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Respiratory Physiology & Neurobiology 151 (2006) 109–123
RESPIRATORY PHYSIOLOGY & NEUROBIOLOGY
www.elsevier.com/locate/resphysiol

What makes a champion? Explaining variation in human athletic performance☆

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Accepted 21 December 2005

Abstract

Variation in human athletic performance is determined by a complex interaction of socio-cultural, psychological, and proximate physiological factors. Human physiological trait variance has both an environmental and genetic basis, although the classic gene–environment dichotomy is clearly too simplistic to understand the full range of variation for most proximate determinants of athletic performance, e.g., body composition. In other words, gene and environment interact, not just over the short term, but also over the lifetime of an individual with permanent effects on the adult phenotype. To further complicate matters, gene and environment may also be correlated. That is, genetically gifted individuals may be identified as children and begin training pulmonary, cardiovascular, and muscle systems at an early critical age. This review covers evidence in support of a genetic basis to human athletic performance, with some emphasis on the recent explosion of candidate gene studies. In addition, the review covers environmental influences on athletic performance with an emphasis on irreversible environmental effects, i.e., developmental effects that may accrue during critical periods of development either before conception (epigenetic effects), during fetal life (fetal programming), or during childhood and adolescence. Throughout, we emphasize the importance of gene–environment interaction (G × E) as a means of understanding variation in human physiological performance and we promote studies that integrate genomics with developmental biology.

Keywords: Gene and environment effects on sports peformance; Gene–environment interaction; Complex traits; Polymorphism; Developmental effects; Fetal programming; Genomics

1. Introduction

Having recently won the Tour de France for a record seventh consecutive year, Lance Armstrong is without a doubt the greatest cyclist of his generation. His performance may come close to a theoretical ceiling of human metabolic potential (for Tour

☆ This paper is part of a special issue entitled "New Directions in Exercise Physiology" guest edited by Susan Hopkins and Peter D. Wagner.

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doi:10.1016/j.resp.2005.12.013

de France riders see Hammond and Diamond, 1997), and indeed many athletes in various disciplines may be pushing up against the limits of what is possible. How do such exceptional athletes arise? In an even broader sense, how do we explain the full range of human athletic ability, from forgettable to incredible? For elite athletes, a reasonable hypothesis is that they possess a fortuitous combination of genes that are either necessary or sufficient to produce their athletic phenotype. However, an equally important consideration is lifelong experience, from early intrauterine exposures to the advanced training techniques employed by professionals. In other words, to understand human variation in performance it is necessary to consider both gene *and* environment (main effects), but also gene–environment interactions ($G \times E$, where the effect of one factor depends on the level of the other factor), and gene–environment correlations. The latter, gene–environment correlation, is not necessarily a trivial issue when it is considered that children tend to gravitate- or are urged towards -athletic disciplines in which they show an early aptitude. Exactly how the totality of such processes account for inter-individual variation in athletic performance is largely unknown. In particular, the process of $G \times E$ acting over a lifetime may be the key to understanding much of human complex trait variability. In this regard, we review evidence in support of a genetic basis for human athletic performance, but we also review the emerging literature that shows lasting effects of environmental experience, particularly early in-utero experience, on the adult athletic performance phenotype. Neither topic is reviewed exhaustively, but rather the overarching purpose of the paper is to draw attention to a new direction in exercise physiology (variation in human performance) which demands an integrative research approach, i.e., simultaneous consideration of gene and environment effects.

2. Genetics and human physical performance

"Champions, they are naturally selected. They begin at their own level, and Lance was at that level, for sure." -Dr. Michele Ferrari, commenting on the first time he conducted physiological tests on a young Lance Armstrong (Coyle, 2005).

