Genetic Variation in Physical Performance

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Abstract: In this overview the genetic contributions to physical performance will be outlined with a special focus on strength, power and endurance characteristics. Two basic approaches have been used to study the genetic basis of performance phenotypes and related characteristics: the unmeasured genotype approach (top-down) and the measured genotype approach (bottom up). Assessment of heritability is based on the model that total variation (V_{tot}) in a phenotype is partitioned into genetic (V_G), common environmental (V_C) and individual-specific environmental (V_E) components ($V_{tot}=V_G+V_C+V_E$). Heritability (h^2) refers to the proportion of the total variation that can be attributed to genetic effects (V_G/V_{tot}). Estimated heritabilities for strength vary widely between 0.27 and 0.58 in family studies and between 0.14 and 0.83 in twin studies. Heritabilities for dynamic strength of arm and leg muscle groups range from 0.29 to 0.87. For aerobic performance estimated heritabilities vary between 0.40 and 0.94. There is good evidence for genotype*training interaction for strength and aerobic performance. Association and linkage studies have indicated a number of potential interesting regions in the human genome. However few replications have been observed with the exception of associations between strength and ACE, ACTN3 and VDR and ACE for aerobic performance.

Keywords: Genetic determination, heritability, association, linkage, strength, power, aerobic performance.

INTRODUCTION

Performance characteristics are not only of major relevance in a variety of sports but fitness is also related to chronic disease, cardiovascular risk factors, bone health, sarcopenia, and premature mortality. Analyses of the genetic contribution to physical performance phenotypes provide not only insight into the importance of genetic factors but also in the contribution of environmental factors. In this overview the genetic contributions to physical performance will be outlined with a special focus on strength, power and endurance characteristics.

METHODOLOGICAL CONSIDERATIONS

Physical performances and related factors are evaluated on a continuous scale of measurement. Distributions in the general population are Gaussian or skewed, which is typical for quantitative, multifactorial phenotypes that are influenced by multiple genes (polygenic) and environmental factors. As such, the issue is not a question of 'nature' versus 'nurture' [1]. Both nature and nurture and their interactions are important to understanding performance phenotypes.

Two basic approaches have been used to study the genetic basis of performance phenotypes and related characteristics: the unmeasured genotype approach (top-down and the measured genotype approach (bottom up) [1, 2]. When the measured genotype is not available, inferences about genetic influences on a phenotype are based on statistical analyses of the distributions of measures in related individuals and families based on the theoretical framework of biometrical genetics [3]. Two major strategies are used: twin studies and family studies. The former includes both monozygotic (MZ) and dizygotic (DZ) twins. Since MZ twins have an identical genetic background, they will be more similar (higher intra-pair correlation) in a trait that is under genetic control than DZ twins who share on average one-half of their genes. With twin data, genetic and environmental factors unique to the individual and environmental factors shared within families can be estimated and under certain assumptions dominant genetic effects can also be identified. In family studies, the similarities among parents and offspring and among siblings are studied, although generational differences imply both age-specific genetic and environmental effects, which increase complexity of analysis. The family approach permits the identification of genetic plus cultural transmission of traits and estimates of maximum heritability. If data from more extended or combined pedigrees are available, more sophisticated models can be tested.

Assessment of heritability is based on the model that total variation (V_{tot}) in a phenotype is partitioned into genetic (V_G), common environmental (V_C) and individual-specific environmental (V_E) components ($V_{tot}=V_G+V_C+V_E$). Heritability (h^2) refers to the proportion of the total variation that can be attributed to genetic effects (V_G/V_{tot}). It is generally assumed that the effects of different genes are additive (a^2) meaning that the genotypic effect of the heterozygote genotype on the phenotype falls exactly between the genotypic effects of both homozygote genotypes. Dominance genetic effects refer to the interaction between alleles at the same locus (heterozygote effect does not fall exactly in the middle between the two homozygote genotype effects) and epistasis describes the interaction between alleles at different loci. The

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contribution of environmental factors shared by family members (common environmental factors, $c^2=V_C/V_{tot}$) and the proportion of environmental factors that act on an individual can also be estimated ($e^2=V_E/V_{tot}$).

Several assumptions should be met when using the additive model: no interaction between gene action and environment (different genotypes all react equally to similar environmental factors), no gene*environment correlation (similar exposure of environments for different genotypes), no gene*gene interaction and finally, no assortative mating for the trait studied (one assumes people mate randomly for the phenotype in question). In all likelihood, influences on performance phenotypes do not follow all assumptions, and gene action/environmental influences are more or less important at different ages, in each sex, in specific ethnic populations and/or in affluent versus developing countries. Longitudinal (transmission) models are needed to study age-specific influences on the decomposition of inter-age correlations within MZ and DZ pairs into genetically and environmentally transmitted or time-specific sources of variance [4-6].

