The Human Gene Map for Performance and Health-Related Fitness Phenotypes: The 2006–2007 Update

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ABSTRACT

BRAY, M. S., J. M. HAGBERG, L. PÉRUSSE, T. RANKINEN, S. M. ROTH, B. WOLFARTH, and C. BOUCHARD. The Human Gene Map for Performance and Health-Related Fitness Phenotypes: The 2006–2007 Update. *Med. Sci. Sports Exerc.*, Vol. 41, No. 1, pp. 34–72, 2009. This update of the human gene map for physical performance and health-related fitness phenotypes covers the research advances reported in 2006 and 2007. The genes and markers with evidence of association or linkage with a performance or a fitness phenotype in sedentary or active people, in responses to acute exercise, or for training-induced adaptations are positioned on the map of all autosomes and sex chromosomes. Negative studies are reviewed, but a gene or a locus must be supported by at least one positive study before being inserted on the map. A brief discussion on the nature of the evidence and on what to look for in assessing human genetic studies of relevance to fitness and performance is offered in the introduction, followed by a review of all studies published in 2006 and 2007. The findings from these new studies are added to the appropriate tables that are designed to serve as the cumulative summary of all publications with positive genetic associations available to date for a given phenotype and study design. The fitness and performance map now includes 214 autosomal gene entries and quantitative trait loci plus seven others on the X chromosome. Moreover, there are 18 mitochondrial genes that have been shown to influence fitness and performance phenotypes. Thus, the map is growing in complexity. Although the map is exhaustive for currently published accounts of genes and exercise associations and linkages, there are undoubtedly many more gene–exercise interaction effects that have not even been considered thus far. Finally, it should be appreciated that most studies reported to date are based on small sample sizes and cannot therefore provide definitive evidence that DNA sequence variants in a given gene are reliably associated with human variation in fitness and performance traits.
Key Words: CANDIDATE GENES, QUANTITATIVE TRAIT LOCI, LINKAGE, GENETIC VARIANTS, MITOCHONDRIAL GENOME, NUCLEAR GENOME, GENETICS

In this seventh installment of the human gene map for performance and health-related fitness phenotypes published in this journal, we cover the peer-reviewed literature published by the end of December 2007. The focus of the review is on the new material published in 2006 and 2007. The search for relevant publications is 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 (e.g., exercise, physical activity [PA], performance, training, genetics, genotype, polymorphism, mutation, linkage). Electronic prepublications, that is, articles that are made available on the Web site of a journal before being published in print are not included in the current review if there were not available in print by the end of December 2007. The literature search is limited to articles published in English, French, German, and Finnish.

The goal of the human gene map for fitness and performance is to review all genetic loci and markers

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Submitted for publication April 2008.
Accepted for publication June 2008.

0195-9131/09/4101-0034/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0b013e3181844179

shown to be related to physical performance or health-related fitness phenotypes in at least one study. Negative studies are briefly reviewed for a balanced presentation of the evidence. However, the nonsignificant results are not incorporated in the summary tables. Although this review focuses on the advances reported in 2006 and 2007, the summary tables are meant to represent a full compendium of all positive findings reported to date for a given fitness or performance phenotype and a particular study design.

The *physical performance* phenotypes for which genetic data are available include cardiorespiratory endurance, elite endurance athlete status, muscle strength, other muscle performance traits, and exercise intolerance of variable degrees. Consistent with the previous reviews, the phenotypes of *health-related fitness* are grouped under the following categories: hemodynamic traits including exercise heart rate (HR), blood pressure (BP), and heart morphology; anthropometry and body composition; insulin and glucose metabolism; and blood lipid, lipoprotein, and hemostatic factors. Here, we are not concerned about the effects of specific genes on these phenotypes unless the focus is on exercise, exercise training, athletes or active people compared with controls or inactive individuals, or exercise intolerance. For instance, genetic studies that have focused

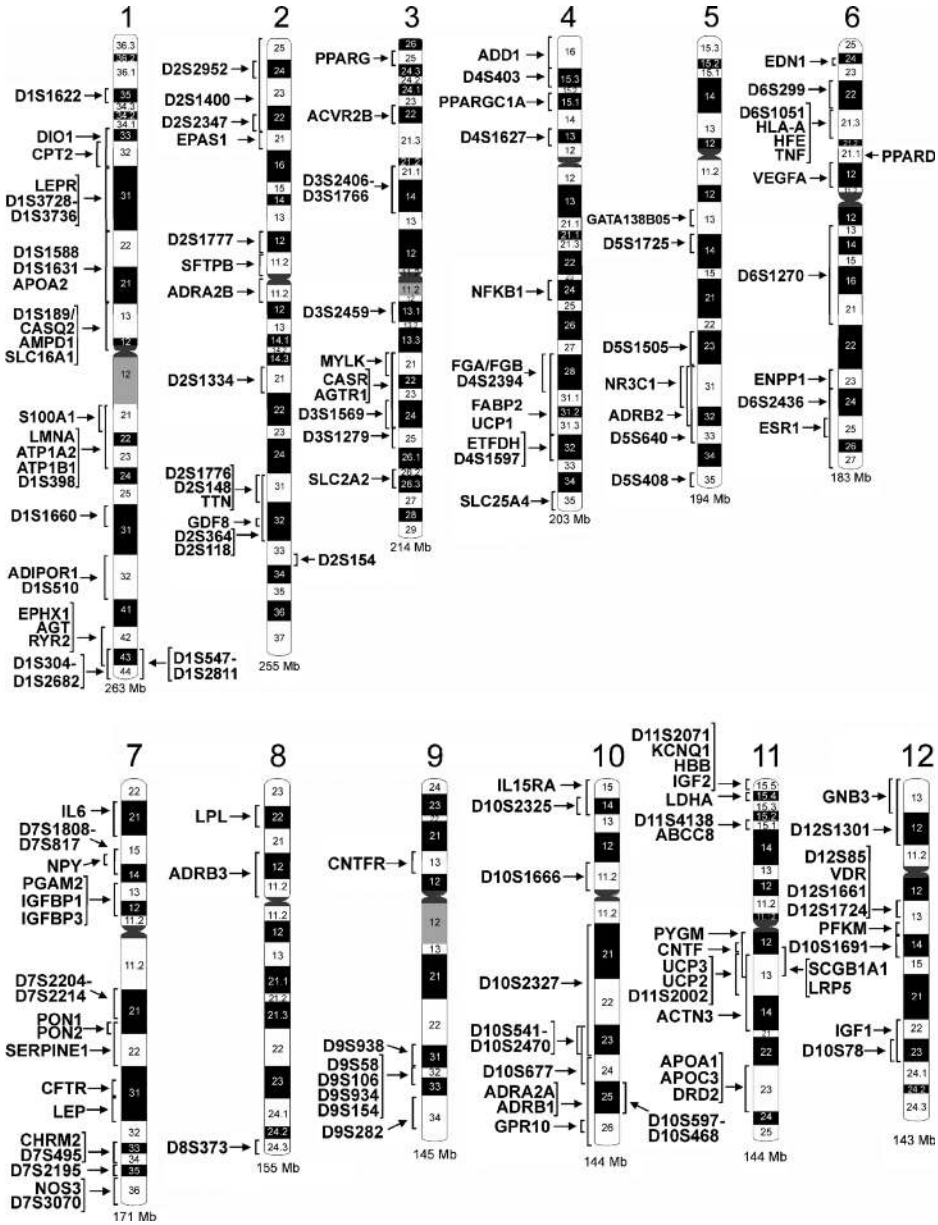

FIGURE 1—The 2006–2007 human performance and health-related fitness gene map. The map includes all gene entries and QTL that have shown associations or linkages with exercise-related phenotypes summarized in the article. The chromosomes and their regions are from the Gene Map of the Human Genome Web site hosted by the National Center for Biotechnology Information, National Institutes of Health, Bethesda, MD (http://www.ncbi.nlm.nih.gov/). The chromosome number and the size of each chromosome in Megabases (Mb) are given at the top and bottom of the chromosomes, respectively. Loci abbreviations and full names are given in Table 1.

on body mass index (BMI), adiposity, fat-free mass, adipose tissue distribution, or various abdominal fat phenotypes are not considered unless there was an exercise-related issue addressed in the articles.

The studies incorporated in the review are fully referenced so that the interested reader can access the original articles. Of interest to some could be the early observations made on athletes, particularly Olympic athletes. The results of these early case–control studies typically based on common red blood cell antigens or enzymes were essentially negative and are not reviewed in this edition of the map. The interested reader can consult the first installment of the gene map for a complete summary of these early reports (235).

The 2007 synthesis of the human performance and health-related fitness gene map for the autosomes and the sex chromosomes is summarized in Figure 1. The 2007 update includes 239 gene entries and quantitative trait loci (QTL), 52 more than the 2005 depiction of the map. We have also depicted in Figure 2 the mitochondrial genes that have been shown to be associated with fitness and performance phenotypes. Table 1 provides a list of all genes or loci, cytogenic locations, and conventional symbols used in this review. The terminology and the symbols used are as defined in the legend to Table 1.

In 2007, an expert panel from the National Cancer Institute and the National Human Genome Research Institute of the US National Institutes of Health published a comprehensive set of recommendations on factors to consider in evaluating genotype–phenotype association reports in assessing the soundness of an initial association report and in establishing the conditions for valid replication studies (36). The report contains a wealth of information on what constitutes high-quality association studies with complex human traits. Some of the topics raised are of particular importance to those interested in evaluating the quality of the information available on specific genes and fitness and performance phenotypes. These topics have to do with sample size, quality of the phenotype measurement, quality of the exercise or activity exposure, study design, adjustment for multiple testing, population stratification, publication biases, genotyping errors, and replication studies.

Most studies reviewed in this inventory were underpowered to establish a definitive genotype–phenotype relationship. Because the effect size of a given gene on fitness or performance-related traits is generally small, the sample size necessary to achieve a significant risk ratio with a credible, very small P value is quite high, well above 1000 and preferably above 10,000 cases with as many controls. The optimal sample size will vary depending on whether the phenotype is precisely and reliably measured; the less error variance, the lower the sample size. The same is true for the "exposure to exercise" variable. If the study deals with the response to exercise and the subjects are exercise trained in a well-controlled and fully monitored laboratory environment, the sample size required to have sufficient power will be lower than in a situation where subjects are asked to exercise on their own at home during their leisure time. Even when a study generates a very small P value for the risk ratio associated with a genotype at a given gene, the results should be interpreted with caution until replication studies confirm the initial finding.

In assessing the quality of the studies reviewed in this inventory, the reader should also consider whether the

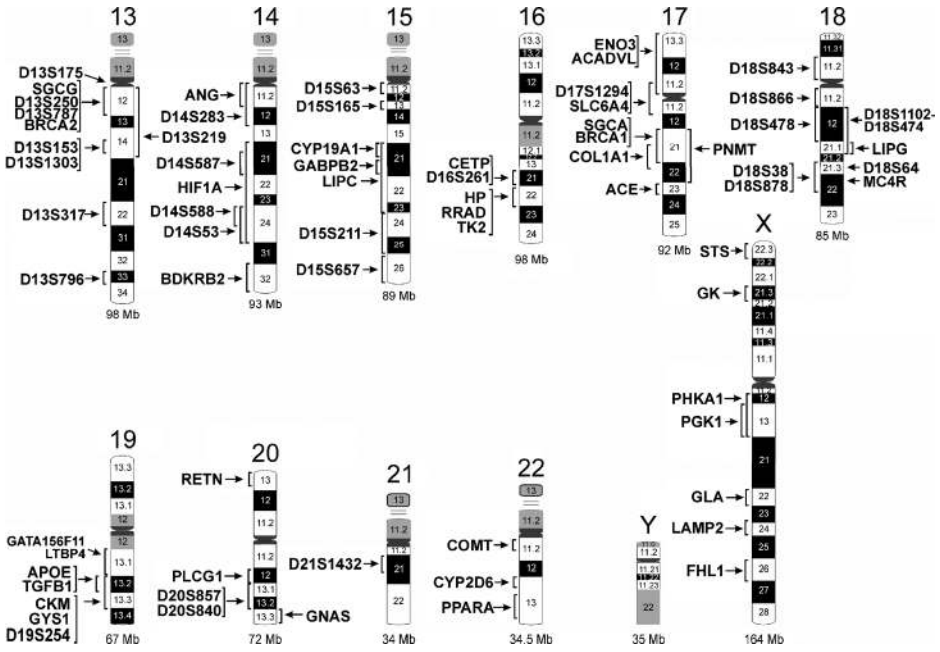

FIGURE 1 —(Continued).

threshold *P* value reported was adjusted for multiple testing, population stratification, or some other uncontrolled factor, including nonrandom genotyping errors, which could have created a spurious association. It is important to verify if the design of the study and the analytical approaches were appropriate and sufficiently described to allow replication in another laboratory. It is also useful to recognize that there is a very strong tendency to publish studies with positive results despite all their weaknesses. Indeed, in the end, very few negative studies reach publication. This strong bias precludes the use of published reports on a given gene–phenotype association to produce a meaningful meta-analysis with the hope that the latter will compensate somehow for the chronic lack of statistical power in the individual studies.

It remains our collective goal to make this publication a useful resource for those who teach undergraduate and graduate students about the role of inheritance on fitness and performance traits and the impact of genetic variation on health and prevention of diseases. It is our hope that these updates of the fitness and performance gene map will increase the interest and motivation of exercise scientists and physicians for genetic studies. It is also our hope that this compendium will motivate scientists from other fields to evaluate the contribution of exercise or leisure-time PA in their genetic studies.

PERFORMANCE PHENOTYPES

Endurance Phenotypes

Case–control studies. A total of 10 articles from case–control studies were published in the 2006–2007 period (Table 2). The functional bradykinin beta 2 receptor (BDKRB2) −9/+9 polymorphism, which consists of the presence/absence of a 9-base pair (bp) repeat sequence in exon 1, was investigated in ironman triathlon athletes and healthy controls (267). The fast finishers of the triathlon showed a higher number of −9/−9 genotypes compared with the controls. The nitric oxide synthase 3 (NOS3) G894T genotypes were also investigated for association in this athlete group, and a significant linear trend of increasing frequency of the G/G genotypes among tertiles of the triathlon finishers from fastest to slowest was observed. The same linear trend was observed for the combined +9/+9 and GG multivariate genotype groups. In addition, the combination of −9/−9 genotypes and G-allele

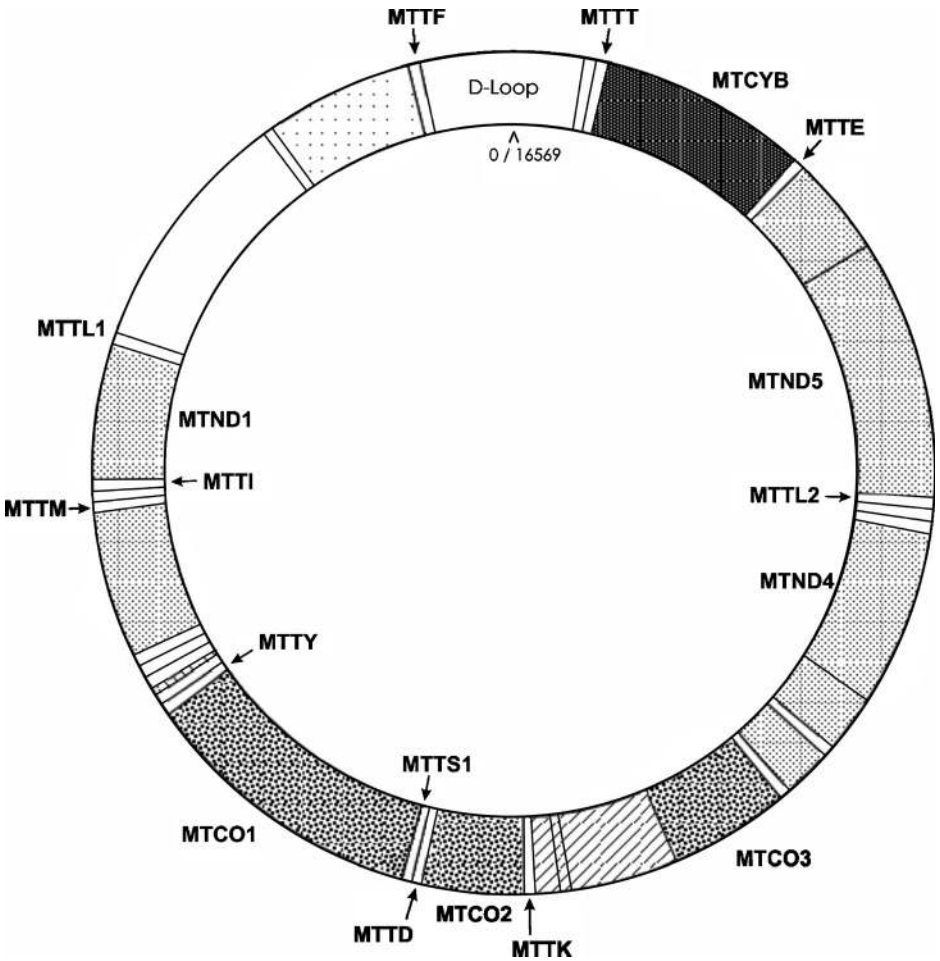

FIGURE 2—Mitochondrial genes that have been shown to be associated with exercise intolerance, fitness, or performance-related phenotypes. The location of the specific sequence variants is defined in Tables 3 and 14. The mitochondrial DNA locations are available at http://www.mitomap.org.