The genetic basis of human athletic performance has been reviewed previously and readers are referred to a number of excellent papers and volumes that treat this topic in detail (Bouchard and Malina, 1983; Bouchard et al., 1997; Patel and Greydanus, 2002; Myburgh, 2003; Rupert, 2003; Heck et al., 2004; Macarthur and North, 2005). Three introductory points are worth making. First, the cumulative evidence, going back more than one century, is all but overwhelming in support of the general idea that genes are responsible for some of the variation in human athletic performance. The sub-sections below detailing this evidence are organized by methodological approach including quantitative genetics and segregation analysis, linkage analysis, and candidate gene studies. The second point is that despite the obvious role of genetics in human physical performance, there is little unequivocal evidence in support of a specific genetic variant with a major gene effect on a relevant performance phenotype, at least across the normal range of human trait distributions. This may be because complex traits are fundamentally polygenic (many genes with small effects), or because researchers have failed to take into consideration the full range of environmental effects, or both. Third, there has been a recent explosion of interest in the genetic basis of human athletic performance paralleling the development of new and accessible genotyping and DNA sequencing technologies. This growth of interest is well documented in the yearly human gene map for performance and health-related fitness phenotypes which was first published in 2001 and which is now in its fifth iteration (Rankinen et al., 2001b, 2002b, 2004; Perusse et al., 2003; Wolfarth et al., 2005). The number of yearly publications identifying genes, genetic markers, or chromosomal regions in the context of human athletic performance has increased dramatically since the early 1990s, as shown in Fig. 1.

2.1. Quantitative genetics and segregation analysis

The analysis of quantitative traits in family based studies provided the first direct evidence of a genetic basis for human athletic ability. The theoretical and mathematical foundations of this discipline were established at the beginning of the 20th century by plant and animal breeders with two major goals: (1) to infer the amount and nature of genetic variation *within* a

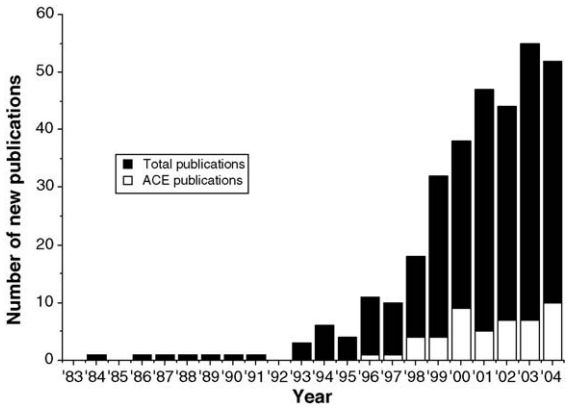

Fig. 1. Growth of candidate gene and linkage based studies focused on performance and fitness related health phenotypes from the early 1980s to 2003 from data reported in Rankinen et al. (2001b, 2002b, 2004), Perusse et al. (2003), and Wolfarth et al. (2005). Of the total number of studies, nearly 17% were candidate gene studies focused on the angiotensin converting enzyme (ACE) insertion/deletion polymorphism.

breeding population and (2) to predict the response to selection in a breeding program (Lynch and Walsh, 1998). The former goal is most relevant here as quantitative genetic approaches provide a means to infer the genetic and/or environmental causal influences on a trait of interest. While the statistics are complex, quantitative genetics is based on a very simple idea, known as Fisher's basic theorem, which states that the degree of phenotypic correlation (resemblance) between individuals is proportional to the number of genes that they share (Fisher, 1918). If continuously varying quantitative traits are studied between individuals with *known* biological relationships, then total phenotypic variance (σ_P^2) can be partitioned into genetic (σ_G^2) and environmental (σ_E^2) components where $\sigma_P^2 = \sigma_G^2 + \sigma_E^2$ (Falconer, 1981; Lynch and Walsh, 1998). The proportion of the total phenotypic variance that is due to genetic differences between individuals is described by a population summary statistic termed *heritability* (h^2), where heritability in the *broad sense* refers to the proportion of phenotypic variance attributable to all genetic effects (i.e., σ_G^2/σ_P^2). Sophisticated quantitative genetic models have become available, e.g., (Blangero, 1993), however it is important to emphasize that most studies apply assumptions that may or may not be realistic. These include that there is random mating within the population, no linkage between multiple genes influencing the quantitative trait under consideration, no gene–environment correlation, and no G × E. In particular, the ubiquity of G × E, or at least genetic marker × E interaction, is becoming evident as demonstrated in a number of recent candidate gene studies described below. Further, as described in the introduction to this paper, gene–environment correlation may be the rule rather than the exception.