The effects of gene*environment interaction in the responsiveness of individuals to physical training and specific skill training protocols is an important effect that is largely unstudied. Specific designs can be used to study this interaction [7, 8].

Two major complementary strategies are available in humans to identify genes that explain variability in human physical performance using the measured genotype approach. First, the localization and identification of individual loci that make-up the genetic component of performance phenotype by Quantitative Trait Loci (QTL) linkage analysis, and second, ***allelic association*** studies. Within the scope of the present review, only general descriptions of both approaches can be presented.

Linkage analysis is an important, initial tool for the mapping of genetic loci. It has the advantage that no knowledge of physiological mechanisms is required. A total genome linkage study uses several hundreds of highly variant DNA markers, regularly spaced (e.g. each 10 cM) throughout the human genome.

Multipoint linkage mapping refers to the fact that genotypic data of flanking markers is used together with the marker of interest to better estimate the number of alleles shared by individuals at the marker of interest.

A second set of strategies concerns allelic association studies in which one studies the effect of a specific (polymorphic) marker allele, mostly within a candidate gene, with the mean physical performance level in groups of different genotypes for this polymorphism (ANOVA). One can also test for significant differences in allele frequencies in a case-control design, comparing the allele frequencies of strength athletes and controls (Chi² test). Single nucleotide polymorphisms (SNPs, two different chromosomes have a change in one nucleotide at a certain position); insertion/deletion polymorphisms or multi-allelic variants can be used in allelic association studies. Association studies do not need genetically related subjects. The success of association analysis depends largely on the choice of the candidate gene under study. But, given the increasing knowledge about the human genome and the enormous advances in genotyping technology, 'Genome wide association studies (GWAS)' are now carried out and result in the detection of polymorphic markers that are highly replicable. During the past 2 years, genome wide association studies have identified more than 250 genetic loci in which common genetic variants occur that are reproducibly associated with polygenic traits" [9].

UNMEASURED GENOTYPE APPROACH

Muscular Strength and Power

Genetic contributions to muscular strength and muscle power have been recently summarised [10]. Estimated h² in five family studies varied between 0.27 and 0.58 for static strength of different muscle groups and with adjustment for covariates such as sex, age and sometimes body mass. Estimates tended to be higher in twin studies, although the range of h^2 in 20 studies, 0.14 to 0.83, was greater than in family studies. Apart from limitations related to sample sizes and methodology used to obtain heritabilities, it should be noted that these estimates are based on samples that span childhood through adolescence into old-age. While adjusting for age and sex is essential in family-studies, many twin studies encompass broad age-ranges without correction for age and do not always test for potential sex-differences. More recent twin-studies based on structural equation modelling are consistent in showing no evidence of a shared (familial) environment effect for static strength in adolescents of both sexes, young adult men, and elderly women [10]. The heritabilities in Belgian adolescents ranged from 0.52 to 0.82 for boys (from 1 year before peak height velocity (PHV)until 3 years after PHV) and were somewhat lower in girls, 0.22 to 0.75 with one outlier of 0.07 [4]. The h² at 3 years after PHV, which approximates young adulthood, of 0.52 in boys and 0.48 in girls were consistent with those for young adult Swedish, 0.50 and 0.60 and Belgian, 0.70 men, and for elderly women, 0.49 [10]. These estimates based on similar analytical techniques suggest that the heritability for static strength may be somewhat higher during adolescence than in young adulthood and old age.

For maximal dynamic strength as measured by isokinetic dynamometry there is a paucity of data since the protocol is more impractical in large field-studies. Heritabilities of eccentric and concentric dynamic strength of arm and leg muscles ranged from 0.29 to 0.87 [10].

Muscular power or explosive strength as measured by jumping tasks or the Wingate test provide additional insights into the heritability of dynamic strength. In a summary of six early twin and family studies characterized by small sample sizes and questionable zygosity determination, heritabilities for the vertical jump ranged between 0.82 and 0.93 for twin studies and 0.22 and 0.68 for family studies [10]. More recent twin studies based on the vertical and standing long jump or maximal power output in the Wingate test indicate comparable heritabilities, though analytical strategies vary. Estimated heritabilities were 0.67 for the squat jump, 0.45 for the counter-movement jump and 0.74 for maximal power developed in 5s in a Wingate test in 16 young adult male twin pairs [10]. With data aligned on age at PHV, sex differences were less apparent and reached significance only 3 years after PHV, 0.89 in girls and 0.61 in boys [5]. Limiting the analysis to twins at 10 years of age and including data for

parents suggested some genetic dominance was included in the heritability of 0.65, which was slightly lower than a heritability of 0.72 when only twins were used in the analyses [10]. In summary, data for adolescence do not provide evidence for clear age or sex differences either, although a divergence in heritabilities is suggested towards later adolescence in Belgian twins [5].