TABLE 1. Symbols, full names, and cytogenic location of nuclear and mitochondrial genes of the 2006–2007 human gene map for performance and health-related fitness phenotypes.

Gene or Locus	Name	Location
A B		
ABCC8 (SUR1)	ATP-binding cassette, subfamily C (CFTR/MRP), member 8	11p15.1
ACADVL	Acyl-coenzyme A dehydrogenase, very long chain	17p13–p11
ACE	Angiotensin I converting enzyme	17q23
ACTN3	Actinin, alpha 3	11q13–q14
ACVR2B	Activin A receptor, type IIB	3p22
ADD1	Adducin 1 (alpha)	4p16.3
ADIPOR1	Adiponectin receptor 1	1q32
ADRA2A	Adrenergic, alpha 2A, receptor	10q24–q26
ADRA2B	Adrenergic, alpha 2B, receptor	2q11.1–q11.2
ADRB1	Adrenergic, beta 1, receptor	10q24–q26
ADRB2	Adrenergic, beta 2, receptor	5q31–q32
ADRB3	Adrenergic, beta 3, receptor	8p12–p11.2
AGT	Angiotensinogen	1q42–q43
AGTR1	Angiotensin II receptor, type 1	3q21–q25
AMPD1	Adenosine monophosphate deaminase 1	1p13
ANG	Angiogenin, ribonuclease, RNase A family, 5	14q11.1–q11.2
APOA1	Apolipoprotein A-I	11q23
APOA2	Apolipoprotein A-II	1q21–q23
APOC3	Apolipoprotein C-III	11q23
APOE	Apolipoprotein E	19q13.2
ATP1A2	ATPase, Na^+/K^+ transporting, alpha 2(+) polypeptide	1q21–q23
ATP1B1	ATPase, Na^+/K^+ transporting, beta 1 polypeptide	1q22–q25
BDKRB2	Bradykinin receptor B2	14q32.1–q32.2
BRCA1	Breast cancer 1, early onset	17q21
BRCA2	Breast cancer 2, early onset	13q12.3
C D E F G		
CASQ2	Calsequestrin 2 (cardiac muscle)	1p13.3–p11
CASR	Calcium-sensing receptor	3q21–q24
CETP	Cholesteryl ester transfer protein, plasma	16q21
CFTR	Cystic fibrosis transmembrane conductance regulator, ATP-binding cassette (subfamily C, member 7)	7q31.2
CHRM2	Cholinergic receptor, muscarinic 2	7q31–q35
CKM	Creatine kinase, muscle	19q13.2–q13.3
CNTF	Ciliary neurotrophic factor	11q12.2
CNTFR	Ciliary neurotrophic factor receptor	9p13
CPT2	Carnitine palmitoyltransferase II	1p32
COL1A1	Collagen, type I, alpha 1	17q21.3–q22.1
COMT	Catechol-O-methyltransferase	22q11.21
CYP19A1	Cytochrome P450, family 19, subfamily A, polypeptide 1 (aromatase)	15q21.1
CYP2D6	cytochrome P450, family 2, subfamily D, polypeptide 6	22q13.1
DIO1	Deiodinase, iodothyronine, type I	1p33–p32
DRD2	Dopamine receptor D2	11q23
EDN1	Endothelin 1	6p24.1
ENO3	Enolase 3 (beta, muscle)	17pter-p11
ENPP1	Ectonucleotide pyrophosphatase/ phosphodiesterase 1	6q22–q23
EPAS1	Endothelial PAS domain protein 1	2p21–p16
EPHX1	Epoxide hydrolase 1, microsomal (xenobiotic)	1q42.1
ESR1	Estrogen receptor 1	6q25.1
ETFDH	Electron-transferring flavoprotein dehydrogenase	4q32–q35
FABP2	Fatty acid binding protein 2, intestinal	4q28–q31
FGA	Fibrinogen, A alpha polypeptide	4q28
FGB	Fibrinogen, B beta polypeptide	4q28
FHL1	Four and half LIM domains 1	Xq26
GABPB2	GA binding protein transcription factor, beta subunit 2	15q21.2
GDF8 (MSTN)	Growth differentiation factor 8 (myostatin)	2q32.2
GK	Glycerol kinase	Xp21.3
GLA	Galactosidase, alpha	Xq22
GNAS	GNAS complex locus	20q13.3

TABLE 1. (Continued).

Gene or Locus	Name	Location
C D E F G		
GNB3	Guanine nucleotide binding protein (G protein), beta polypeptide 3	12p13
GPR10	G-protein-coupled receptor 10	10q26.13
GYS1	Glycogen synthase 1 (muscle)	19q13.3
H I K L M		
HBB	Hemoglobin, beta	11p15.5
HFE	Hemochromatosis	6p21.3
HIF1A	Hypoxia-inducible factor 1, alpha subunit	14q21–q24
HLA-A	Major histocompatibility complex, class I, A	6p21.3
HP	Haptoglobin	16q22.1
IGF1	Insulin-like growth factor 1	12q22–q23
IGF2	Insulin-like growth factor 2	11p15.5
IGFBP1	Insulin-like growth factor binding protein 1	7p13–p12
IGFBP3	Insulin-like growth factor binding protein 3	7p13–p12
IL15RA	Interleukin 15 receptor, alpha	10p15–p14
IL6	Interleukin 6	7p21
KCNQ1	Potassium voltage-gated channel, KQT-like subfamily, member 1	11p15.5
LAMP2	Lysosomal-associated membrane protein 2	Xq24
LDHA	Lactate dehydrogenase A	11p15.4
LEP	Leptin	7q31.3
LEPR	Leptin receptor	1p31
LIPC	Lipase, hepatic	15q21–q23
LIPG	Lipase, endothelial	18q21.1
LMNA	Lamin A/C	1q21.2–q21.3
LPL	Lipoprotein lipase	8p22
LRP5	Low-density lipoprotein receptor-related protein 5	11q13.4
LTBP4	Latent transforming growth factor beta binding protein 4	19q13.1–q13.2
MC4R	Melanocortin 4 receptor	18q22
MTCO1	Cytochrome *c* oxidase subunit I	mtDNA 5904–7445
MTCO2	Cytochrome *c* oxidase subunit II	mtDNA 7586–8269
MTCO3	Cytochrome *c* oxidase subunit III	mtDNA 9207–9990
MTCYB	Cytochrome *b*	mtDNA 14747–15887
MTND1	NADH dehydrogenase subunit 1	mtDNA 3307–4262
MTND4	NADH dehydrogenase subunit 4	mtDNA 10760–12137
MTND5	NADH dehydrogenase subunit 5	mtDNA 12337–14148
MTTD	Transfer RNA, mitochondrial, aspartic acid	mtDNA 7518–7585
MTTE	Transfer RNA, mitochondrial, glutamic acid	mtDNA 14674–14742
MTTF	Transfer RNA, mitochondrial, phenylalanine	mtDNA 577–674
MTTI	Transfer RNA, mitochondrial, isoleucine	mtDNA 4263–4331
MTTK	Transfer RNA, mitochondrial, lysine	mtDNA 8295–8364
MTTL1	Transfer RNA, mitochondrial, leucine 1 (UUR)	mtDNA 3230–3304
MTTL2	Transfer RNA, mitochondrial, leucine 2 (CUN)	mtDNA 12266–12336
MTTM	Transfer RNA, mitochondrial, methionine	mtDNA 4402–4469
MTTS1	Transfer RNA, mitochondrial, serine 1 (UCN)	mtDNA 7445–7516
MTTT	Transfer RNA, mitochondrial, threonine	mtDNA 15888–15953
MTTY	Transfer RNA, mitochondrial, tyrosine	mtDNA 5826–5891
MYLK	Myosin, light polypeptide kinase	3q21
N O P Q R S T U V		
NFKB1	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (p105)	4q24
NOS3	Nitric oxide synthase 3 (endothelial cell)	7q36
NPY	Neuropeptide Y	7p15.1
NR3C1	Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	5q31
PFKM	Phosphofructokinase, muscle	12q13.3
PGAM2	Phosphoglycerate mutase 2 (muscle)	7p13–p12
PGK1	Phosphoglycerate kinase 1	Xq13
PHKA1	Phosphorylase kinase, alpha 1 (muscle)	Xq12–q13
PLCG1	Phospholipase C, gamma 1	20q12–q13.1
PNMT	Phenylethanolamine *N*-methyltransferase	17q21–q22
PON1	Paraoxonase 1	7q21.3

(continued on next page)

TABLE 1. (Continued).

Gene or Locus	Name	Location
N O P Q R S T U V		
PON2	Paraoxonase 2	7q21.3
PPARA	Peroxisome proliferative activated receptor, alpha	22q13.31
PPARD	Peroxisome proliferative activated receptor, delta	6p21.2–p21.1
PPARG	Peroxisome proliferative activated receptor, gamma	3p25
PPARGC1A	Peroxisome proliferative activated receptor, gamma, coactivator 1, alpha	4p15.1
PYGM	Phosphorylase, glycogen, muscle	11q12–q13.2
RETN	Resistin	19p13.2
RYR2	Ryanodine receptor 2 (cardiac)	1q42.1–q43
S100A1	S100 calcium binding protein A1	1q21
SCGB1A1	Secretoglobin, family 1A, member 1	11q12.3–q13.1
SERPINE1	serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	7q21.3–q22
SFTPB	Surfactant, pulmonary-associated protein B	2p12–p11.2
SGCA	Sarcoglycan, alpha (50 kDa dystrophin-associated glycoprotein)	17q21
SGCG	Sarcoglycan, gamma (35 kDa dystrophin-associated glycoprotein)	13q12
SLC16A1	Solute carrier family 16, member 1 (monocarboxylic acid transporter 1)	1p12
SLC25A4	Solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4	4q35
SLC2A2 (GLUT2)	Solute carrier family 2 (facilitated glucose transporter), member 2	3q26
SLC6A4	Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	17q11.1
STS	Steroid sulfatase (microsomal)	Xp22.32
TGFB1	Transforming growth factor, beta 1	19q13.1
TK2	Thymidine kinase 2, mitochondrial	16q22–q23.1
TNF	Tumor necrosis factor (TNF superfamily, member 2)	6p21.3
TTN	Titin	2q31
UCP1	Uncoupling protein 1	4q28–q31
UCP2	Uncoupling protein 2	11q13
UCP3	Uncoupling protein 3	11q13
VDR	Vitamin D (1,25-dihydroxyvitamin D3) receptor	12q13.11
VEGFA	Vascular endothelial growth factor A	6p12

The gene symbols, names, and cytogenetic locations are from the Entrez Gene Web site (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene) available from the National Center for Biotechnology Information. For mitochondrial DNA, locations are from the human mitochondrial genome database (http://www.mitomap.org).

carriers of the NOS3 polymorphism was significantly higher in the fast triathletes (267).

Two case–control studies found significant results for the angiotensin-converting enzyme (*ACE*) insertion/deletion (I/D) polymorphism. Hruskovicova et al. (110) reported significantly different genotype and allele distributions between elite marathon runners and in-line marathoners compared with a group of sedentary controls. In Israeli endurance athletes, a higher number of D-allele carriers and D/D genotypes was seen comparing those athletes to healthy individuals ($P = 0.01$), with an even higher level of significance for the comparison with sprint athletes ($P = 0.002$) (5). Significantly different genotype frequencies ($P < 0.0001$) were reported for the intron 7 G/C genetic variant in the peroxisome proliferator-activated receptor alpha (*PPARA*) gene between endurance- and power-oriented athletes and nonathlete controls. In addition, the authors reported an association between the intron 7 G/C genotypes and the muscle fiber type distribution, with G/G homozygotes having a significantly higher percentage of slow-twitch fibers ($P = 0.003$) (3). Wolfarth et al. (344) compared elite endurance athletes with sedentary controls for the Arg16Gly polymorphism in the beta 2 adrenergic receptor (*ADRB2*) gene. An excess of Gly-allele carriers was seen in the sedentary controls indicating a negative association of this allele with respect to the performance status.

Three different case–control cohorts were investigated with respect to the actinin alpha 3 (*ACTN3*) gene R577X polymorphism. None of the articles reported different allele or genotype distributions comparing professional cyclists, ironman triathletes, and a mixed group of different Italian athletes with healthy controls (163,209,266). The distribution of the *ACE* I/D polymorphism was investigated in Korean male elite athletes, but no difference in genotype or allele distribution was found between this group and unrelated nonathletes (200). Finally, in a South African cohort of ironman triathlon athletes, there was no difference for the growth hormone 1 (*GH1*) 1663 T > A polymorphism genotype frequencies for 155 control subjects in comparison to the 169 fastest finishers of the triathlon event (331).

Cross-sectional association studies. $\dot{V}O_{2max}$ and vascular endothelial growth factor A (*VEGFA*) haplotype data were analyzed by Prior et al. (223) in 148 white and black subjects (Table 3). Besides an association of these haplotypes with $\dot{V}O_{2max}$ before and after training, they were able to show an impact of the gene polymorphisms on *VEGFA* gene expression in human myoblasts. In a large cohort of CAD patients, the associations of two beta 1 adrenergic receptor (*ADRB1*) gene polymorphisms, Ser49Gly and Gly389Arg, were tested before and after 3 months of exercise training. They found an association between the Ser49Gly polymorphism and the haplotypes of the Ser49Gly and the Gly389Arg polymorphisms with aerobic power but not with the response to physical training (51). In premenopausal sedentary women, different measures of body composition and performance were obtained and analyzed for association with variation in the insulin-like growth factor 1 (*IGF1*) gene. Results showed that carriers of a 189-bp allele of a CT repeat ($IGF1_{189}$) perform better in activities requiring exercise economy and endurance performance (157). Dekany et al. (53) investigated 74 subjects analyzing exercise efficiency associated with the *ACE* I/D polymorphism. They described the *ACE* I-allele as a genetic marker for higher endurance efficiency in acute physical activities. Tanabe et al. (295) examined the *ACE* I/D genotype for association with clinical characteristics and survival. D-allele carriers also had a significantly lower 6-min walk test distance compared with homozygotes for the I-allele (330 ± 102 vs 381 ± 85 m; $P < 0.046$). This association remained when only the medically treated patients were examined, with D carriers having a mean distance of 337 ± 92 m compared with 418 ± 62 m for the I/I homozygotes ($P < 0.05$) (295).