Despite such limitations, numerous studies (Bouchard et al., 1997) demonstrate or suggest significant h^2 for traits of interest to exercise physiology. These include studies of aerobic performance and response to training (Bouchard et al., 1998, 1999; Rodas et al., 1998), anaerobic performance (Gaskill et al., 2001; Calvo et al., 2002), muscle strength and power (Arden and Spector, 1997; Beunen and Thomis, 2004; Tiainen et al., 2004), neuromuscular coordination (Missitzi et al., 2004), bone density (Nordstrom and Lorentzon, 1999), body size and composition (Rice et al., 1997, 1999; Hong et al., 1998; Katzmarzyk et al., 1999, 2000; Perusse and Bouchard, 1999), muscle fiber type distributions (Komi et al., 1977; Komi and Karlsson, 1979; Bouchard et al., 1986; Suwa et al., 1996; Barrey et al., 1999), cardiovascular variables including blood pressure (Bielen et al., 1990, 1991a,b,c; Rice et al., 2000b; An et al., 2003), blood lipid biochemistry (Beekman et al., 2002), blood glucose, insulin, and peripheral insulin sensitivity (Hong et al., 1998; Poulsen et al., 1999, 2005; Freeman et al., 2002), substrate utilization and metabolic rate (Bouchard et al., 1989; Rice et al., 1996; Goran, 1997), pulmonary function (Mueller et al., 1980; Kramer, 1992; Beall et al., 1994, 1997, 1999), and hormones and hormonal response to training (An et al., 2000, 2001; Hong et al., 2001). One frequently cited study is that by Bouchard and colleagues revealing significant familial aggregation (h^2 near 50%) for $V_{O_2\,max}$ and $V_{O_2\,max}$ trainability for individuals in the sedentary state, after controlling for age, sex, body mass, and body composition (Bouchard et al., 1998, 1999).

It is in fact is difficult to find a physiological trait that does not show significant h^2, and in aggregate these studies provide strong support for the hypothesis that genetic factors determine both proximate measures of human performance (e.g., $V_{O_2\,max}$) and ultimately athletic ability in various sporting disciplines. However, h^2 studies reveal little about the causal spectrum and genetic architecture of complex traits. That is,

significant h^2 does not indicate whether a phenotypic distribution is determined by polygenes, or whether a large part of the phenotypic variance is explained by the action of a single major gene. Likewise, heritability values say nothing about allele frequencies, the mode of inheritance, specific chromosomal locations of genes, gene products, or the functional effects of gene products on the phenotype. One further step is segregation analysis which may allow strong inference of major gene effects (Elston and Stewart, 1971; Blangero and Konigsberg, 1991; Blangero, 1993), and in such cases a typical progression would be to search out chromosomal locations via linkage analysis.

2.2. Linkage based studies

To identify specific genes, two major approaches are widely applied including family-based linkage analyses and the candidate gene association approach. In this section, we describe the former, and in the next section the latter. It is important to realize that only a handful of linkage based genome-wide scans have been conducted to study human performance phenotypes, in part because such studies are logistically complex and expensive. Linkage analysis is based on the co-segregation of a putative (causal) trait locus with a known marker locus, and linkage implies the close proximity on the chromosome of causal and marker loci. Linkage is typically determined by proposing a model of inheritance to best explain the patterns of both marker genotypes and phenotypes in a pedigree. Intuitively, this involves trying to determine, in a probabilistic sense, whether related individuals share 0, 1, or 2 alleles identical by descent (IBD) at a given marker locus. If there is linkage with a nearby trait locus, then relatives who share more alleles IBD will show stronger trait covariance than relatives with no alleles IBD. Maximum likelihood methods are used to test for a linked genetic effect, and the results are often reported as a LOD score (log base 10 of the odds ratio). Because it is typical to test many loci simultaneously, LOD scores greater than 3 are considered the threshold for significance, limiting the report of false positive associations to less than 5% (Risch, 2000).

