 577X genotype had a significantly lower baseline isometric strength using maximal voluntary contraction. The frequency of the ACTN3 polymorphism and the significant association of this gene with both increased endurance (577X) and increased and increased power/sprint ability (577R) suggests that the 577X polymorphism has evolved and proliferated as a result of environmental adaptation. Potential alternative uses of these evolutionary advantages are discussed below.

While the desire and search to find a gene that confers athletic prowess is intense, sometimes our search leads to genetic changes that confer decreased rather than increased ability. The ciliary neurotrophic factor (CNTF) is known to influence motor neuron survival, muscle fiber development, and muscle regeneration (Marques & Neto, 1997; Peroulakis & Forger, 2000). Due to these important functions in muscle development and growth, the CNTF gene, in particular a nonsense mutation at $-6$bp in exon 2, has been investigated with respect to many neuromuscular diseases; despite this, no causal relationship has been found (Takahashi et al., 1994). Once the disease association has been ruled out, CNTF became a prime candidate for mediating differences between healthy individuals in muscle mass and strength. In a study of nearly 500 healthy adults Roth et al. (2001) found that individuals homozygous for the null allele (a/a genotype) have a lower baseline strength than individuals who are heterozygous or homozygous for the wildtype allele. However, in the same population, heterozygotes were found to have higher strength and muscle quality than homozygotes for either the wildtype or the null mutation (Fig. 1).

In addition to the functional association between the CNTF gene and muscle, the CNTF specific alpha receptor subunit (CNTFR) has also been shown to be expressed in muscle with increased expression levels following muscle damage (Kami, Morikawa, Sekimoto, & Senba, 2000). Further study of CNTFR receptor, has revealed several polymorphisms, one of which, although rare in the homozygous state (occurring in less than 1% of Caucasians and 1.6% of African Americans) results in the increased fat free mass in the heterozygotes and homozygotes compared to individuals who are homozygous for the wildtype. After using fat free mass as a covariate, no changes in strength were found (Roth, Metter, Lee, Hurley, & Ferrell, 2003). This C → T change at position 174 in exon 9 lies in the 3' untranslated region of the gene. Although the C174T polymorphism does not directly alter the protein, variants in untranslated regions are known to modify gene expression and therefore can have significant functional implications.

As with all aspects of genetics research, the investigation into polymorphisms that modulate muscle function and structure continues with new associates revealed on a daily basis. Recently the interleukin-15 protein and its receptor have been studied with respect to responses to resistance training. IL-15 receptor is expressed in multiple tissue types but is found at high levels in muscle tissue (Quinn, Haugk, & Damon, 1997). Two different functional polymorphisms have been identified in the IL-15 receptor gene. The PsI variant (an A to C in the 3' UTR) located in exon 7 has been found to be associated with greater muscle mass but reduced muscle quality (as measured by strength testing). In addition, the BstNI variant (which results in a change in the amino acid sequence from Threonine to Asparagine) in exon 4 was also found to be associated with increased muscle mass. Although statistical analyses indicate that the observed differences are independent of one another, the BstNI variant and the PsI variant are in linkage disequilibrium ($p < 0.001$, $D' = 0.875$) suggesting that one variant may be more functionally relevant. This is likely to be the exon 7 polymorphism as this variant creates an isoform of the IL-15 receptor (Rieckman, Balasekaran, Roth, & Ferrell, 2004).

Another polymorphism associated with body composition has been identified in the glucocorticoid receptor gene. The glucocorticoid receptor regulates glucocorticoids which are known to influence lipid metabolism and insulin sensitivity. While it has been...
postulated that glucocorticoids could influence body composition this had not been investigated until recently. van Rossum et al. (2004) established an association between the ER22/23EK polymorphism in the glucocorticoid receptor and increased muscle mass and strength in males. Although females were not found to have the same increases in mass and strength, females were found to have decreased waist and hip circumference compared to individuals homozygous for the wildtype. Like the glucocorticoid receptor, the human vitamin D receptor gene has been studied for years for reasons other than body composition. Until a 2004 study examining muscle strength, fat mass and body weight, the human vitamin D receptor had been the focus of many association studies relating to bone mineral density. A previously identified poly A microsatellite (which varies in length between 11 and 23) in intron 8 of the gene was investigated in 175 healthy Swedish women. Individual homozygous for the shorter allele were found to have 11.5% greater strength in the hamstrings as well as higher body weight and fat mass compared to the group homozygous for the longer allele (Grundberg et al., 2004). Although this study was conducted with pre-menopausal women, a separate study of post-menopausal women found similar results with respect to strength when the cohort was controlled for obesity (Geusens et al., 1997).