Polymorphisms in several xenobiotic metabolizing enzyme genes, glutathione S transferase pi (*GSTP1*), microsomal epoxide hydrolase (*EPHX1*), transforming growth factor beta 1 (*TGFB1*), serpin peptidase inhibitor E2 (*SERPINE2*), and surfactant, pulmonary-associated protein B (*SFTPB*), were examined for association to exercise capacity phenotypes in patients with emphysema enrolled in the National Emphysema Treatment Trial. Maximal exercise capacity was determined for all subjects via the use of cycle ergometry. Single nucleotide polymorphisms (SNP) in *EPHX1* (rs1877724 and rs1051740) were associated with maximum work and low exercise capacity (P = 0.0002–0.03), whereas polymorphisms in *LTBP4* (rs2303729, rs1131620, rs1051303, and rs2077407) were associated with maximum work (P = 0.0001–0.03), low exercise capacity (P = 0.0001–0.02), and 6-min walking test distance (P = 0.04–0.05). A short tandem repeat marker in the *SFTPB* gene (D2S388) was associated with low exercise capacity (P = 0.05) and 6-min walking test distance (P = 0.005) in these patients (106).

In addition, four articles with pure cross-sectional approaches showed no significant associations of endurance phenotypes and different polymorphisms in *ADRB2* (285), *NOS3* (96), *ACE* (45), and solute carrier family 6 (neurotransmitter transporter, serotonin) member 4 (*SLC6A4*) (265) genes.

Association studies with training response phenotypes. In the HERITAGE Family Study, a peroxisome proliferator-activated receptor delta (*PPARD*) polymorphism was associated with physical performance. In black subjects, the exon 4 + 15 C/C (rs2016520) homozygotes showed a smaller training-induced increase in maximal oxygen consumption compared with the C/T and the T/T genotypes. Similarly, in black subjects, a lower training response in maximal power output was observed in the exon 4 + 15 C/C homozygotes compared with carriers of the T-allele. In white subjects, a similar trend was observed (99). In a lifestyle intervention study of diet and PA, the rs2267668 SNP in the *PPARD* and the Gly482Ser polymorphism in the peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (*PPARGC1A*) gene showed associations with the changes in anaerobic threshold (289). The authors reported lower anaerobic threshold response in carriers of the G-allele of SNP rs2267668 compared with the A/A genotype. Less increase in anaerobic threshold was also observed in carriers of the Ser482-encoding allele compared with the Gly/Gly genotype (P < 0.004). In addition, the authors reported evidence for additive effects of the *PPARD* and the *PPARGC1A* SNP on the effectiveness of aerobic exercise training to increase anaerobic threshold (289). In an 18-wk training study with 102 recruits from China, two polymorphisms in the hemoglobin beta (*HBB*) gene were associated with the training response of running economy (103). In the same cohort, associations between $\dot{V}O_{2max}$ values and beta 2 subunit of GA binding protein transcription factor (*GABPB2*) genotype were observed for the rs12594956, rs8031031, and rs7181866 loci. Individuals carrying the ATG haplotype of all three loci had 57.5% greater exercise training-related improvement in running economy (measured as $\dot{V}O_2$ during submaximal exercise) than noncarriers (102).

Three *ACE* articles showed associations in the context of training response. Seventeen Korean women participated in a 12-wk endurance training program. The *ACE* T3892C polymorphism was significantly associated with the response in $\dot{V}O_{2max}$ after the endurance training. Angiotensinogen (*AGT*) and angiotensin II receptor type 1 (*AGTR1*) and type 2 (*AGTR2*) polymorphisms showed no association with the training effects (16). A study with 933 CAD patients from the CAREGENE cohort showed an independent association of the *ACE* I/D polymorphism with the aerobic power response to physical training in favor of the I/I genotype (52). A Turkish cohort of 55 nonathlete females trained three times per week for 6 wk. The major measurements were 30-min running performance and other submaximal measures. The authors report an association of the *ACE* I/I genotype with better improvements in medium duration aerobic endurance performance, whereas *ACE* D/D genotype was more advantageous for shorter duration and higher intensity activities (32). In an investigation of the muscle creatine kinase (*CKM*) *Nco*I polymorphism after an 18-wk 5000-m running program, Zhou et al. (356) reported a significant increase in running economy and adaptation to training for the A/G genotype compared with the A/A and G/G genotypes.

Polymorphisms of the mitochondrial transcription factor A were investigated before and after an 18-wk controlled endurance training program in Chinese nonathletes. They found no association and concluded that these polymorphisms do not predict endurance capacity or its trainability in Chinese male (101). Two more studies investigated endurance phenotypes before and after training targeting polymorphisms in the muscarinic 2 cholinergic receptor (*CHRM2*) gene and a promoter polymorphism in the apolipoprotein A1 (*APOA1*) gene. Both studies found no associations with $\dot{V}O_{2max}$ at baseline or after the training intervention (100,259).

Linkage studies. No new linkage studies on performance-related phenotypes were published in 2006–2007 (Table 4).

Muscle Strength Phenotypes

Case–control studies. In 2006–2007, three studies reported case–control associations for athletes specializing in strength-related or anaerobic performance activities. All such studies are shown in Table 5, although some crossover exists with Table 2 for those studies that also include endurance athletes.

Ahmetov et al. (3) investigated the intron 7 G/C polymorphism in the peroxisome proliferator-activated receptor

TABLE 2. Endurance phenotypes and case–control studies (DNA polymorphisms).

		Athletes			Controls			
Gene	**Location**	***N***	**Sports**	**Frequency**	***N***	**Frequency**	***P* Value**	**Reference**
AMPD1	1p13	104	Endurance	C: 0.045 T: 0.955	100	C: 0.085 T: 0.915	<0.05	(261)
PPARGC1A	4p15.1	104	Endurance	Ser: 0.29 Gly: 0.71	100	Ser: 0.40 Gly: 0.60	0.01	(161)
ADRB2	5q31–q32	303	Endurance	Arg/Arg: 0.14 Arg/Gly: 0.45 Gly/Gly: 0.38 Arg: 0.39 Gly: 0.61	297	Arg/Arg: 0.09 Arg/Gly: 0.50 Gly/Gly: 0.41 Arg: 0.35 Gly: 0.65	0.03	(344)
ADRA2A	10q24–q26	140	Endurance	6.7/6.7: 0.77 6.7/6.3: 0.21 6.3/6.3: 0.02 6.7: 0.88 6.3: 0.12	141	6.7/6.7: 0.62 6.7/6.3: 0.34 6.3/6.3: 0.04 6.7: 0.8 6.3: 0.2	0.037 0.011	(345)
BDKRB2	14q32.1	144	Triathlon	−9/−9: 0.30 −9/+9: 0.46 +9/+9: 0.24 −9: 0.51 +9: 0.49	202	−9/−9: 0.19 −9/+9: 0.58 +9/+9: 0.23 −9: 0.46 +9: 0.54	0.042	(267)
CE	17q23	64	Endurance	II: 0.30 ID: 0.55 DD: 0.16 I: 0.57 D: 0.43	118	II: 0.18 ID: 0.51 DD: 0.32 I: 0.43 D: 0.57	0.03 0.02	(79)
		79	Running	I: 0.57 D: 0.43	Ref. Pop.	I: 0.49 D: 0.51	0.039	(189)
		25	Mountaineering	NA	Ref. Pop.	NA	0.02 0.003	(180)
		60	Elite athletes (cycling, running, handball)	II: 0.25 ID: 0.58 DD: 0.17 I: 0.54 D: 0.46	Ref. Pop.	II: 0.16 ID: 0.45 DD: 0.39 I: 0.38 D: 0.62	0.0009	(4)
		35	Middle distance athletes (subsample of 217 Russian athletes)	II: 0.37 ID: 0.51 DD: 0.12 I: 0.63 D: 0.37	449	II: 0.23 ID: 0.52 DD: 0.24 I: 0.5 D: 0.5	0.032	(193)
		33	Olympic aerobic athletes	II: 0.30 ID: 0.30 DD: 0.39 I: 0.45 D: 0.55	152	II: 0.13 ID: 0.43 DD: 0.44 I: 0.34 D: 0.66	0.05	(269)
		80	University athletes	II: 0.14 ID: 0.36 DD: 0.5 I: 0.32 D: 0.68	80	II: 0.11 ID: 0.19 DD: 0.70 I: 0.21 D: 0.79	0.026	(312)
		100	Triathlon	I: 0.52 D: 0.48	166	I: 0.42 D: 0.58	0.036	(39)
		50	Cyclists	I: 0.35 D: 0.65	119	I: 0.42 D: 0.58	<0.001	(162)
		27	Runners	I: 0.54 D: 0.46				
		20	Elite marathon runners	II: 0.30 ID: 0.70 DD: 0.00 I: 0.65 D: 0.35	252	II: 0.30 ID: 0.70 DD: 0.00 I: 0.65 D: 0.35	<0.001 <0.001	(110)
		18	In-line skaters	II: 0.28 ID: 0.67 DD: 0.05 I: 0.61 D: 0.39			<0.001 <0.01	
		79	Marathon runners	II: 0.09 ID: 0.29 DD: 0.62 I: 0.23 D: 0.77	247	II: 0.10 ID: 0.46 DD: 0.43 I: 0.34 D: 0.66	0.01 0.01	(5)
PPARA	22q13.31	491	Endurance	GG: 0.80 GC: 0.18 CC: 0.02	1242	GG: 0.70 GC: 0.27 CC: 0.03	0.0001	(3)

(continued on next page)

TABLE 2. (Continued).

Gene	Location	Athletes N	Athletes Sports	Athletes Frequency	Controls N	Controls Frequency	P Value	Reference
				G: 0.89		G: 0.84	0.0001	
				C: 0.11		C: 0.16		
		115	Mixed	GG: 0.67			0.012	
				GC: 0.25				
				CC: 0.08				
				G: 0.80			NS	
				C: 0.20				
mtDNA haplogroup*	mtDNA*	52	Endurance	H: 0.52	1060	H: 0.48	0.023†	(198)
				V: 0.058		V: 0.048		
				U: 0.21		U: 0.24		
				K: 0		K: 0.045		
				T: 0.058		T: 0.036		
				J: 0.019		J: 0.048		
				W: 0.058		W: 0.044		
				I: 0.077		I: 0.028		
				X: 0		X: 0.011		
		89	Sprint	H: 0.47				
				V: 0.079				
				U: 0.15				
				K: 0.09				
				T: 0.045				
				J: 0.067				
				W: 0.067				
				I: 0				
				X: 0.023				

* Haplogroups were constructed from several mitochondrial DNA polymorphisms.
† *P* value for the difference between endurance and sprint athletes; significance between athletes and controls was not reported.
NA, not applicable; NS, not significant.

alpha (*PPARA*) gene in 786 Russian male and female athletes and 1242 controls. The genotype frequencies did not differ between athletes and controls when sport stratification was ignored; however, when sport stratification was considered, a higher C-allele frequency was observed in anaerobic power athletes compared with controls ($P < 0.001$) as well as a lower C-allele frequency in aerobic athletes ($P = 0.029$). This finding was observed in both men and women. Analysis of muscle fiber type in a subset of 40 control men revealed significantly lower type I fiber proportions in the C/C genotype carriers ($P < 0.001$).

Yang et al. (351) studied the *ACTN3* gene locus and its nonsense R577X polymorphism in African athletes and examined X-allele frequencies in relation to African controls. The authors did not observe any significant genotype frequency differences between Nigerian sprinters and controls, although the very low X-allele frequency in this population prevented complete analysis. Nonetheless, the authors were able to conclude that the low X-allele frequency in the population in general points to at most a limited role for this polymorphism in African athletes.

An examination of the *ACE* I/D polymorphism in Korean athletes and controls did not yield significant results, although the 139 male athletes had heterogeneous sport backgrounds, which limited analysis against the 163 controls (200).

Association studies. The studies reporting candidate gene associations with muscle strength or anaerobic performance phenotypes are summarized in Table 6. In 2006–2007, 16 studies reported positive genetic associations with muscle strength-related phenotypes, although several studies reported mixed findings for specific genes or polymorphisms within gene regions.

The *ACTN3* gene and its nonsense R577X polymorphism has generated considerable attention in the past few years and was the focus of three association studies in this area in 2006–2007. Moran et al. (184) examined 40-m sprint performance in 992 Greek adolescents genotyped for the *ACTN3* R/X polymorphism. Male, but not female, carriers of the X/X genotype exhibited slower sprint times compared with R/R carriers ($P = 0.003$), as shown in Figure 3. Delmonico et al. (56) examined knee extensor concentric peak power before and after a 10-wk unilateral knee extensor strength training intervention in 157 older men and women. In women, X/X carriers exhibited greater baseline relative peak power (at 70% of one repetition maximum [1RM]) than both R/X and R/R genotypes (both $P < 0.01$) but a lower change in relative peak power in response to the training compared with the R/R group ($P = 0.02$). In men, no genotype differences were observed at baseline, but the change in absolute peak power in response to training tended to be higher in R/R compared with X/X genotypes ($P = 0.07$). Vincent et al. (322) studied the *ACTN3* R577X polymorphism in relation to isometric and isokinetic knee extensor strength in 90 young men and observed lower concentric peak torque at $300°\cdot s^{-1}$ in X/X compared with R/R homozygotes ($P = 0.04$). In a subset of these subjects, the authors also reported a lower proportion of type IIx muscle fibers in X/X vs R/R homozygotes ($P < 0.05$).

Three studies examined the *ACE* I/D genotype in relation to a variety of strength-related measures. Moran et al. (182)

TABLE 3. Endurance phenotypes and association studies with candidate genes.