Linkage analysis is not new and it has a long history of success in mapping loci for simple monogenetic (Mendelian) disease traits in humans, e.g., Huntington's disease (Gusella et al., 1983). The approach may also work for complex traits, but generally only if the causal locus has high penetrance and a large effect on the trait in question. For example, one well-known linkage success story is the discovery the BRCA family of breast cancer genes. Early family studies demonstrated a significant familial aggregation, i.e., heritability of breast cancer, and subsequent linkage analysis and cloning work showed localization to chromosome 17q for genes encoding tumor suppressor proteins (Hall et al., 1992; Lalle et al., 1994; Kent et al., 1995; Zweemer et al., 1999). Mutations in these genes generally do not rise to polymorphic frequency within populations (>0.01), and thus account for only a small proportion of the overall breast cancer prevalence. Therefore, an important question for exercise physiology is whether linkage analysis can identify loci with modest or small effects harboring common allelic variants. In other words, much like the complex genetic and environmental etiology of chronic disease, athletes likely emerge on a predisposing and favorable genetic background where individual alleles are both common and have only modest effects. This is a critical issue because family-based linkage analysis, as currently applied, may not have adequate statistical power and mapping resolution to detect genes of modest effect (Risch and Merikangas, 1996).

In the 2004 update of the human gene map for performance phenotypes (Rankinen et al., 2004), only 20 publications were from linkage-based analyses. These represented about 7% of the total literature seeking to identify the genetic basis for human performance, but nearly all were reports from one study, the HERITAGE family study (Bouchard et al., 2000). In total, about 60 marker loci have been linked to traits which include $V_{O_2\,max}$ and $V_{O_2\,max}$ response to training (Rivera et al., 1999; Bouchard et al., 2000; Rankinen et al., 2000; Rico-Sanz et al., 2004), physical activity level (Simonen et al., 2003), muscle strength (Huygens et al., 2004, 2005; Thomis et al., 2004), stroke volume, cardiac output, and blood pressure during exercise (Grunig et al., 2000; Rice et al., 2000a; Rankinen et al., 2001a, 2002a, 2003), training induced changes in body composition (Sun et al., 1999; Chagnon et al., 2001; Lanouette et al., 2002; Rice et al., 2002), and insulin and glucose response to habitual physical activity or exercise (Lakka et al., 2003). It should also be noted that genome scans in the HERITAGE family study, to date, have applied only a relatively modest number of

marker loci numbering in the hundreds. These markers span the entire genome but with high intermarker distances encompassing very large regions that could harbor many hundreds of candidate gene loci. Thus, identification of causative genes will require additional fine mapping efforts. Additionally, most of the positive results by linkage analysis have not been replicated in association studies. This could be due to the inherent limitations of both linkage-based and candidate gene approaches, and/or to the possibility that outcome measures (i.e., performance phenotypes) differ between studies.

In the near future, it will be possible to conduct whole-genome association studies with much higher marker densities. For example, a large-scale multicenter effort, the "HapMap project" is currently under way to identify 200,000 to 1 million tag single nucleotide polymorphisms (SNPs) to be used in haplotype mapping (http://www.hapmap.org/). Still, given the number of SNPs that will have to be genotyped (hundreds of thousands), and the sample sizes that will be required to detect genes of modest effect (Risch and Merikangas, 1996), the costs of genome-wide association studies will still be enormous. High throughput genotyping methods may change the cost equation considerably, and some recent effort has focused on new and more efficient association-based linkage approaches (Risch, 2000). For example, in recently admixed populations an attractive alternative to the whole-genome association strategy is admixture mapping. This approach exploits the information about linkage created when previously isolated populations admix, and is more analogous to linkage analysis of an experimental cross than to conventional linkage disequilibrium mapping (Chakraborty and Weiss, 1988; Briscoe et al., 1994; Stephens et al., 1994; McKeigue, 1997, 1998; McKeigue et al., 2000; Hoggart et al., 2004; Patterson et al., 2004). The advantages of this approach include the fact that it does not require the recruitment of family members, has higher power to detect loci with more modest effects, is not affected by allelic heterogeneity, and represents a 100-fold reduction in cost relative to whole-genome association approaches (Terwilliger and Weiss, 1998). The latter is due to the substantially fewer numbers of genetic markers that need to be genotyped versus whole-genome association approaches (1000–3000 markers versus 200,000–1,000,000 markers) because in recently admixed populations regions of identical ancestry will span several cM (Hoggart et al., 2004).