4. Sources of SNPs

Information on human SNPs is available from several sources. Public databases of more than 5 million human SNPs are available on the World Wide Web at several sites. The major repositories of this data include the National Center for Biotechnology Information (NCBI) database (dbSNP) and the Human Genome Variation database (HGVbase) (Reich, Gabriel, & Altshuler, 2003). Many smaller and more specific SNP databases such as JSNP, a database of common SNPs in the Japanese population, also exist (Hirakawa et al., 2002).

While these publicly available databases are easily accessed and searched, they have limits that the researcher should be aware of. Only a small fraction of the database SNPs are well characterized and validated, and they have extensive coverage of common SNPs, but less coverage of the rarer, but still important, SNPs (Reich et al., 2003).

5. Understanding SNP association studies

Recent advances in technology have led to the design and development of molecular genetic techniques allowing the cost effective and efficient methods to evaluate the role of genetic variants in humans. This has led to an exponential increase in the number of genetic association studies performed and reported in the literature. Before 1992, less than 10 genetic association studies were published per year. by 2000, the number had increased to 120 (Hirschhorn, Lohmueller, Byrne, & Hirschhorn, 2002). Many of these published associations report conflicting results, many are never replicated, and many do not report the necessary information for the reader (Freely Associating, 2000). The studies are often plagued with problems of small sample sizes, consistent analysis methods, and inadequate power. The informed reader needs to understand the strengths and the limits of association studies so they may judge the study’s merits for themselves.

A well designed and well reported study will have several important components (Gambaro, Anglani, & D’Angelo, 2000; Little et al., 2002). These include a plausible biological context, a clear discussion of the analytic validity of both the genotyping methods and the samples chosen for inclusion in the study, a strong definition of the phenotype under study, and an appropriate statistical analysis with methods to correct for multiple testing (Altshuler, Kruglyak, & Lander, 1998; Becker, Nieters, & Rittgen, 2003; Little et al., 2002). Although not often feasible, replication of findings should be done. While few published association studies fit all of the above criteria, they are all important components that should be considered and a good publication will address them.

6. Societal implications

Whether we are striving for the gold medal in the Olympics or hoping to create a child that will always be picked first in gym class there are many possible applications of the human and animal SNPs discussed above. To date there are at least six companies offering

In our society, the line between disease/illness and health begins to blur as we assign disability to characteristics such as short stature or athleticism. With our increasing knowledge of genetics, the inclination to modify these traits with the help of genetics heightens (Lippman, 1991). This has already occurred with respect to prenatal and preconception sex selection where genetic testing using FISH (fluorescence in situ hybridization) or Microsort® (sperm sorting) allows individuals to choose sex for non-medical reasons. While many couples choosing sex selection do so to avoid a sex-linked disease, others pursue it for the purpose of “family balancing”. Sex selection is just one example of the use of genetic technologies for non-disease traits. In order to prevent future uses, some countries have established laws limiting the use of genetic technologies for these purposes (Knoppers & Isasi, 2004). While current regulations limit the use of genetic testing for assisted reproduction and prenatal testing they do not limit testing in childhood, nor will they likely stand as a barrier to the creation of “designer” babies forever.

The concern over the use of genetic testing for genetic variants is not limited to future generations. If in one trip to the doctor for gene therapy you could leap tall buildings in a single bound or lift the car with your bare hands, who could resist? In the United States, this issue has been a mute point for many years due to a 1985 NIH moratorium on funding for gene therapy for the purpose of enhancement (NIH, 1985); as well as strict and restrictive guidelines for the use of enhancement therapies (such as human growth hormone) by the American Medical Association (AMA, 1994). Despite these limitations, there are already several possible applications of genetic enhancement, as they relate to exercise and sport. Possibilities ranging from gene therapy with EPO to increase red blood cell levels and increased oxygen transport (Longman, 2001) to gene therapy with PGC-1 which can dictate the development of slow and fast twitch fibers (Lin et al., 2002). While gene doping is vehemently opposed by both the International Olympic Committee and World Anti-Doping Agency as interfering with fair play and potentially harming athletes (IOC, 2001; WADA, 2002); the Australian Law Reforms Council (ALRC) has expressed significant concerns regarding the use of gene therapy and genetic testing in sports for other reasons. The ALRC is concerned about a perceived risk of genetic discrimination (i.e. limiting participation to those genetically predisposed to success or limiting access for those who are genetically predisposed to injury). The sheer fact that the ALRC includes in their discussion genetically modified individuals, serves as an acknowledgement of a realistic future (ALRC, 2001). This acknowledgement suggests that the restrictive approach to gene therapy in sports is may not be sustainable and that further ethical debates will need to continue as well as methods for testing for genetic enhancement if the ban remains in place.

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