Gene	Location	No. Subjects	Phenotype	*P* Value	Reference
Acute exercise					
AMPD1	1p13	400 whites	RPE	0.0002	(246)
EPHX1	1q42.1	304 COPD patients	W_{max}	0.0002	(106)
SFTPB	2p12–p11.2	304 COPD patients	6-min walk test	0.005	(106)
PPARGC1A	4p15.1	599 healthy subjects	PAEE/$\dot{V}O_{2max,\ pred}$	0.009	(72)
ADRB2	5q31–q32	232 HF patients	$\dot{V}O_{2peak}$	0.0001	(329)
		63 PM women	$\dot{V}O_{2max}$	<0.05	(181)
		62 PM women	$\dot{V}O_{2max}$	<0.05	(171)
		62 PM women	Maximum a-vO_{2diff}	0.006	
			Submaximal a-vO_{2diff}	0.004	
VEGFA	6p12	61 men 85 women	$\dot{V}O_{2max}$	<0.05	(223)
HLA-A	6p21.3	8 MZ and 8 DZ twin pairs	$\dot{V}O_{2max}$	0.001	(255)
IL6	7p21	479 young smokers	PWC_{max}	0.002	(202)
CFTR	7q31.2	97 CF patients	$\dot{V}O_{2peak}$	<0.05	(277)
NOS3	7q36	443 triathlon athletes	Competition performance	0.039	(267)
ADRB1	10q24–q26	263 cardiomyopathy patient	$\dot{V}O_{2peak}$	<0.05	(330)
			Exercise time	<0.05	
			VE/VCO_2	<0.05	
		83 heart failure patients	$\dot{V}O_{2peak}$	<0.05	(264)
			Exercise time	<0.05	
		892 Caucasian CAD patients	$\dot{V}O_{2peak}$	<0.05	(51)
SCGB1A1	11q12.3–q13.1	96 asthmatic children	FEV_1 after exercise	<0.04	(279)
UCP2	11q13	16 healthy subjects	Exercise efficiency (gross)	0.02	(29)
			Exercise efficiency (incremental)	0.03	
IGF1	12q22–q23	114 premenopausal women	Exercise economy	<0.05	(157)
			Treadmill time	<0.05	
HIF1A	14q21–q24	125 whites	$\dot{V}O_{2max}$ (age interaction)	NS (55 yr)	(224)
				0.012 (60 yr)	
				0.005 (65 yr)	
		29 blacks	$\dot{V}O_{2max}$	0.033	
BDKRB2	14q32.1–q32.2	73 male army recruits 42 female sedentary Caucasians	Muscle efficiency	0.003	(339)
HP	16q22.1	96 PAOD patients	Walking distance	<0.05	(54)
ACE	17q23	58 PM women	$\dot{V}O_{2max}$	<0.05	(91)
		47 PM women	Maximum a-vO_{2diff}	<0.05	
		91 (79 Caucasians)	running distance	0.009	(189)
		57 cardiomyopathy patients	$\dot{V}O_{2peak}$	0.05	(1)
			Exercise time	0.04	
		62 PM women	$\dot{V}O_{2max}$	<0.05	(92)
		36 COPD patients	Postexercise lactate	<0.0001	(125,126)
		43 COPD patients	Postexercise lactate	0.01	
		60	VE during hypoxia	0.008	(212)
		67 Chinese men	$\dot{V}O_{2max}$	0.04	(355)
		33 COPD patients	DO_2	<0.05	(129)
		88 nonelite athletes	Middle distance running performance	0.026	(31)
		51 untrained Caucasians	$\dot{V}O_{2max}$	<0.001	(132)
		29 strength trained athletes		<0.001	
		63 CTPH patients	6-min walk test	0.046	(295)
		74 athletes and nonathletes	Exercise efficiency	<0.05	(53)
LTBP4	19q13.1–q13.2	304 COPD patients	W_{max}	0.0001	(106)
CKM	19q13.2–q13.3	160 white parents	$\dot{V}O_{2max}$	0.007	(251)
		80 white offspring	$\dot{V}O_{2max}$	NS	
MTND5	12337–14148*	46	$\dot{V}O_{2max}$	<0.05	(61)
MTTT	15888–15953*	46	$\dot{V}O_{2max}$	<0.05	(61)
Training responses					
AMPD1	1p13	400 whites	$\dot{V}O_{2max}$	0.006	(246)
			$\dot{V}_{Emax}$	0.006	
ATP1A2	1q21–q23	472 whites	$\dot{V}O_{2max}$	0.018	(233)
		294 white offspring	$\dot{V}O_{2max}$	0.017	
PPARGC1A	4p15.1	125	Anaerobic threshold	0.005	(289)
PPARD	6p21	264 blacks	$\dot{V}O_{2max}$	0.028	(99)
			W_{max}	0.005	
HBB	11p15.5	102 males	Running economy	<0.05	(103)
HIF1A	14q21–q24	101 whites	$\dot{V}O_{2max}$ (age interaction)	NS (55 yr)	(224)
				0.005 (60 yr)	
				0.006 (65 yr)	
GABPB2	15q21.2	102 males	Running economy	<0.05	(102)
ACE	17q23	294 white offspring	$\dot{V}O_{2max}$	0.008–0.150	(234)
			Power output	0.0001–0.003	
		78 army recruits	Maximum duration for repetitive elbow flexion with 15 kg	0.001	(180)
		58 army recruits	Muscle efficiency	<0.025	(340)
		58 army recruits (24II, 26DD)	Exercise efficiency	0.02	(349)
		95 COPD patients	Maximum workload	0.04	(83)

(continued on next page)

TABLE 3. (Continued).

Gene	Location	No. Subjects	Phenotype	*P* Value	Reference
Training responses					
		17 women	$\dot{V}O_{2max}$	<0.05	(16)
		933 CAD patients	$\dot{V}O_{2peak}$	<0.05	(52)
		55 female nonelite athletes	V-HRR_{70} ($km \cdot h^{-1}$)	<0.05	(32)
			V-HRR_{90} ($km \cdot h^{-1}$)	<0.05	
			V-30 min ($km \cdot h^{-1}$)	<0.05	
APOE	19q13.2	51	$\dot{V}O_{2max}$	<0.05	(90)
		120	$\dot{V}O_{2max}$	<0.001	(300)
CKM	19q13.2–q13.3	160 white parents	$\dot{V}O_{2max}$	0.004	(251)
		80 white offspring	$\dot{V}O_{2max}$	<0.025	
		102 males	Running economy	<0.05	(356)
MTND5	12337–4148*	46	$\dot{V}O_{2max}$	<0.05	(61)

* Mitochondrial DNA.

$\dot{V}O_{2max}$, maximal oxygen uptake; VE/VCO_2, ratio of ventilation to carbon dioxide consumption; W_{max}, maximal power output; a-vO_{2diff}, arterial-venous oxygen difference; PM, postmenopausal; HF, heart failure; MZ, monozygous; DZ, dizygous; CF, cystic fibrosis; exercise efficiency, decrease in oxygen consumption on given workloads; PAOD, peripheral arterial occlusive disease; VE, ventilation; RPE, rating of perceived exertion; PWC, physical working capacity; FEV, forced expiratory volume; DO_2, oxygen delivery; V-HRR_{70}, running speed at 70% of HR reserve; V-HRR_{90}, running speed at 90% of HR reserve; V-30 min, 30-min running speed performance; CTPH, chronic thromboembolic pulmonary hypertension.

examined handgrip strength and vertical jump in 1027 Greek teenagers and identified significantly higher handgrip strength and vertical jump scores (both $P < 0.001$) in females carrying the I/I genotype. No significant associations were observed in the males for either performance measure. The authors performed haplotype analysis of the *ACE* gene region using three polymorphisms and determined that the I/D polymorphism explained the bulk of the explained genetic variance. Pescatello et al. (216) studied the *ACE* I/D genotype in relation to elbow flexor strength before and after unilateral upper arm strength training in 631 young men and women. They reported no association with muscle strength at baseline in either arm but reported greater improvements in isometric strength (maximum voluntary contraction (MVC)) in the trained arm after training in carriers of the I-allele ($P < 0.01$). Consistently, MVC increased in the untrained arm after training only in I-allele carriers ($P < 0.01$), with no change in D/D genotype carriers. In a biomechanical analysis, Wagner et al. (328) examined leg press strength variables and used discriminant analysis to determine the association of the *ACE* I/D genotype with muscle performance in 62 young men and women. The researchers showed that no single muscle phenotype was consistently associated with *ACE* I/D

TABLE 4. Linkage studies with endurance and strength phenotypes.

Gene	Marker	Location	No. Pairs	Phenotype	*P* Value	Reference
QTL	LEPR	1p31	90 blacks	$\Delta\dot{V}O_{2max}$	0.0017	(247)
			102 blacks	$\dot{V}O_{2max}$	0.01	
ATP1A2		1q21–q23	309 white	$\Delta\dot{V}O_{2max}$	0.054	(233)
				ΔW_{max}	0.003	
QTL	S100STU1	1q21	316 white	ΔW_{max}	0.0091	(247)
QTL	D1S398	1q22	90 blacks	ΔW_{max}	0.0033	(247)
QTL	D2S118	2q32.2	204 white	Knee extension	0.0002	(112)
				Knee flexion	0.004	
QTL	D4S1627	4p13	315 white	ΔW_{max}	0.0062	(247)
QTL	FABP2	4q28–q31	315 white	$\Delta\dot{V}O_{2max}$	0.009	(23,247)
OTL	D5S1505	5q23	315 white	ΔW_{max}	0.002	(247)
QTL	D6S1051	6p21.3	204 white	Knee extension	0.009	(112)
				Knee flexion	0.004	
QTL	LEP	7q32	102 blacks	$\dot{V}O_{2max}$	0.0068	(247)
QTL	D7S495	7q34	315 white	$\Delta\dot{V}O_{2max}$	0.0089	(247)
QTL	NOS3	7q36	102 blacks	$\dot{V}O_{2max}$	0.003	(247)
OTL	D10S677	10q23	315 white	W_{max}	0.0014	(247)
QTL	D11S4138	11p15	204 white	Knee extension	0.004	(112)
				Knee flexion	0.002	
QTL	SUR	11p15.1	315 white	$\dot{V}O_{2max}$	0.0014	(23,247)
QTL	D12S1042	12p11	367 white	Multiple knee strength measures	<0.05	(114)
QTL	D12S85	12q13	367 white	Multiple knee strength measures	<0.05	(114)
QTL	D12S78	12q23	367 white	Multiple knee strength measures	<0.05	(114)
QTL	D13S153	13q14.2	204 white	Trunk flexion	0.0002	(113)
QTL	D13S1303	13q21	367 white	Multiple knee strength measures	<0.05	(114)
QTL	D13S175	13q11	90 blacks	ΔW_{max}	0.0055	(247)
QTL	D13S787	13q12	315 white	$\Delta\dot{V}O_{2max}$	0.0087	(247)
QTL	D13S796	13q33	351 white	W_{max}	0.0098	(247)
QTL	RADI	16q22	90 blacks	$\Delta\dot{V}O_{2max}$	0.0041	(247)
QTL	D18S478	18q12	351 white	W_{max}	0.0064	(247)
CKM		19q13.2	260 white	$\Delta\dot{V}O_{2max}$	0.04	(254)
QTL	D20S857	20q13.1	90 blacks	$\Delta\dot{V}O_{2max}$	0.0028	(247)

Δ, response to an exercise training program; $\dot{V}O_{2max}$, maximal oxygen uptake; W_{max}, maximal power output.

genotype, but that combinations of traits including contraction velocity, isometric force, and optimum contraction velocity could discriminate the three genotype groups with substantial accuracy in both men ($P = 0.02$) and women ($P = 0.03$). In these analyses, the I/I genotype carriers exhibited lower maximum and optimum contraction velocity compared with the I/D and the D/D genotype groups.

The vitamin D receptor (*VDR*) locus was the focus of two studies. Windelinckx et al. (342) examined the *Bsm*I, *Taq*I, and *Fok*I *VDR* polymorphisms in 493 middle-aged and older men and women for association with various muscle strength measures. *Fok*I was analyzed independently, whereas *Bsm*I and *Taq*I were combined in a haplotype analysis. In women, the *Fok*I polymorphism was associated with quadriceps isometric ($P < 0.05$) and concentric ($P = 0.06$) strength, with higher levels in f/f homozygotes compared with F-allele carriers. In men, the *Bsm*I/*Taq*I haplotype was associated with quadriceps isometric strength ($P < 0.05$), with Bt/Bt homozygotes exhibiting greater strength than bT haplotype carriers. Wang et al. (334) examined the *Apa*I, *Bsm*I, and *Taq*I *VDR* polymorphisms in 109 young Chinese women in relation to knee and elbow torque measures. At the *Apa*I locus, A/A women exhibited lower elbow flexor concentric peak torque compared with a/a carriers ($P < 0.04$) as well as lower knee extensor eccentric peak torque compared with both A/a and a/a carriers ($P < 0.01$). For the *Bsm*I locus, the b/b carriers demonstrated lower knee flexor concentric peak torque ($180°\cdot s^{-1}$) than the B-allele carriers ($P = 0.03$). No associations were observed for the *Taq*I locus.

Ciliary neurotrophic factor (*CNTF*)-related genes were the focus of two reports in 2006–2007. Arking et al. (13) examined eight polymorphisms surrounding the *CNTF* locus, including the rare rs1800169 nonsense polymorphism (A/G; A = null allele), in 363 older Caucasian women. Haplotype analysis revealed a significant association with handgrip strength, which was completely explained by the rs1800169 A-allele, such that individuals homozygous for the null A-allele ($n = 16$) exhibited lower handgrip strength compared with A/G and G/G genotypes ($P < 0.006$).

TABLE 5. Muscular strength and anaerobic phenotypes and case–control studies.

		Athletes			Controls			
Gene	**Location**	***N***	**sports**	**Frequency (Haplotype)**	***N***	**Frequency (Haplotype)**	***P* Value**	**Reference**
EPAS1	2p21–p16	242	Swimmers, runners, rowers	GCCG: 0.09 ATGG: 0.07	444	GCCG: 0.17 ATGG: 0.11	0.01	(105)
ACTN3	11q13–q14	107	sprinters	RR: 0.49 RX: 0.45 XX: 0.06 R: 0.72 X: 0.28	436	RR: 0.30 RX: 0.52 XX: 0.18 R: 0.56 X: 0.44	<0.001	(350)
ACE	17q23	35	Elite swimmers, 400 m or less (subsample of 103 swimmers)	II: 0.14 ID: 0.34 DD: 0.51 I: 0.31 D: 0.69	1248	II: 0.24 ID: 0.49 DD: 0.27 I: 0.48 D: 0.52	0.005	(347)
		30	Short distance athletes	II: 0.07 ID: 0.43 DD: 0.50 I: 0.28 D: 0.72	449	II: 0.23 ID: 0.52 DD: 0.24 I: 0.5 D: 0.5	0.001	(193)
PPARA	22q13.31	180	Power athletes (subset of 786 athletes)	GG: 0.51 GC: 0.44 CC: 0.05 G: 0.27 C: 0.73	1242	GG: 0.70 GC: 0.27 CC: 0.03 G: 0.16 C: 0.84	<0.001	(3)
mtDNA haplogroup*	mtDNA*	52	Endurance	H: 0.52 V: 0.058 U: 0.21 K: 0 T: 0.058 J: 0.019 W: 0.058 I: 0.077 X: 0	1060	H: 0.48 V: 0.048 U: 0.24 K: 0.045 T: 0.036 J: 0.048 W: 0.044 I: 0.028 X: 0.011	0.023†	(198)
		89	Sprint	H: 0.47 V: 0.079 U: 0.15 K: 0.09 T: 0.045 J: 0.067 W: 0.067 I: 0 X: 0.023				

* Haplogroups were constructed from several mitochondrial DNA polymorphisms.
† *P* value for the difference between endurance and sprint athletes; significance between athletes and controls was not reported.

De Mars et al. (49) examined multiple polymorphisms at both the *CNTF* and the *CNTF* receptor (*CNTFR*) loci in a study of 493 middle-aged and older men and women with measures of knee flexor and extensor strength. T-allele carriers of the C-1703T *CNTFR* polymorphism exhibited higher strength levels for multiple measures compared with CC homozygotes (all $P < 0.05$), including all knee flexor torque values. In middle-aged women, A-allele carriers at the T1069A *CNTFR* locus exhibited lower concentric knee flexor peak torque at multiple speeds and isometric torque at 120° compared with T/T homozygotes (all $P < 0.05$). The *CNTF* null allele was not associated with any strength measures nor were any *CNTF* × *CNTFR* interactions observed.

The study of De Mars et al. (49) is one of several that examined groups of genes within a physiological pathway in relation to strength phenotypes. For example, Walsh et al. (332) examined the genetic association of haplotype

TABLE 6. Muscular strength and anaerobic phenotypes and association studies with candidate genes.