2.3. Measured genotypes or candidate gene studies

Candidate gene studies are relatively new and have proliferated greatly since the early 1990s (Fig. 1). A few early studies in the 1970–1980s demonstrated no association of physical performance phenotypes with the many classical blood group polymorphisms (see Bouchard et al., 1997), but as of 2004, measured genotype association studies comprised the majority (∼93%) of the total literature seeking to identify the genetic basis for variation in human athletic performance. Of these, nearly 17% were focused on one specific gene polymorphism, the angiotensin converting enzyme (ACE) insertion/deletion polymorphism (Fig. 1). Despite the number of studies, the significance of the ACE polymorphism in a genetic causal sense remains controversial, and this may prove to be paradigmatic for the candidate gene approach in general. That is, measured gene studies are observational not experimental, and so there is the problem of false association due to chance, bias, or confounding (Campbell and Rudan, 2002). This is true both for case-control studies, i.e., comparing allele frequencies in elite athletes with the general population, or in studies that evaluate mean phenotypic values by genotype in a "homogenous" study group. For this reason, significant gene–trait associations can (and should) only be cautiously interpreted vis-à-vis putative physiological mechanisms.

Potential confounders of candidate gene studies are factors that associate with *both* the phenotype and the candidate gene, and these can be either genetic or environmental factors that have the effect of falsely creating, obscuring, amplifying, or diminishing true gene–trait causal associations. One common example, at the genomic level, is the spurious association that can arise due to population stratification. Kittles et al. studied the CYP3A4-V gene variant previously associated with prostate cancer in African Americans (Kittles et al., 2002). Genetic causality was suspect because African Americans have a relatively high prevalence of prostate cancer a priori and because the CYP3A4-V variant is generally at higher frequency in populations of African compared to European ancestry.

These authors measured the association of CYP3A4-V and prostate cancer in an African American population, and when genomic control was incorporated using unlinked ancestry informative loci, the association between marker and disease went from highly significant (uncorrected $P = 0.007$) to non-significant (corrected $P = 0.25$). This kind of confounding has the potential to work both ways. In our studies, we measured arterial blood oxygen saturation (SaO_2) at rest and during exercise in 69 Peruvian men and women from sea-level who traveled to 4338 m altitude (manuscript in preparation). The uncorrected association between ACE I-allele and higher saturation at 4338 m in this population was not significant at $P = 0.104$. However, when population stratification was taken into account using 80 ancestry informative loci, the association approached significance at $P = 0.05$ and a measure of the strength of association increased by 33%. To make the issue of stratification even more explicit, consider Fig. 2 showing ACE I-allele frequencies for worldwide populations grouped according to geographic region. There is substantial variation in I-allele frequency within all geographic regions. Thus, even if investigators confine their study sample to a homogenous group with a specific ancestry, e.g., U.S. residents of European ancestry, there may still be population sub-structure leading to spurious association (Campbell et al., 2005).

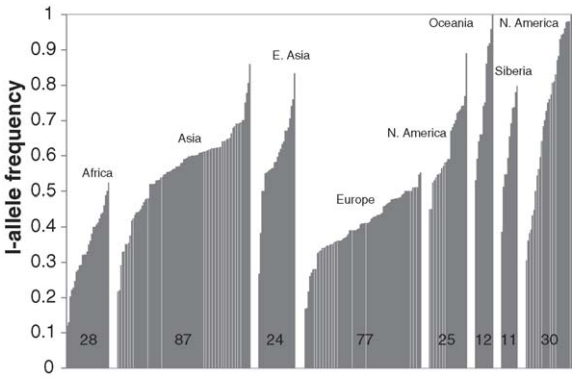

Fig. 2. Geographic patterning of the ACE I-allele frequency shows significant variation of the I-allele within geographic regions, where each bar represents a single studied population within a region. This suggests the potential problem of confounding due to population stratification in gene association studies (see text for details). Data are from the Allele Frequency Database (ALFRED); http://alfred.med.yale.edu/alfred/index.asp; (Osier et al., 2002), and represent independent reports of I-allele frequency in populations sampled from major geographic areas worldwide including Africa ($n = 28$, indicated on graph), Asia ($n = 87$), East Asia ($n = 24$), Europe ($n = 77$), North America ($n = 25$), Oceania ($n = 12$), Siberia ($n = 11$), and South America ($n = 30$).