Aerobic Performance

Aerobic performance tests are both maximal and submaximal. Maximal aerobic power (maximal oxygen uptake) is measured under standardized laboratory conditions on a cycle ergometer or a treadmill and maximal or peak oxygen uptake is expressed per unit body mass. Submaximal aerobic performance is usually measured as the power output, at a heart rate of 150 or 170 beats per minute and is expressed per kg body mass (W/kg). Estimated heritabilities vary from 0.40 to 0.94 [9] which are due to the unequal quantitative value of reported data. If studies with largest samples size and best quality control are selected, results are more concordant. More recently structural equation modeling has been applied to aerobic performance. Genetic estimates vary between 0.69 and 0.87 for adjusted and unadjusted maximal aerobic performance [10]. Sibling correlations for submaximal aerobic performance in Canadian youth range between 0.12 and 0.45 with estimated heritabilities between 0.38 and 0.52. Estimates based on structural equation modeling vary between 0.28 and 0.55. However, spouse correlations for maximal and submaximal tests vary between 0.17 and 0.42 [2]. If the effect of this positive assortative mating is not taken into account in twin models, heritability estimates are theoretically biased downward.

Responsiveness to Training

Unmeasured genotype studies are still useful to estimate genetic variation in responses to training. Highly controlled studies with MZ and DZ twins and families have been performed using intermittent, aerobic and resistance strength training protocols.

Strength Training

Genotype*strength training interaction has been studied in a training study of 25 MZ and 16 DZ young adult male twin pairs, both F-tests and bivariate longitudinal model fitting were used to study evidence for strength-training specific genes or genotype-dependent responses to concentric high resistance strength training [8]. There was considerable interindividual variability in response to the 10-week resistance training protocol for the elbow flexors and the intrapair correlation for changes in 1RM in MZ twins was 0.46. Bivariate longitudinal model fitting indicated evidence for a 'training-induced' set of genes that explained about 19%-23 % of the post-training variance in 1RM, isometric and concentric strength at 120°/sec arm flexion. Although there was some evidence for genotype*strength training interaction, most of the genetic variance in post-training strength measures was shared with genetic factors that also explained pre-training variability.

Intermittent and Aerobic Training

Already in 1984 the group of Bouchard demonstrated a genotype*training interaction using standardized training protocols to improve maximum oxygen uptake in MZ twins [2]. Among 10 pairs of male MZ twins submitted to a standardized laboratory-controlled training program for 20 weeks, gains in absolute VO2max showed almost eight times more variance between pairs of twins than within pairs of twins. These results were confirmed in two additional twin studies [2].

THE MEASURED GENOTYPE APPROACH

Strength and Power

Linkage analysis was performed with polymorphic markers in genes of the myostatin pathway in the Leuven Genes for Muscular Strength Study, with suggestive linkage for knee extension and flexion with markers D2S118, D6S1051 and D11S4138, D13S1303, D12S1042, D12S85 and D12S78, but not with myostatin itself [11, 12]. Further fine-mapping of these regions (12q12-14 and 12q22-23) resulted in the identification of Activin receptor 1B and ATPase Ca++ transporting, cardiac slow twitch 2 as strength related genes [13, 14]. Genome wide linkage analyses by the same group identified regions in chromosomes 14 (14q24.3, 14q32.2), 2 (2q23.3, 2p24.2) and 18 (18q11.2, 18p11.31) to be linked with muscle size or strength [15].

The most recent update of the 'Human Gene Map for Performance and Health-Related Fitness Phenotypes [16] identified 20 genes associated with strength or anaerobic phenotypes. However, only a few showed replications, especially studies which showed associations with ACE (angiotensin I converting enzyme), ACTN3 (actinin alpha 3) and VDR (vitamin D receptor).

Aerobic Performance

The numbers of linkage studies that verify loci linked with aerobic performance are also limited. Linkage has been found with loci on 10 chromosomes (chromosomes 1, 4, 5, 7, 10, 13, 16, 18, 19 and 20). Association studies, both case-control studies (n=18) and cross-sectional studies (n=51) identified 22 genes associated with aerobic performance and another 7 genes associated with response to endurance training. Again, ACE was the gene with the highest number of positive findings. But the authors conclude (Bray *et al.* 2009, pp. 62) that; "The conflicting findings among the many studies for ACE gene exemplify the complexity of genetic studies for complex traits. Indeed despite the enormous amount of attention that the ACE gene has received, it is still not possible to conclude with certainty whether the common polymorphism in ACE is truly involved in human variation in fitness and performance phenotypes and their response to regular exercise".

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