Gene	Location	No. Subjects	Phenotype	*P* Value	Reference
AMPD1	1p13	139 men and women	Wingate anaerobic power	0.004	(69)
DIO1	1p32–p33	350 men, >70 yr	Grip strength	0.047	(213)
GDF8	2q32.2	286 women	Hip flexion	0.01	(275)
		55 AA women (subsample of 286)	Overall strength	<0.01	(275)
			Hip flexion	<0.01	
			Knee flexion	<0.01	
ACVR2B	3p22	593 men and women	KE con, sv	0.04	(332)
MYLK	3q21	157 men and women	Isometric strength	0.019	(38)
			Δ Elbow flexor strength after ecc exercise	<0.05	
NR3C1	5q31	158 men, 13–36 yr	Arm strength	<0.05	(319)
			Leg strength	<0.05	
TNF	6p21.3	214 men and women, ≥60 yr	Δ Stair-climb time	0.007	(197)
CFTR	7q31.2	97 CF patients	Peak anaerobic power	<0.05	(277)
CNTFR	9p13	465 men and women	KE ecc, sv	<0.05	(256)
			KE ecc, fv	<0.05	
		493 men and women	KF con, sv	0.04	(49)
			KF con, fv	<0.02	
			KF isometric	<0.04	
			KE isometric	0.02	
IGF2	11p15.5	397 men, 64–74 yr	Grip strength	0.05	(268)
		239 women, 20–94 yr	Elbow flexor con	<0.05	(272)
			Elbow flexor ecc	<0.05	
			KE con, sv	<0.05	
			KE con, fv	<0.05	
		151 men and women	Δ Elbow flexor isometric strength aff ecc exercise	<0.05	(59)
CNTF	11q12.2	494 men and women	KE con, fv	<0.05	(257)
			KE ecc	<0.05	
			KF con	<0.05	
			KF con	<0.05	
			KF ecc	<0.05	
		363 women, 70–79 yr	Handgrip strength	<0.006	(13)
ACTN3	11q13–q14	355 women, <40 yr	Baseline isometric strength	<0.05	(37)
			Δ 1RM	<0.05	
		507 boys, 11–18 yr	40-m sprint	0.003	(184)
		86 women, 50–85 yr	Relative peak power	<0.01	(56)
		48 women, 50–85 yr	Relative peak power response to strength training	0.02	
		90 men, 18–29 yr	KE con, fv	0.04	(322)
VDR	12q13.11	501 PM women	Grip and quadriceps strength	<0.01	(82)
		175 women, 20–39 yr	KF isokinetic torque	<0.05	(86)
		302 men, >50 yr	KE isometric torque	<0.05	(258)
		493 men and women	KE isometric	<0.05	(342)
		109 young Chinese women	Elbow flexor con	<0.04	(334)
			KE ecc	<0.01	
			KF con, fv	0.03	
IGF1	12q22–q23	67 men and women	KE 1RM	0.02	(140)
BDKRB2	14q32.1	110 COPD patients	KE isometric strength	<0.01	(107)
COL1A1	17q21.3–q22.1	273 men (71–86 yr)	Grip strength	0.03	(318)
			Biceps strength	0.04	
ACE	17q23	33	Δ KE isometric strength	<0.05	(71)
		83 PM women	Specific muscle strength of adductor pollicis	0.017	(348)
		103 COPD patients	KE maximal strength	<0.05	(108)
			KE twitch force	<0.05	
		81 men	KE isometric strength	0.026	(338)
		479 girls, 11–18 yr	Handgrip strength	<0.001	(182)
			Vertical jump height	<0.001	
		631 men and women	Elbow flexor isometric strength response to training	<0.01	(216)
		62 men and women	Discriminant analysis, including isometric force and contraction velocity	0.03	(328)
RETN	19p13.2	482 men and women	Δ 1RM	0.03	(221)
			Δ Isometric strength	0.03	

PM, postmenopausal; Δ, training response, KE, knee extensor; KF, knee flexor; con, concentric; ecc, eccentric; sv, slow velocity (0.52 rad·s^{-1}); fv, fast velocity (3.14 rad·s^{-1}); AA, African American; CF, cystic fibrosis.

structure in the myostatin receptor, activin-type II receptor B (*ACVR2B*), and follistatin (a myostatin inhibitor) loci with muscle strength and mass phenotypes in 593 men and women across the adult age span. In women but not men, *ACVR2B* haplotype was significantly associated with knee extensor concentric peak torque ($P = 0.04$). Although follistatin haplotype was associated with leg fat-free mass in men, no associations were observed with muscle strength. Hand et al. (95) examined promoter region polymorphisms in insulin-like growth factor (IGF) pathway genes in relation to the response of muscle strength and volume to strength training in 128 older men and women. The genes under study included insulin-like growth factor 1 (*IGF1*), calcineurin (*PPP3R1*), and insulin-like growth factor binding protein 3 (*IGFBP3*). The *IGF1* gene promoter CA repeat polymorphism was associated with the one-repetition maximum (1RM) response to strength training ($P < 0.01$), and a possible interaction with the *PPP3R1* I/D polymorphism was noted ($P = 0.07$). The −202 A/C polymorphism in *IGFBP3* was not associated with any phenotype. Hopkinson et al. (107) examined the bradykinin type 2 receptor (*BDKRB2*) gene as well as the *ACE* I/D polymorphism in relation to quadriceps strength in 110 chronic obstructive pulmonary disease (COPD) patients. A 9-bp insertion/deletion polymorphism (−9/+9) in the *BDKRB2* gene was associated with quadriceps isometric strength (MVC), with lower values for +9/+9 homozygotes compared with −9-allele carriers ($P = 0.02$), although the association appeared to be driven by higher fat-free mass in +9/+9 homozygotes ($P = 0.04$). As these authors also showed previously (108), the *ACE* D-allele was associated with greater quadriceps MVC compared with II homozygotes in the present study, but no *BDKRB2* × *ACE* interaction was observed, indicating independent influences of these two genes on muscle strength phenotypes.

Pistilli et al. (221) examined six polymorphisms in the resistin gene in relation to muscle and bone phenotypes in 482 young white men and women who performed upper-arm strength training. With regard to strength phenotypes, the 398 C/T polymorphism was significantly associated with training-induced change in 1RM (T/T > C/T and C/C; $P < 0.05$) and MVC (C/C > C/T; $P = 0.04$) in women. In men, the −420 C/G polymorphism was associated with the training-induced change in 1RM ($P = 0.03$) and MVC ($P = 0.03$), with C/C homozygotes having greater responses compared with G/G carriers; the 540 G/A polymorphism was also associated with the training-induced change in 1RM strength ($P < 0.05$), with G/G carriers greater than A/A carriers. Fischer et al. (69) examined the adenosine monophosphate deaminase 1 (*AMPD1*) gene, in which multiple rare polymorphisms result in AMP deaminase deficiency in approximately 2% of Caucasians. Anaerobic performance was measured during a 30-s Wingate cycle test in 139 men and women, 12 of whom were AMP deaminase deficient. Deficient subjects exhibited a more rapid decline in power output ($P < 0.001$) and a lower mean power ($P = 0.004$) compared with other genotypes. Finally, Devaney et al. (59) studied the association of several polymorphisms in the insulin-like growth factor 2 (*IGF2*) gene in relation to exertional muscle damage of the elbow flexors in 151 young men and women. After a damaging eccentric contraction protocol, loss of isometric strength in response to the damaging exercise protocol was significantly different among genotype groups for multiple polymorphisms in the *IGF2* gene region ($P < 0.05$).

Linkage studies. No new linkage studies were published in 2006–2007 (Table 4).

HEALTH-RELATED FITNESS PHENOTYPES

Hemodynamic Phenotypes

Acute exercise. During 2006 and 2007, 17 studies were published that assessed the impact of genetic variants on hemodynamic responses to acute exercise (Table 7). Snyder et al. (285) studied the cardiovascular (CV) hemodynamics of 64 young Caucasian men at rest and during a continuous exercise protocol consisting of 9 min at 40% and another 9 min at 75% of their peak cycle ergometer work rate. They fairly consistently found that Arg16/Arg16 genotype individuals at the Arg16Gly *ADRB2* locus had lower plasma norepinephrine levels and lower cardiac output ($\dot{Q}$), stroke volume (SV), and mean arterial pressure at both work rates compared with Gly16/Gly16 genotype individuals.

Nieminen et al. assessed the effect of several genes on heart rate (HR) and blood pressure (BP) responses to exercise in 890 middle- to older-age men and women in the Finnish CV Study (199). Their Gly389 homozygotes at the *ADRB1* gene locus had higher maximal exercise systolic BP ($P = 0.04$) and a greater change in systolic BP from rest to

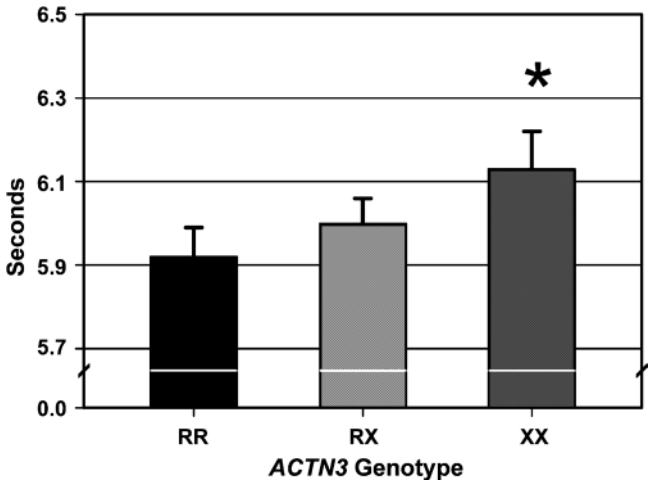

FIGURE 3—Forty-meter sprint times for 507 adolescent males grouped by alpha actinin 3 (*ACTN3*) R577X genotype. Sample sizes: R/R: 172; R/X: 242; X/X: 93. *$P = 0.003$ vs R/R genotype group. Adapted with permission from Macmillan Publishers Ltd: *European Journal of Human Genetics,* Moran et al. (184), copyright (2007).

TABLE 7. Summary of the association studies between candidate gene markers and acute exercise-related hemodynamic phenotypes as well as gene–PA interactions on hemodynamic traits.

Gene	Location	No. Subjects	Phenotype	*P* Value	Reference
AMPD1	1p13	400 whites	Maximal exercise SBP	0.003	(246)
AGT	1q42–q43	25	Submaximal exercise DBP	<0.01	(142)
		190 sedentary white men	DBP_{max}	0.007	(232)
		61 PM women	HR_{max}	0.008	(170)
DRA2B	2p13–q13	78 women	BP and HR response to handgrip test	<0.05	(314)
			Normalized low- and high-frequency domains on HR spectral analysis during exercise	<0.05	
AGTR1	3q21–q25	50 white men	Submaximal exercise SBP	<0.05	(215)
ADD1	4p16.3	48 white HT men	Change in ambulatory SBP after 40% $\dot{V}O_{2max}$ exercise	<0.05	(215)
ADRB2	5q31–q32	232 HF patients	Exercise cardiac index	<0.05	(329)
			Exercise systemic vascular resistance	<0.05	
			Exercise SV	<0.05	
		12 obese women	Exercise DBP	0.01	(164)
		31	HR during handgrip exercise	0.001	(63)
		64 women	Handgrip exercise FBF	<0.05	(305)
		47 men and women	Handgrip exercise HR and $\dot{Q}$	0.03	(62)
		64 whites	Plasma NE, $\dot{Q}$, SV, MAP, SBP, and DBP during submaximal (40% peak WR) exercise	<0.05	(285)
			$\dot{Q}$, SV, and MAP during submaximal (75% peak WR) exercise	<0.05	
EDN1	6p24.1	873	SBP_{max}	0.03	(301)
		372 with BMI > 26	SBP_{max}	<0.0001	
HFE	6p21.3	40 hemochromatosis patients 21 healthy controls	HR recovery after maximal exercise	<0.01	(12)
CHRM2	7q31–q35	80 whites	HR recovery 1 min after maximum exercise	0.008	(100)
NOS3	7q36	269 Japanese	Hypertensive response to exercise	0.016	(136)
		62 white women	Submaximal exercise HR and SV, maximal exercise HR	<0.05	(96)
DRB1	10q24–q26	16 white men	Plasma NE response to exercise while under atropine blockade	0.013	(152)
		890 whites	Maximum exercise SBP	0.04	(199)
			Change in SBP from rest to maximum	0.03	
			Ventricular extrasystoles during exercise	0.009	
GNB3	12p13	437 whites	SBP at 50 W	0.036	(237)
ANG	14q11.1–q11.2	257 blacks	SBP at 60% and 80% $\dot{V}O_{2max}$	<0.05	(252)
			SBP_{max}	<0.05	
ACE	17q23	58	Maximum HR	<0.05	(91)
		66	DBP_{max}	0.010	(74)
		96	Exercise ANP	0.043	(75)
		19 COPD patients	Exercise Ppa	0.008	(127)
			Exercise Rpv	<0.05	
		39 COPD patients	Postexercise Ppa	<0.01	(128)
		62 PM women	Submaximal exercise HR	0.04	(92)
		37 COPD patients	Postexercise Ppa	<0.01	(125)
		43 COPD patients	Postexercise Rpv	<0.01	(126)
		33 COPD	Exercise mPAP	<0.05	(129)
			Exercise Rpv	0.001	
		50 white men	Submaximal exercise SBP and DBP	<0.05	(217)
		47 white men	Submaximal exercise SBP	<0.05	(20)
		85 endurance athletes	Decline in LV function after 300 mile race	0.017	(14)
			BP high-frequency domain after 300 mile race	<0.01	
TGFB1	19q13.2	480 whites	SBP at 50 W, 60% $\dot{V}O_{2max}$	<0.05	(253)
			SBP_{max}	<0.05	
GNAS1	20q13.3	890 whites	HR during maximum exercise and recovery	0.04	(199)
CYP2D6	22q13.1	81 hypertensives	Reductions in maximal exercise HR with betaxalol treatment	0.043	(353)
Gene–PA interactions					
ADRB2	5q31–q32	62 PM women	Submaximal exercise a-vO_{2diff}	0.05	(171)
NOS3	7q36	63	FBF	0.03	(44)
			FVR	0.0003	
		832	Resting SBP	0.0062	(137)
EDN1		607 HT cases, 586 controls	Risk of hypertension	0.0025	(231)
GPR10	10q26.13	687 men and women	Resting DBP	0.006	(73)
			Resting SBP	0.008	
GNB3	12p13	14,716 blacks and whites	Hypertension risk	0.02	(85)
ACE	17q23	56 male and female athletes	FMD	0.0001	(296)
Familial cardiac arrhythmias*					
CASQ2	1p13.3–p11	41	AR-FPVT	Coseg†	(145)
		29	AR-FPVT	Coseg†	(222)
RYR2	1q42.1–q43	26	AD-FPVT	Coseg†	(146)
		24	AD-FPVT	Coseg†	(225)
KCNQ1	11p15.5		Long QT syndrome 1	Coseg†	(335), see also (274) for a review

* Genes causing exercise-related familial cardiac arrhythmias. Only familial cardiac arrhythmias where acute exercise has been shown to trigger cardiac event have been listed.
† Mutations cosegregate with the phenotype in affected families.
PM, postmenopausal; HF, heart failure; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; Ppa, mean pulmonary artery pressure; Rpv, pulmonary vascular resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RPP, rate pressure product; BMI, body mass index; SV, stroke volume; $\dot{Q}$, cardiac output; FBF, forearm blood flow; FVR, forearm vascular resistance; AR, autosomal recessive; AD, autosomal dominant; FPVT, familial polymorphic ventricular tachycardia.

TABLE 8. Summary of the association studies between candidate gene markers and hemodynamic phenotype training responses.