Confounding due to the environment is even more problematic and has the same potential to fully explain or obscure causal gene–trait associations. With respect to obscuring a true association, recent studies show the value considering $G \times E$ explicitly in order to detect gene–trait associations. For example, Hagberg et al. (2002) detected significant ACE genotype associations with exercise systolic blood pressure in untrained but not trained women. This may represent a "norm of reaction" for the ACE genotype, or the idea that ACE gene effects are a continuous function of a variable training environment. The challenge for exercise science is to incorporate an even broader concept of the environment to include environmental influences that act, not just over the short term, but during critical periods of development including prenatal life, early child-hood, and adolescence. As described in the next section, these constitute periods where environmental factors are likely to have irreversible (permanent) effects on the adult phenotype.

3. The environment and human physical performance

"Your past forms you, whether you like it or not. Each encounter and experience has its own effect, and you're shaped the way the wind shapes a mesquite tree on a plain."
-Lance Armstrong (Armstrong and Jenkins, 2000).

"She is 5-foot-3 and weighs about 105 pounds, and I don't know how somebody so tiny delivered me, because I weighed in at 9 pounds, 12 ounces".
-Lance Armstrong describing his mother (Armstrong and Jenkins, 2000).

Elite athletes may be born with a favorable genetic constitution, but to realize athletic potential requires years of focused training. Training is itself a kind of self-imposed environmental exposure, and when gifted athletes train this could be considered an example of gene–environment correlation. The effects of training on performance variation can be dramatic.

For example, the world record time in the women's marathon has decreased by more than 1 h. since just the 1960s certainly due in part to improved training techniques. Among researchers, training per se also seems to loom large on the environmental side of the gene–environment dichotomy. For example, the human gene map for performance phenotypes identifies a number of studies which show G × E, but many of these are examples of G-by-training interaction, i.e., differential training responses based on genotype. While G-by-training interaction explains variation in performance, it does not necessarily explain *variation in human potential*. In other words, elite athletes are those who respond in extraordinary ways to training in order to unlock an already present potential, and G-by-training interaction may itself be affected by G × E taking place over the lifetime of an individual. Thus, a broader consideration of environmental effects should be emphasized.

Environmental effects can begin pre-conception via gametic imprinting (Barlow, 1995). Imprinting is achieved through methylation of DNA during gametogenesis (Razin and Cedar (1994)), and this in turn can modify parental gene expression resulting in parental-dependent traits in offspring. DNA modifications due to methylation are heritable and thus constitute a type of epigenetic effect. However, DNA methylation is also fully reversible and the process can be modified by environmental exposure. For example, Cooney et al. (2002) showed that maternal dietary manipulation in mice increased DNA methylation and affected health and longevity phenotypes in offspring. It is not currently known whether important complex traits in humans have significant epigenetic components, but a number of studies suggest that this is the case for some cancers and for chronic disease traits (Ahuja and Issa, 2000; Petronis, 2001). Petronis (2001) argue that poorly understood epigenetic processes are partly to blame for the slow pace in elucidating the genetic basis of chronic disease using conventional association approaches. This issue certainly applies to human performance phenotypes, although we are not aware of any specific studies addressing epigenetic effects and human athletic ability.

Perhaps the best characterized environmental effects with long term consequences on the adult phenotype are those which occur during fetal life. Barker and colleagues, in a series of epidemiological studies, were the first to show strong negative associations of birth weight and adult prevalence of type 2 diabetes, insulin resistance, hypertension, and cardiovascular diseases (Hales et al., 1991; Barker et al., 1993a,b; Phipps et al., 1993; Phillips et al., 1994; Fall et al., 1995). For example, after adjusting for body mass index, the prevalence of impaired glucose tolerance or diabetes fell from 27% to 6% in subjects who weighed less than 2.50 kg or more than 3.41 kg at birth, respectively ($P < 0.002$) (Phipps et al., 1993). Strong associations were also evident with the ponderal index (cm/kg^3) as a proxy measure of suboptimal fetal growth (Barker et al., 1993b). Since these reports, numerous additional human and animal studies have replicated the basic findings and support the idea that sub-optimal fetal nutrition, especially during mid- to late-gestation, works to program fetal metabolism with lifelong consequences (Armitage et al., 2004; Gonzalez-Barranco and Rios-Torres, 2004; Wu et al., 2004). The discovery of fetal programming may prove to be a crucial development in our understanding of complex trait architecture for the simple reason that it forces consideration of the early environment as a profound determinant of the adult phenotype. Importantly, these types of environmental effects are graded and probably operate across the normal range of human variation (Jackson, 2000). That is, the early studies by Barker and colleagues showed a dose-response of risk for chronic disease across the entire range of normal birth weights, not just increased risk below a critical low birth weight (Hales et al., 1991; Barker et al., 1993a).