Gene	Location	No. Cases	Phenotype	*P* Value	Reference
AMPD1	1p13	400 whites	DBP at maximum	0.03	(246)
AGT	1q42–q43	226 white males	DBP at 50 W	0.016	(232)
		70 older men and women	Resting SBP	0.05	(55)
		120 males	Resting SBP	<0.01	(239)
			Resting DBP	<0.01	
TTN	2q31		SV and $\dot{Q}$ at 50 W	0.005	(236)
AGTR1	3q21–q25	70 older men and women	Resting DBP	0.05	(55)
NFKB1	4q24	36 hypertensives	Reactive hyperemic blood flow	0.006	(210)
FABP2	4q28–q31	69	SBP	<0.05	(46)
EDN1	6p24.1	473 whites	SBP at 50 W	0.0046	(231)
			PP at 50 W	0.0016	
CHRM2	7q31–q35	80 whites	HR recovery after maximal exercise	0.038	(100)
NOS3	7q36	471 whites	DBP at 50 W	0.0005	(238)
			HR at 50 W	0.077	
			RPP at 50 W	0.013	
		67 CAD patients	APV response to acetylcholine	<0.05	(64)
LPL	8p22	18	Resting SBP	<0.05	(89)
			Resting DBP	<0.05	
		146 British Army recruits	LV mass	0.015	(70)
KCNQ1	11p15.5	7 familial LQT syndrome patients	Resting and recovery QTc, QT interval dispersion at rest	<0.05	(214)
HBB	11p15.5	102 Chinese men	Submaximal exercise HR	<0.05	(103)
GNB3	12p13	163 black women	Resting SBP	0.0058	(237)
			Resting DBP	0.032	
		255 blacks	HR at 50 W	0.013	
		473 whites	HR at 50 W	0.053	
			SV at 50 W	0.012	
BDKRB2	14q32.1–q32.2	109 white army recruits	LV mass	0.009	(24)
ACE	17q23	28 male soccer players	LV mass	0.02	(65)
		140 white army recruits	Septal thickness	0.0001	(178)
			Posterior wall thickness	0.0001	
			End-diastolic diameter	0.02	
			LV mass	0.0001	
			LV mass index	0.0001	
		49 white army recruits	BNP	<0.05	
		18	Resting DBP	0.005	(89)
		294 white offspring	HR at 50 W	0.0006	(232)
		144 white army recruits	LV mass	0.002	(190)
		64 hypertensives	Resting DBP	<0.05	(354)
			Resting MAP	<0.05	
		31 blacks	24-h Na^+ excretion	0.04	(119)
APOE	19q13.2	18	Resting SBP	<0.05	(89)
PPARA	22q13.31	144 white army recruits	LV mass	0.009	(118)

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RPP, rate pressure product; SV, stroke volume; $\dot{Q}$, cardiac output; BNP, brain natriuretic peptide; LV, left ventricular; MAP, mean arterial pressure; APV, average peak velocity.

maximal exercise ($P = 0.03$) than heterozygotes and Arg homozygotes at this locus. Furthermore, in women, Gly389 homozygotes had lower maximal exercise HR than the two other genotype groups ($P = 0.04$). They also found that Arg homozygotes at this locus were less likely to have ventricular extrasystoles during exercise (odds ratio [OR] = 0.68, $P = 0.009$) than Gly-allele carriers at this locus. They also reported a tendency for the *ADRB1* Ser49Gly polymorphism to affect exercise HR ($P = 0.06$). The T393C polymorphism at the *GNAS1* gene locus significantly affected the HR response during exercise and recovery ($P = 0.04$).

Kim et al. (136) studied 269 Japanese hypertensives and found that a hypertensive response to maximal exercise (systolic BP >210 mm Hg in men and >190 mm Hg in women) was significantly more frequent in G/G homozygotes at the *NOS3* Glu298Asp locus ($P = 0.016$). In fact, this difference in exercise-induced hypertension was primarily accounted for by genotype-dependent response differences in women ($P < 0.001$), whereas there was not a significant association in the men. Also, in the G/G homozygote women, the increase in systolic BP from rest to maximal exercise was significantly greater than that in women who were T-allele carriers at this locus (49 ± 23 vs 34 ± 13 mm Hg; $P < 0.001$).

The effect of the alpha adducin 1 (*ADD1*) Gly460Trp polymorphism on ambulatory BP after 30 min of exercise at both 40% and 60% $\dot{V}O_{2max}$ in 48 overweight, hypertensive Caucasian men was studied by Pescatello et al. (215). They found that heterozygotes at this locus elicited greater reductions in 9-h ambulatory systolic BP after 40% $\dot{V}O_{2max}$ exercise than Gly homozygotes (−7.8 ± 2.3 vs −0.6 ± 1.3 mm Hg; $P < 0.05$). They reported no significant effects of this variant on ambulatory diastolic BP after exercise at either intensity or on ambulatory systolic BP changes after the higher intensity exercise. In addition, they found that plasma renin levels increased significantly more after the 60% $\dot{V}O_{2max}$ exercise (7.3 ± 1.3 vs 2.7 ± 2.2 $\mu U \cdot mL^{-1}$; $P < 0.05$) but not after the 40% $\dot{V}O_{2max}$ exercise (3.1 ± 0.8 vs 2.0 ± 1.4 $\mu U \cdot mL^{-1}$; $P > 0.05$) in Gly homozygotes compared with heterozygotes at this locus.

Pescatello et al. (217) investigated the effects of several renin–angiotensin system polymorphic variants and their interaction with dietary calcium intake on ambulatory BP

after 30 min of cycle ergometer exercise at 40% and 60% $\dot{V}O_{2max}$ in 50 men with high normal BP or stage 1 hypertension. During the intake of a low-calcium diet, systolic BP reductions after 40% $\dot{V}O_{2max}$ (3.5 vs 9.8 mm Hg; $P < 0.05$) and 60% $\dot{V}O_{2max}$ exercise (5.7 vs 2.6 mm Hg; $P < 0.05$) differed between the *ACE* I-allele carriers and D homozygotes, respectively. Diastolic BP did not differ between *ACE* genotype groups after either exercise intensity under these conditions. Also during the low-calcium diet, the systolic BP reductions after 60% $\dot{V}O_{2max}$ exercise differed between *AGTR1* A homozygotes and C-allele carriers (7.5 vs 2.1 mm Hg; $P < 0.05$), whereas no such differences were evident for systolic BP after 40% $\dot{V}O_{2max}$ exercise or for diastolic BP after either exercise intensity. During high dietary calcium intake, *ACE* I/D genotype again significantly affected systolic BP ($P < 0.05$) and tended to affect the diastolic BP response ($P = 0.065$) after the 60% $\dot{V}O_{2max}$ exercise, but no such differences were evident after the 40% $\dot{V}O_{2max}$ exercise. During high-calcium dietary intake, systolic BP reductions after 60% $\dot{V}O_{2max}$ exercise tended to differ between *AGTR1* A homozygotes and C-allele carriers (6.9 vs 1.2 mm Hg, respectively; $P = 0.086$) with no such differences being evident for diastolic BP after this exercise intensity or either systolic or diastolic BP after the lower intensity exercise.

TABLE 9. Exercise-related hemodynamic phenotypes and linkage studies.

Gene	Marker	Location	No. Pairs	Phenotype	*P* Value/LOD Score	Reference
QTL	D1S3728–D1S3736	1p32.1–p31.1	1068 subjects from 291 families	Submaximal exercise HR	LOD = 1.91	(115)
QTL	D1S1588, D1S1631	1p21.3	102 black	SV at 50 W	0.005	(229)
QTL	D1S189, CASQ2	1p13–p21	42 members from 7 families	AR-FPVT	LOD = 8.24	(144,145)
QTL	D1S510	1q32.1	1068 subjects from 291 families	Submaximal exercise systolic BP	LOD = 2.02	(115)
QTL	D1S547–D1S2811	1q43–q44	1068 subjects from 291 families	Systolic BP during recovery	LOD = 2.59	(115)
QTL	D2S2952	2p24	344 white	SBP at 80% $\dot{V}O_{2max}$	0.0026	(230)
QTL	D2S1400	2p22–p25	102 black	DBP at 50 W	0.0044	(230)
QTL	D2S1777	2p12	1068 subjects from 291 families	Systolic BP during recovery	LOD = 1.68	(115)
QTL	D2S1334	2q21	344 white	SBP at 80% $\dot{V}O_{2max}$	0.0031	(230)
QTL	D2S148, D2S384 (TTN)	2q31	328 white	ΔSV and $\Delta\dot{Q}$ at 50 W	0.0002	(236)
QTL	D2S364	2q31–q32	52 members from 2 families (14 affected)	Abnormal PASP response to exercise	LOD = 4.4	(87)
QTL	D2S154	2q33.3	328 white	HR at 50 W training response	LOD = 2.13	(287)
QTL	D3S1447–D3S2406	3p21.1–p14.1	102 black	Resting HR training responses	0.0016	(6)
QTL	D3S2459	3q13.11	102 black	HR at 50 W	LOD = 1.88	(287)
QTL	D4S403–ATT015	4p15.3	1068 subjects from 291 families	Diastolic BP during recovery	LOD = 2.37	(115)
QTL	D4S2394	4q28.2	1068 subjects from 291 families	Diastolic BP during recovery	LOD = 1.93	(115)
QTL	GATA138B05	5q13.2	1068 subjects from 291 families	Submaximal exercise systolic BP	LOD = 1.57	(115)
QTL	D5S1725	5q14.3	1068 subjects from 291 families	Submaximal exercise HR	LOD = 2.09	(115)
QTL	D5S640	5q31–q33	344 white	ΔDBP at 50 W	0.0046	(230)
QTL	D5S408	5q35.3	1068 subjects from 291 families	HR during recovery	LOD = 1.60	(115)
QTL	D6S1270	6q13–q21	344 white	DBP at 80% $\dot{V}O_{2max}$	0.0037	(230)
QTL	D6S2436	6q24–q27	344 white	DBP at 50 W	0.0041	(230)
QTL	D7S1808–D7S817	7p15.1–14.3	1068 subjects from 291 families	Submaximal exercise HR	LOD = 1.73	(115)
QTL	D7S2204–D7S2212	7q21.1	1068 subjects from 291 families	Submaximal exercise HR	LOD = 1.67	(115)
QTL	D7S2195	7q35	102 black	SBP at 80% $\dot{V}O_{2max}$	0.0046	(230)
QTL	D8S373	8q24.3	344 white	ΔSBP at 50 W	0.0005	(230)
QTL	D9S58, 106, 934	9q32–q33.3	328 white	SV at 50 W	0.003 to 0.006	(229)
QTL	D9S154	9q33.1	102 black	HR at 50 W	LOD = 1.93	(287)
QTL	D10S2325	10p14	102 black	$\dot{Q}$ at 50 W	0.0045	(229)
QTL	D10S1666	10p11.2	328 white	ΔSV at 50 W	0.00005	(229)
QTL	D10S2327	10q21–q23	102 black	ΔDBP at 80% $\dot{V}O_{2max}$	0.0019	(230)
QTL	rs1887922	10q23.3	1068 subjects from 291 families	Submaximal exercise systolic BP	LOD = 1.57	(115)
QTL	D10S597–D10S468	10q25.1–q25.3	102 black	HR at 50 W	LOD = 1.84	(287)
				HR at 60% $\dot{V}O_{2max}$	LOD = 2.43	
QTL	D10S677	10q23–q24	344 white	SBP at 80% $\dot{V}O_{2max}$	0.0018	(230)
QTL	D11S2071	11p15.5	102 black	DBP at 50 W	0.0042	(230)
QTL	UCP3	11q13	102 black	DBP at 80% $\dot{V}O_{2max}$	0.0023	(230)
QTL	D12S1301	12p12–p13	102 black	SBP at 80% $\dot{V}O_{2max}$	0.005	(230)
QTL	D12S1724	12q13.2	102 black	SV at 50 W	0.0038	(229)
QTL	D13S250	13q12	91 black	Resting ΔSBP	0.004	(244)
QTL	D14S283	14q11.1–q12	344 whites	SBP at 80% $\dot{V}O_{2max}$	0.0034	(230)
QTL	D14S588	14q24.1	1068 subjects from 291 families	Submaximal exercise HR	LOD = 1.91	(115)
QTL	D14S53	14q31.1	328 whites	SV at 50 W	0.0019	(229)
QTL	D15S211	15q24–q25	344 whites	DBP at 80% $\dot{V}O_{2max}$	0.0024	(230)
QTL	D15S657	15q26	102 blacks	SBP at 80% $\dot{V}O_{2max}$	0.0035	(230)
QTL	D16S261	16q21	344 white	SBP at 80% $\dot{V}O_{2max}$	0.0026	(230)
QTL	D17S1294	17p11–q11	102 blacks	SBP at 80% $\dot{V}O_{2max}$	0.0031	(230)
QTL	D18S843	18p11.2	102 blacks	DBP at 50 W	0.0012	(230)
QTL	D18S866	18q11.2	102 blacks	$\dot{Q}$ at 50 W	0.0022	(229)
QTL	D18S38	18q21.32	328 white	HR at 50 W	LOD = 2.64	(287)
QTL	D18S878	18q22.1	328 white	HR at 60% $\dot{V}O_{2max}$ training response	LOD = 2.10	(287)
QTL	GATA156F11	19q13.1	1068 subjects from 291 families	Submaximal exercise diastolic BP	LOD = 1.63	(115)
QTL	D21S1432	21q21.1	1068 subjects from 291 families	HR during recovery	LOD = 1.66	(115)

Δ, response to an exercise training program; $\dot{V}O_{2max}$, maximal oxygen uptake; LOD, logarithm of odds; PASP, pulmonary artery systolic pressure; AR-FPVT, autosomal recessive familial polymorphic ventricular tachycardia; SV, stroke volume; SBP, systolic blood pressure; DBP, diastolic blood pressure; $\dot{Q}$, cardiac output.

Blanchard et al. (20) studied the effects of several genetic variants within the renin–angiotensin–aldosterone system on ambulatory BP after 30 min of cycle ergometer exercise at 40% and 60% $\dot{V}O_{2max}$ in 47 men with pre- to stage 1 hypertension. In men, homozygosity for the *ACE* D-allele systolic BP after the 40% $\dot{V}O_{2max}$ exercise was significantly lower compared with men carrying at least one *ACE* I-allele (128 ± 2 vs 132 ± 3 mm Hg; $P = 0.047$). They found no effect of *ACE* genotype on systolic BP after the 60% $\dot{V}O_{2max}$ exercise or on diastolic BP after either intensity of exercise. The *AGTR1* A/C and aldosterone synthase (*CYP11B2*) intron 2 W/C variants did not independently influence systolic or diastolic BP responses after 40% or 60% $\dot{V}O_{2max}$ exercise. Individuals carrying variant alleles at all three of these loci had significantly lower systolic (128 ± 3 vs 133 ± 3 mm Hg; $P = 0.03$) and diastolic BP (79 ± 2 vs

TABLE 10. Evidence for the presence of associations between the candidate genes and the response of BMI, body composition, or fat distribution phenotypes to habitual PA or regular exercise.

Gene	Location	No. Cases	Phenotype	*P* Value	Reference
Interactions with exercise/PA					
GDF8 (MSTN)	2q32.2	18 men and 14 women	Leg muscle volume	NS (all) 0.067 (women)	(117)
ADRB2	5q31–q32	420 men	Weight	0.0001	(174)
			BMI	0.0001	
			Waist circumference	0.0001	
			Hip circumference	0.0007	
			WHR	0.02	
		252 women	Obesity, BMI	$0.005 < P < 0.05$	(41)
NPY	7p15.1	9 Leu7/Leu7 and	Plasma NPY during exercise	<0.05	(123,124)
		9 Leu7/Pro7	Plasma GH during exercise	<0.05	
ADRB3	8p12–p11.2	61 obese	Weight	<0.001	(262)
		Diabetic women	BMI	<0.001	
			WHR	<0.001	
UCP3	11q13	368 obese patients	BMI	0.015	(204)
LRP5	11q13.4	868 men	BMD (spine)	<0.05	(134)
GNB3	12p13	3728 men and women	Obesity	<0.001	(85)
VDR	12q13.11	33 women	BMD	0.03	(311)
		120 girls	BMD	0.04	(138)
		99 girls	BMD	0.02	(160)
		575 PM women	BMD	0.04	(21)
		44 male athletes; 44 controls	Bone mineral content; bone mineral volume	<0.02	(192)
		190 women	BMD	<0.05	(81)
ACE	17q23	481 teen-aged girls	Subscapular and triceps skinfolds	<0.012	(183)
		3075 subjects, aged 70–79 yr	%FAT, intermuscular thigh fat	0.02	(141)
COMT	22q11.21–q11.23	1,068 men	Body mineral density (whole body)	<0.0001	(158)
Training responses or acute exercise					
ADRA2B	2p13–q13	98 men and women	Intermuscular fat	0.04	(352)
PPARG	3p25	490 subjects	Body weight	0.04	(155)
		29 healthy offspring of type 2 diabetics	Body weight	0.05	(203)
ADRB2	5q31–q32	12 obese women	RER	<0.05	(164)
		482 men and women	BMI, FM, %FAT, subcutaneous fat	$0.0003 < P < 0.03$	(78)
		70 men and women	%FAT, trunk fat	<0.02	(219)
ENPP1	6q22–q23	84 women	Body weight	0.02	(211)
			BMI	0.03	
ESR1	6q25.1	140 men	BMD	0.007	(242)
LPL	8p22	249 white women	BMI, fat mass, %FAT	$0.01 < P < 0.05$	(77)
		171 black women	Abdominal visceral fat	0.05	
ADRB3	8p12–p11.2	106 men	Leptin	<0.05	(122)
		76 women	Body weight, BMI, waist circumference	$0.001 < P < 0.02$	(282)
		70 men and women	Fat mass, %FAT, trunk fat	<0.05	(219)
IL6	7p21	130 men	Cortical bone area	0.007	(60)
IL15RA	10p15–p14	153 men and women	Lean mass	<0.05	(249)
			Arm circumference	<0.05	
			Leg circumference	<0.05	
UCP3	11q13	503 whites	Subcutaneous fat	0.0006	(151)
GNB3	12p13	255 blacks	FM	0.012	(237)
				%FAT 0.006	
VDR	12q13.11	20 men	1,25-dihydroxyvitamin D3 plasma level	<0.05	(294)
		83 older men and women	Femoral neck BMD	<0.05	(228)
IGF1	12q22–q23	502 men and women	Fat-free mass	0.005	(291)
BDKRB2	14q32.1	428 triathletes	Weight loss during triathlon competition	<0.05	(265)
CYP19A1	15q21.1	173 women	BMI, fat mass, %FAT	<0.05	(313)
SLC6A4	17q11.1	428 triathletes	Weight loss during triathlon competition	<0.05	(265)
PNMT	17q21–q22	149 women	Body weight	0.002	(218)
ACE	17q23	81 men	Body weight	0.001	(177)
			Fat mass	0.04	
			Fat-free mass	0.01	
RETN	19p13.2	120 men	Upper arm cortical bone volume	0.0006	(221)
		203 women	Upper arm cortical bone volume	<0.003	
COMT	22q11.21–q11.23	173 women	%FAT	<0.05	(313)
PPARA	22q13.31	146 men	Upper arm subcutaneous fat	0.002	(315)

BMI, body mass index; WHR, waist-to-hip ratio; GH, growth hormone; RER, respiratory exchange ratio; FM, fat mass; %FAT, percent body fat.

83 ± 2 mm Hg; $P = 0.00$) after 40% $\dot{V}O_{2max}$ exercise. The number of variant alleles carried by participants did not significantly affect either systolic or diastolic BP after the 60% $\dot{V}O_{2max}$ exercise.

In a unique study, Scharin Tang et al. (270) investigated the impact of the *ADRB1* Ser49Gly variant in the transplanted heart in 20 heart transplant patients on HR responses during a cycle ergometer test. They found a tendency for individuals with a Gly homozygote transplanted heart to have greater HR responses to maximal cycle ergometer exercise than individuals with transplanted hearts carrying at least one Ser allele at this locus (64 ± 13 vs 47 ± 16 beats·min^{-1}; $P = 0.056$).

Leineweber et al. (152) studied the effect of the *ADRB1* Arg389Gly gene variant on the hemodynamic responses of 16 Caucasian men to supine cycle ergometer exercise while also undergoing atropine blockade. They found that HR, left ventricular (LV) contractility, plasma renin activity, and systolic and diastolic BP responses to the exercise were the same between genotype groups, whereas at the two highest work rates, plasma norepinephrine responses were significantly greater in Gly compared with Arg homozygotes at this locus (473 ± 154 vs 215 ± 166 pg·mL^{-1}; $P = 0.013$).

Ueno et al. (314) studied the impact of the *ADRA2B* 12Glu9 variant on cardiac autonomic responses to sustained handgrip exercise in 78 normotensive obese women. They found that Glu12 homozygotes and heterozygotes increased mean BP and HR with handgrip exercise (both $P < 0.05$), whereas the Glu9 homozygotes did not increase either mean BP or HR with handgrip exercise. The same trends were evident with normalized low-frequency components assessed by R-R interval power spectral analysis increasing during exercise in Glu12 carrier groups but not Glu9 homozygotes. In fact, during the handgrip exercise, Glu12 carriers had higher normalized low-frequency component levels on power spectral analysis than Glu9 homozygotes. On the other hand, normalized high-frequency components decreased with exercise in Glu12 homozygotes but not the other two genotype groups (314).

Hand et al. (96) assessed the effects of two *NOS3* genotypes on submaximal and maximal exercise hemodynamic responses in 62 Caucasian postmenopausal women of differing PA levels. *NOS3* T-786C genotype did not significantly influence BP, HR, cardiac output ($\dot{Q}$), stroke volume (SV), arterial-venous oxygen difference (a-vO_{2diff}), or total peripheral resistance (TPR) during submaximal or maximal exercise when averaged across all habitual PA levels. However, *NOS3* G894T genotype significantly or tended to affect submaximal exercise diastolic BP ($P = 0.06$), HR ($P = 0.007$), and SV ($P = 0.03$) and maximal exercise HR ($P = 0.04$) and SV ($P = 0.08$) when averaged across all PA groups. Systolic BP, $\dot{Q}$, a-vO_{2diff}, and TPR during submaximal exercise and systolic and diastolic BP, $\dot{Q}$, a-vO_{2diff}, and TPR during maximal exercise were not significantly associated with *NOS3* G894T genotype when averaged across all habitual PA groups.

Arena et al. (12) studied HR responses after supine leg ergometer exercise in 40 patients with hereditary hemochromatosis who were homozygous for a C282Y hemochromatosis (*HFE*) gene mutation compared with 21 age- and gender-matched healthy controls. The patients were found to have a significantly smaller reduction in HR 1 min after the exercise test compared with the healthy control subjects (29 ± 9 vs 35 ± 9 beats·min^{-1}; $P < 0.01$). No other differences were noted between the groups for peak exercise HR, systolic BP, or double product.

Perhonen et al. (214) in Finland studied the responses of seven symptomatic potassium voltage-gated channel, KQT-like subfamily, member 1 (*KCNQ1*) G589D missense mutation carriers, which cause the familial long QT syndrome LQT1 subtype, to a maximal cycle ergometer exercise test. They found that the patients had a lower maximal HR than healthy controls (160 ± 3 vs 180 ± 2 beats·min^{-1}; $P < 0.05$). However, the patients had similar resting HR, left ventricular (LV) mass, and resting LV ejection fraction as the healthy controls.

Ashley et al. (14) assessed the effect of the *ACE* I/D polymorphism on the degree to which 85 highly trained athletes (23 women, 62 men) reduced their LV function after a 300-mile race requiring many modes of exercise; the range of times required to complete the event was 84–110 h. Interestingly, these authors did not find an excess of

TABLE 11. Summary of linkage studies with training-induced changes in body composition phenotypes.

Gene	Marker	Location	No. Pairs	Phenotype	*P* Value	Reference
QTL	S100A1	1q21	291 white	FFM	0.0001	(35)
	ATP1A2	1q21–q23	291 white	%FAT	0.001	(35)
QTL	S100A1, ATP1A2, ATP1B1	1q21–q23	72 black	ATF	<0.01	(243)
QTL	D1S1660	1q31.1	291 white	FM, %FAT	0.0007	(35)
QTL	D5S1725	5q14.1	291 white	BMI	0.0004	(35)
QTL	D7S3070	7q36	72 black	ATF	0.00032	(243)
QTL	D9S282	9q34.11	291 white	FM, %FAT, Sum of skinfolds	$0.001 < P < 0.04$	(35)
QTL	ADRA2A	10q24–q26	72 black	ASF	<.01	(243)
QTL	IGF2	11p15.5	72 black	ATF	<.01	(243)
QTL	UCP2	11q13	291 white	%FAT	0.0008	(35,151)
				FM	0.004	
IGF1		12q22–q23	308 white	FFM	0.0002	(291)
QTL	IGF1	12q22–q23	291 white	FFM	0.0001	(35)
QTL	D18S878, 1371	18q21–q23	291 white	FM, %FAT	$0.001 < P < 0.04$	(35)

QTL, human quantitative trait locus identified from a genome scan; FFM, fat-free mass; FM, fat mass; %FAT, percent body fat; ATF, total abdominal fat; ASF, abdominal subcutaneous fat.

ACE I-alleles in this highly trained endurance athlete population. However, individuals homozygous for the *ACE* I-allele experienced a significantly greater decline in LV ejection fraction after the event compared with D-allele homozygotes (approximately −14% vs −6%; $P = 0.017$); heterozygotes had responses intermediate between the two homozygote groups. *ACE* genotype did not have a significant effect on diastolic function changes after the event. *ACE* genotype differentially affected the changes in autonomic function after the event as measured by BP spectral analyses with a significant decline in the high-frequency domain in D/D genotype individuals ($P < 0.01$). There tended to be an increase in the low-frequency domain in BP spectral analysis in D/D individuals ($P = 0.06$), whereas I/I and I/D genotype individuals showed no change in this domain.

Hautala et al. (100) studied the effects of six SNP within the *CHRM2* locus on HR recovery after a maximal exercise test in 80 Finnish men and women. SNP in *CHRM2* were not associated with maximal HR but did influence HR recovery after exercise. Individuals homozygous for the T-allele at the rs324640 locus exhibited significantly greater HR recovery 1 min after maximal exercise (−40 ± 11 beats·min^{-1}; $P = 0.008$) than heterozygotes (−33 ± 7 beats·min^{-1}) or homozygotes for the C-allele at this locus (−33 ± 10 beats·min^{-1}). In addition, A-allele carriers at the rs8191992 locus showed significantly less HR recovery after exercise than T homozygotes at this locus ($P = 0.025$). Similar trends were seen for systolic BP, but the differences were not significant. Haplotypes constructed based on the rs8191992 and the rs324640 SNP showed generally stronger statistical trends for these same hemodynamic phenotypes.

Zateyshchikov et al. (353) studied the effects of common variants in the *CYP2D6* and *ADRB1* genes on exercise responses in 81 essential hypertensive patients undergoing treatment with betaxalol. They found that the Pro34Ser genotype affected some hemodynamic responses to maximal exercise with heterozygotes having greater reductions in maximal exercise HR (−30 ± 3 vs −24 ± 3 beats·min^{-1}; $P = 0.043$) and maximal exercise diastolic BP (−13 ± 1 vs −9 ± 2 mm Hg; $P = 0.022$) with betaxalol treatment than Ser homozygotes. However, they did not find any significant effects of Ser49Gly and Arg389Gly *ADRB1* genotypes on hemodynamic responses to maximal exercise in these individuals before or after betaxalol treatment.

In addition to performing genome-wide linkage scans (see Linkage studies section), Ingelsson et al. (115) also assessed genotype associations for 235 SNP in 14 putative CV genes relative to exercise treadmill test responses in 2982 participants in the Framingham Offspring Study. They found the following nominal associations: *ADRA1A* (rs489223) and exercise systolic BP ($P = 0.004$); *AGT* (rs2493136; $P = 0.003$), *ADRA1D* (rs835873; $P = 0.008$), and exercise diastolic BP; *ACE* (rs4305; $P = 0.01$), *ADRA1A* (rs544215; $P = 0.005$), *ADRA1D* (rs3787441; $P = 0.007$), and exercise HR; *ADRA1A* (rs483392; $P = 0.005$), *ADRA1A* (rs7820633; $P = 0.005$), and recovery systolic BP; *ADRA1A* (G2286a1) and recovery diastolic BP ($P = 0.009$); and *ADRA1B* (rs11953285) and recovery HR ($P = 0.01$). However, none of these associations remained significant after accounting for multiple testing.

Vasan et al. (320) performed a genome-wide association study for hemodynamic responses to acute treadmill exercise using 70,987 SNP in 1238 related middle- to older-age

TABLE 12. Evidence for the presence of associations between the candidate genes and the responses of glucose and insulin metabolism phenotypes to habitual PA or regular exercise.

Gene	Location	No. Subjects	Phenotype	*P* Value	Reference
Interactions with exercise/PA					
PPARG	3p25	566	T2DM	0.02	(196)
VDR	12q13.11	1,539 subjects	Fasting glucose	<0.001	(201)
Training responses or acute exercise					
ADIPOR1	1p36.1–q41	45 subjects	Insulin sensitivity	0.03	(288)
ADRA2B	2p13–q13	481 subjects	Incidence of T2DM	0.03	(143)
PPARG	3p25	123 men	Fasting insulin, HOMA	$0.02 < P < 0.05$	(121)
		139 men	Fasting glucose	0.03	(2)
		32 men	Fasting insulin, insulin AUC	0.003	(337)
SLC2A2 (GLUT2)	3q26	479 subjects	Conversion from IGT to T2DM	<0.05	(135)
UCP1	4q28–q31	106 men	Fasting glucose	<0.01	(122)
ADRB2	5q31–q32	19 obese women	Insulin to glucose ratio	<0.05	(165)
		124 men	Fructosamine	0.0005	(120)
PPARD	6p21.2–p22.1	136 subjects	Fasting insulin, insulin sensitivity	<0.05	(289)
ADRB3	8p12–p11.2	106 men	Fasting glucose, glycosylated hemoglobin levels	<0.05	(262)
LEPR		397 men and women	Insulin sensitivity, glucose tolerance, pancreatic B-cell compensation for insulin resistance	$0.01 < P < 0.05$	(148)
LEP		397 men and women	Fasting insulin	0.02	(148)
IL6	7p21	56 men and women	Glucose tolerance	0.02	(173)
ABCC8 (SUR1)	11p15.1	479 subjects	Conversion from IGT to T2DM	0.007	(135)
LIPC	15q21–q23	522 subjects	Incidence of type 2 diabetes	0.001	(302)
		219 blacks	Insulin sensitivity	0.008	(299)
		443 whites	Insulin sensitivity	0.002	(299)
ACE	17q23	35 men	Insulin sensitivity	<0.05	(57)
FHL1	Xq27.2	221 men 207 women	Insulin sensitivity	<0.05	(298)

AUC, area under the curve.

men and women in the original Framingham Study and the Framingham Offspring Study. In these analyses, the five strongest associations based on general estimating equations (additive genetic models) were rs6847149 ($P = 2.74 \times 10^{-6}$), rs2819770 ($P = 3.53 \times 10^{-6}$), and rs2056387 ($P = 5.17 \times 10^{-6}$) for stage 2 exercise HR; rs746463 ($P = 4.88 \times 10^{-6}$) for 3-min recovery systolic BP; and rs2553268 ($P = 6.32 \times 10^{-6}$) for stage 2 exercise systolic BP. The five strongest associations using family-based association tests were rs1958055 for stage 2 exercise HR ($P = 8.55 \times 10^{-6}$); rs7828552 ($P = 9.34 \times 10^{-6}$) and rs2016718 ($P = 2.20 \times 10^{-7}$) for recovery systolic BP; and rs1029947 ($P = 9.20 \times 10^{-7}$) and rs1029946 ($P = 3.89 \times 10^{-6}$) for recovery HR. However, none of these associations reached statistical significance after accounting for multiple testing.

Gene–PA interactions. During 2006 and 2007, three published studies assessed the interactive effect of genetic variants and PA levels on hemodynamic phenotypes (Table 7). Rankinen et al. (231) in the HYPGENE Study compared *EDN1* genotype and haplotype frequencies between hypertensive cases ($n = 607$) and matched controls ($n = 586$). They found that two SNP (rs2070699 and Lys198Asn) significantly interacted with CV fitness to affect the risk of hypertension with the genotype-dependent relationship for both SNP being evident in the low-fit but not the high-fit individuals. Analyses of haplotypes constructed from these two SNP substantiated the significant effect of these SNP interacting with CV fitness on hypertension risk.