Although most of the research on fetal programming has focused on chronic disease outcomes, a few studies show associations of fetal growth with traits that have direct relevance to exercise physiology including (mostly) body composition traits and the performance characteristics of skeletal muscle. With respect to body composition, in general birth-weight is positively associated with adult BMI and body weight (Sorensen et al., 1997; Rasmussen and Johansson, 1998). However, recent studies suggest that this reflects increments in fat free mass more than increments in body fat (Kahn et al., 2000; Loos et al., 2001, 2002). In other words, small for gestational age babies tend to grow up relatively fatter and at the expense of lean tissue mass. Some have suggested that this reflects a strategy on the part of the fetus to preserve brain growth in the face of intrauterine nutritional deprivation, and perhaps to

survive an anticipated difficult early post-natal period by increasing adiposity (Rudolph, 1984; Barker, 1995; Cameron and Demerath (2002)). Because the formation of muscle occurs early in embryogenesis, Maltin et al. (2001) reviewed evidence of early fetal programming effects on muscle fiber number, fiber type, and fiber size. Apart from severe manipulations such as maternal starvation (Wilson et al., 1988; Dwyer and Stickland, 1992), fetal programming apparently had little effect on muscle histology. However, one study by Taylor et al. (1995) showed an association of impaired fetal growth (low ponderal index) with muscle performance in adult women as assessed by ^{31}P magnetic resonance spectroscopy. Low ponderal index at birth was associated with biochemical differences in adults that were consistent with delayed activation of glycolysis/glycogenolysis at the commencement of hard exercise stressing the anaerobic system. Similarly, a near-infrared spectroscopy study by Thompson et al. (1997) showed no association of ponderal index with muscle histology, but differences in muscle reoxygenation rate. These authors suggested that the reoxygenation differences by ponderal index were consistent with the delay in the activation of anaerobic glycolytic metabolism demonstrated by Taylor et al. There are few such studies, perhaps because birth measures are necessary in the study cohort, and this is a clear area for future research in exercise physiology.

At least two published human studies have evaluated the simultaneous association of birth weight *and* a candidate gene on a health or performance outcome (Sayer et al., 2002; Kajantie et al., 2004). These studies are noteworthy because as candidate gene studies they incorporate the possibility of environmental confounding and/or $G \times E$ interaction, and because they consider the effect of gene and environment as each works through the developmental process, i.e., fetal growth. The study by Kajantie et al. measured oral glucose tolerance in 423 adult women with known birth measurements. These women were also genotyped for the ACE I/D polymorphism, as the renin-angiotensin system has been associated with some of the complications of type 2 diabetes (Kennon et al., 1999). The I-allele was associated with higher insulin response, but this association was conditioned by birth weight, i.e., it was only significant in subjects with low birth weight (P for interaction = 0.003). Thus, consideration of birth weight enabled the detection of an ACE genetic association, suggesting that ACE genotype interacts with intrauterine environment and results in changes in gene expression during fetal life or later that affect adult phenotype. The study by Sayer et al. is more directly relevant to exercise physiology. Grip strength was measured in 693 British men with known birth measurements, and subjects were genotyped for a polymorphism in the insulin-like growth factor (IGF) 2 gene. IGFs regulate cellular growth, and IGF2 is a major determinant of fetal growth (O'Dell and Day, 1998). In this case, both birth-weight and IGF2 genotype were significant independent predictors of adult grip strength, but no interaction effects were apparent. From the genetic point of view, it is just as important to account for independent environmental effects because this will greatly strengthen the inference that the IGF2 gene is causally related to grip strength. Sayer et al.'s study is similar to our work described above with the ACE I/D polymorphism in Peruvians (manuscript in preparation). We detected independent effects of lifelong hypoxic exposure *and* the ACE I-allele on SaO_2 at 4338 in Peru, but no interactions. Lifelong hypoxic exposure was evaluated by selecting subjects who were born and raised at altitude versus those who were born and raised at sea-level. The important conceptual contribution is that studies such as these explicitly consider the issue of developmental plasticity in the evaluation of a putative causal genetic association.

Infancy, childhood, and adolescence also mark periods of rapid growth and development, and may also be sensitive periods where there is the potential for irreversible environmental effects on subsequent adult phenotypes. There is surprisingly little research in this area with relevance to exercise physiology, apart from a rapidly growing interest in the childhood origins of obesity and body composition (Cameron and Demerath, 2002; Williams and Dickson, 2002; Taylor et al., 2004). In part, this is because there is no convenient marker of childhood environmental (nutritional) stress against which to evaluate trait associations using a retrospective study design. Additionally, traits measured in early life that associate with adult phenotypes are very difficult to interpret causally. For example, early sexual maturation is clearly associated with increased risk of adiposity in adulthood (Cameron and Demerath, 2002). This could reflect genetics (pleiotropy), or it could reflect the same set of environmental factors working continuously from childhood through adulthood.

Of course the same issue could apply to the fetal programming hypothesis, but much more corroborative work has been done in this area, including animal studies, which directly support the basic notion that fetal stress produces irreversible metabolic change (Jackson, 2000).

The issue of trait reversibility is critical because trait permanence is what defines the notion of a developmental effect. Unfortunately, trait permanence is often difficult to evaluate. For example, studies show that activity patterns and increased calcium intake during childhood and adolescence relate positively to bone mineral density in adulthood (Slemenda et al., 1991; Johnston et al., 1992; Teegarden et al., 1999). However, other studies show that gains in bone mineral density disappear at 18–36 months follow-up in calcium supplemented children, and so the lasting effects of these exposures are unclear (Lee et al., 1996; Slemenda et al., 1997). Similarly, adolescents who are highly active tend to have higher $V_{O_2\,max}$ as adults (Mirwald et al., 1981; Malina, 2001), but does this reflect a continued environmental effect (training), or a lasting effect of earlier developmental responses in pulmonary, cardiovascular, and/or muscular function? In studies of children exposed to hypobaric hypoxia, the developmental effects are clear and illustrate the potential of such effects on integrated physiological systems. In European children migrant to high altitude in South America, early exposure to hypoxia is associated with higher $V_{O_2\,max}$ and larger total lung volume (Frisancho et al., 1995, 1997). These relationships are evident from early life (1–2 years of age) through adolescence, and the traits are retained in adults. Similarly, people growing up at altitude in Colorado show smaller alveolar–arterial oxygen partial pressure difference during exercise at altitude, suggesting better pulmonary gas exchange as a consequence of a developmental response to hypoxia (Dempsey et al., 1971). Thus, developmental effects based on childhood environmental exposures are a real possibility representing another area that deserves further research in exercise physiology.

4. Summary/future directions

In this paper, we introduced the topic of human variation in athletic performance as a "new direction in exercise physiology". This is true insofar as new technologies and recent advances in developmental biology have made possible a renewed focus on a topic that has always been of fundamental interest to exercise physiology. Specifically, we reviewed some of the traditional evidence that both genetics and early life environmental experience contribute to the adult athletic phenotype, and the main points emerging from this review are summarized here.

It is clear that candidate gene studies account for most of the growing interest in the genetics of human performance, and we may expect this trend to continue given the recent publication of the draft sequence of the human genome in 2001 (Lander et al., 2001; Venter et al., 2001). However, candidate gene studies have some serious limitations vis-à-vis the goal of elucidating genetic causal pathways. One problem, but certainly not the only problem, is unmeasured environmental effects. In particular, we made the point that it is necessary to appreciate a broader time-scale of environmental effects to include developmental responses. Indeed, the genetic potential of any individual is channeled through a lifetime of environmental experiences via the growth and development process. Thus, the concept of G × E, particularly as it takes place over the lifetime of an individual, should be emphasized. As a number of examples from the literature show, the direct assessment of G × E across the lifespan is possible. Thus, understanding the origins of variation in human athletic performance will require an integration of both researchers and research approaches that represent both sides of the traditional gene–environment dichotomy.

Acknowledgement

The authors would like to thank Dr. Timothy B. Gage, The University at Albany, SUNY, for reading and commenting on a draft of this paper.

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