Grove et al. (85) assessed the impact of *GNB3* C825T genotype interacting with habitual PA levels on a person's risk of developing hypertension in 14,716 blacks and whites in the Atherosclerosis Risk in Communities Study. They found a significant ($P = 0.02$) multiplicative interaction between *GNB3* genotype, PA levels, and obesity on risk of hypertension in blacks. After accounting for race, obese 825T homozygotes with low levels of habitual PA had almost a threefold greater risk of being hypertensive (OR = 2.71, $P = 0.018$) than 825C homozygotes who were nonobese and physically active.

Hand et al. (96) assessed the effects of two *NOS3* genotypes on submaximal and maximal exercise hemodynamic responses in 62 Caucasian postmenopausal women of differing PA levels. In this study, *NOS3* G894T and T-786C genotypes did not interact significantly with habitual PA levels to influence BP, HR, $\dot{Q}$, SV, a-vO_{2diff}, or TPR during submaximal or maximal exercise in these women.

Training response. During 2006 and 2007, 10 published studies assessed the effect of genetic variants on hemodynamic responses to exercise training (Table 8). Rankinen et al. (231) in the HERITAGE Cohort assessed the effect of *EDN1* genotypes and haplotypes on exercise training-induced changes in hemodynamic phenotypes to determine whether they supported their cross-sectional findings reported above in the HYPGENE Cohort. They found that in whites in the HERITAGE Cohort, two *EDN1* SNP (Lys198Asn and rs4714383) were significantly associated with the training-induced responses of systolic BP and pulse pressure at a 50-W work rate. They also found that haplotypes across these two loci accounted for 2.6% and 3.5% of the interindividual variance in the training-induced responses of systolic BP and pulse pressure at a 50-W work rate, respectively, whereas the contribution of the individual SNP ranged from 0.8% to 1.7%.

Flavell et al. (70) studied the response of MRI-determined LV mass and BP to 10 wk of military training in young male army recruits. They sought to determine the effect of the lipoprotein lipase (*LPL*) S447X variant on these responses, and they found that X447 carriers showed a smaller increase in LV mass ($2 \pm 2\%$ vs $6 \pm 1\%$; $P = 0.03$) but a greater decrease in systolic BP (-6 ± 2 vs 2 ± 1 mm Hg; $P = 0.015$) in response to the training than men not carrying an X447 allele.

Jones et al. (119) assessed the impact of two common gene variants in the renin–angiotensin system on the changes in 24-h ambulatory BP and sodium (Na^+) excretion with seven to eight consecutive days of exercise training in

TABLE 13. Linkage studies for insulin and glucose metabolism, and lipid and lipoprotein training response phenotypes.

Gene	Markers	Location	No. Pairs	Phenotype	*P* Value/LOD	Reference
QTL	D1S1622	1p35.1	280 white	DI	1.2	(7)
QTL	D1S304–D1S2682	1q43–q44	72 blacks	S_G	1.1–1.7	(7)
QTL	D2S2247–D2S2374	2p22.1–p21	72 blacks	S_G	1.3–1.5	(7)
QTL	D2S1776	2q31	300 white	f-Insulin	0.0042	(149)
QTL	D3S1279	3q25.2	280 white	DI	1.2	(7)
QTL	D6S299	6p22.1	280 white	DI	1.2	(7)
QTL	PON2	7q21	300 white	f-Insulin	0.0035	(149)
QTL	PON1–D7S821	7q21.3	280 white	DI	1.2–1.4	(7)
QTL	LEP	7q31	300 white	f-Insulin	0.0004	(149)
QTL	D10S541–D10S2470	10q23.1–q23.2	72 blacks	S_G	1.0–1.4	(7)
QTL	D10S2470	10q23.2	286 white	HDL-TG	2.2	(68)
QTL	D12S1661–D12S1604	12q13.11–q13.13	72 blacks	S_G	1.0–1.3	(7)
QTL	D12S1691	12q14.1	286 white	LDL-C	2.1	(67)
QTL	D13S219	13q12–q14	286 white	LDL-TG	2.2	(68)
QTL	D15S63	15q11	72 black	f-Insulin	0.0059	(149)
QTL	GYS1–D19S254	19q13.33–q13.43	72 blacks	S_G	1.8–3.1	(7)
QTL	D20S840	20q13	286 white	LDL-apoB	2.2	(67)

f, fasting; DI, disposition index; S_G, glucose effectiveness; LDL-C, low-density lipoprotein cholesterol; LDL-apoB, apolipoprotein B content of the LDL fraction; LDL-TG, triglyceride content of the LDL fraction.

TABLE 14. Blood lipid, lipoprotein, hemostatic, inflammation, and steroid phenotypes and association studies with candidate genes.

Gene	Location	No. Subjects	Phenotype	*P* Value	Reference
Acute exercise					
FGB	4q28	149	Fibrinogen	0.01	(179)
ADRB2	5q31–q32	15 obese women	Lipolysis, fat oxidation	<0.05	(166)
		19 obese women	Fat oxidation	0.024	(165)
NPY	7p15.1	18	Serum FFA	<0.05	(123)
APOC3	11q23.1–q23.2	100 Korean men	Triglycerides	0.042	(346)
STS	Xp22.32	62 men, 58 women	DHEA	0.006	(250)
Exercise training					
APOA1	11q23–q24	75 subjects	Large HDL fraction	0.0005	(259)
			Small HDL fraction	0.005	
IL6		41 women, 24 men	Total HDL-C change	0.003	(94)
			HDL_3-C change	0.001	
			HDL_{4NMR} change	0.04	
			HDL_{5NMR} change	0.04	
			$HDL_{4,5NMR}$ change	0.02	
			HDL_{size} change	0.02	
LIPC	15q21–q23	219 blacks (B),	ApoB levels	0.04 (B only)	(299)
			LIPC activity	0.0001 (W&B)	
		443 whites (W)	LPL activity	0.009 (W&B)	
ADIPOR1	1p36.1–q41	45 subjects	Hepatic lipid content	0.008	(288)
FGA	4q28	125	Fibrinogen	0.002	(241)
FGB	4q28	250	Fibrinogen	0.001	(25)
FABP2	4q28–q31	14 men and 55 women	LDL-C	<0.05	(46)
TNF	6p21.3	456 whites	CRP	0.04	(147)
PPARD	6p21.2–21.1	272 blacks	ApoA1	0.034–0.057	(99)
		478 whites	HDL-C	0.002–0.006	
SERPINE1	7q21.3–q22	132	Plasminogen activator inhibitor, type 1	0.025	(317)
LPL	8p22	18	HDL-C	<0.05	(89)
			HDL_2-C	<0.05	
CETP	16q21	32	$HDL_{3\text{-}5NMR}$ cholesterol	<0.05	(341)
		307 men and women	Total cholesterol	0.048	(15)
		231 men and 255 women	HDL_3-C	0.001–0.09	(286)
			ApoA1	0.001–0.05	
LIPG	18q21.1	83	HDL-C	0.04	(93)
APOE	19q13.2	51	HDL-C	<0.03	(90)
			HDL_2-C	<0.01	
		252 white women	LDL-C	0.022	(153)
			HDL-C	0.0062	(153)
			HDL_2-C	0.013	(153)
			HDL_3-C	0.013	(153)
			VLDL-C	<0.0001	(153)
			Triglycerides	0.0024	(153)
			ApoA1	<0.0001	(153)
		241 white men	Total cholesterol	<0.0001	(153)
			LDL-C	<0.0001	(153)
			HDL-C	0.05	(153)
			Triglycerides	0.011	(153)
			ApoB	0.005	(153)
		177 black women	ApoAI	0.043	(153)
		89 black men	LDL-C	0.017	(153)
		120 men and women	TC/HDL ratio	0.033	(300)
			LDL/HDL	0.015	(300)
			ApoB/AI	0.046	(300)
		60 women	LPLA	0.032	(300)
		51 men and 55 women	Medium LDL	<0.01	(276)
			Small LDL	<0.05	
STS	Xp22.32	62 men, 58 women	DHEA	0.005	(250)
			DHEA/DHEAS	0.022	
Exercise–genotype interactions					
APOA2	1q21–q23	200	Serum triglycerides	<0.05	(220)
FGA	4q28	159	fibrinogen	0.024	(240)
ADRB2	5q31–q32	604	Nonesterified FFA	0.05	(175)
PON1	7q21.3	256	Serum triglycerides	0.017	(280)
			HDL-C	0.018	
		17	PON1 activity	<0.001	(303)
			Oxidized LDL	0.018	
LPL	8p22	379	Serum cholesterol	0.003	(22)
			Apolipoprotein B	0.003	
			HDL-C	0.03	
LIPC	15q21–q23	200	HDL-C	<0.01	(220)
			Apolipoprotein A1	<0.01	
CETP	16q21	52 male CAD cases	HDL-C	0.007	(185)
		15 female CAD cases	HDL-C	0.029	(185)
APOE	19q13.2	713	Serum cholesterol	0.014	(293)

(continued on next page)

TABLE 14. (Continued).

Gene	Location	No. Subjects	Phenotype	*P* Value	Reference
Exercise–genotype interactions					
			LDL-C	0.0082	
			HDL/serum cholesterol	0.0004	
		338	HDL-C	0.001	(42)
		1708	HDL-C	$0.001 < P < 0.008$	(17)
			Triglycerides	0.03	
		200	LDL-C	<0.01	(220)
			Apolipoprotein B	<0.01	
PPARA	22q12–q13.1	989 men, 245 women	HDL-C	<0.05	(191)

HDL, high-density lipoprotein; LDL, low-density lipoprotein; FFA, free fatty acids.

31 hypertensive African Americans. Their *ACE* I/I genotype individuals increased 24-h Na^+ excretion after the 7–8 d of exercise (114 ± 22 to 169 ± 39 mEq·d^{-1}; $P = 0.04$), whereas no such increases were evident in the I/D or the D/D genotype individuals. *ACE* genotype did not significantly affect 24-h ambulatory BP, and the *AGT* M235T variant did not affect either 24-h ambulatory BP or Na^+ excretion.

The impact of the fatty acid binding protein 2 (*FABP2*) Ala54Thr gene variant on BP changes after 3 months of a ifestyle intervention that included hypocaloric diet and exercise was studied in 69 obese men and women by de Luis et al. (46). They reported that individuals carrying at least one Thr allele at this locus decreased their systolic BP significantly with the lifestyle intervention (129 ± 12 to 122 ± 13 mm Hg; $P < 0.05$), whereas Ala homozygotes did not reduce their systolic BP. The *FABP2* Ala54Thr variant did not affect diastolic BP responses to the lifestyle intervention.

He et al. (103) assessed the impact of 18 wk of endurance exercise training in 102 Chinese Han men on several performance-related variables which included exercise HR responses. They found that men homozygous for either the G- or C-allele at the intron 2 16G/C variant at the *HBB* locus decreased their HR during treadmill running at 12 km·h^{-1} more than men heterozygous at this locus (-5 ± 3 and -4 ± 4 vs -2 ± 6 beats·min^{-1}; $P < 0.05$).

Cam et al. (32) studied the effects of 6 wk of endurance exercise training on performance measures and resting HR in 55 Caucasian nonelite Turkish women athletes. They reported that the *ACE* I/D polymorphism had no effect on the changes in resting HR elicited with training in these women.

Park et al. (210) studied the impact of the nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (*NFKB1*) −94 I/D polymorphism relative to changes in endothelial function in humans with endurance exercise training. They found that with 6 months of endurance exercise training in 36 pre- and stage 1 hypertensive men and women, there was a tendency for greater improvements in reactive hyperemic forearm blood flow in *NFKB1* I/I and I/D genotype individuals compared with D/D homozygotes at this locus (39 ± 43%, 6 ± 9%, and −13 ± 17% change in 3-min reactive hyperemic blood flow after training). They also found that the I/I genotype was significantly more frequent (31%, $P = 0.047$) and that the D/D genotype was significantly less frequent (4%, $P = 0.006$) among individuals who responded to exercise training with an improvement in reactive hyperemic blood flow response.

Perhonen et al. (214) in Finland studied the responses of seven symptomatic *KCNQ1* G589D missense mutation carriers, which cause the familial long QT syndrome LQT1 subtype, to a maximal cycle ergometer exercise test before and after 3 months of endurance exercise training. With training, LV mass increased by 8–9% in both the patients and the healthy controls. In the patients, exercise training shortened resting corrected QT interval (QTc) by 10 ± 1% ($P < 0.05$), whereas no changes in QTc occurred in the healthy controls. QT interval dispersion at rest after training decreased by 25 ± 9% in the patients ($P < 0.05$), whereas again no such decreases were evident in the healthy controls. The QTc at 5 min of recovery after the exercise test after training was reduced in the patients by 6 ± 2% ($P < 0.05$) with no such changes evident in the healthy control subjects.

As described above in the Acute exercise section, Hautala et al. (100) studied the effects of six SNP within the *CHRM2* locus on HR recovery after a maximal exercise test in 80 Finnish men. However, in these same individuals, they also studied the impact of a 2-wk endurance exercise training program on numerous hemodynamic phenotypes. After training, HR recovery 1 min after maximal exercise was strongly associated with genotype at the rs324640 locus ($P = 0.001$), and the change in HR recovery with exercise training was significantly associated with genotype at this locus (-3 ± 7, 2 ± 7, and 2 ± 8 beats·min^{-1}, for the C/C, C/T, and T/T genotypes, respectively; $P = 0.038$). Genotype at the rs8191992 locus also was significantly associated with HR recovery after training ($P = 0.005$). They also studied the effects of these variants on overnight HR variability assessed by power spectral analyses in these subjects and found that rs8191992 A/A homozygotes had a significantly higher low- to high-frequency domain ratio than other genotype groups at this locus both before ($P = 0.036$) and after training ($P = 0.046$).

Linkage studies. During 2006 and 2007, two studies was published that assessed linkage and CV hemodynamic phenotype changes with exercise training (Table 9). An et al. (6) performed a genome-wide linkage scan using 654 markers to identify QTL for the response of resting HR to exercise training in the HERITAGE Cohort. In whites, they

found multipoint linkages ($P < 0.01$, logarithm of odds [LOD] >1.18) for the change in resting HR with exercise training at the 1q42.2 and the 21q22.3 chromosomal loci. In blacks, linkage was detected at the 3p14.1, 3p14.2, 3p21.2, 20p11.23, and 21q21.1 chromosomal loci.

Ingelsson et al. (115) performed genome-wide scans for exercise treadmill test responses in 2982 participants in the Framingham Offspring Study. For systolic BP during submaximal exercise, they reported an LOD = 2.02 for chromosomal location 1q32.1, LOD = 1.57 for 5q13.2, and LOD = 1.61 for 10q23.3. Chromosomal location 19q13.1 was the only locus linked with diastolic BP during submaximal exercise (LOD = 1.63). Five loci were linked with HR during submaximal exercise: 1p32.1–31.1 (LOD = 1.91), 5q14.3 (LOD = 2.09), 7p15.1–14.3 (LOD = 1.73), 7q21.1 (LOD = 1.67), and 14q24.1 (LOD = 1.91). Chromosomes 1q43–44 (LOD = 2.59) and 2p12 (LOD = 1.68) showed linkage with systolic BP during recovery. Similarly, two loci were linked to diastolic BP during recovery (4p15.3, LOD = 2.37; and 4q28.2, LOD = 1.93) and another two were linked to HR during recovery (5q35.3, LOD = 1.60; and 21q21.1, LOD = 1.66).

TABLE 15. Genes encoded by nuclear and mitochondrial DNA in which mutations have been reported in patients with exercise intolerance.

Gene	OMIM #	Location	Reference
Nuclear DNA			
CPT2	255110	1p32	(168,292,297,325,326)
SLC16A1	600682	1p12	(205)
AMPD1	102770	1p13	(116,208)
LMNA	150330	1q21.2–q21.3	(154)
ETFDH	231675	4q32–q35	(80)
SLC25A4	103220	4q35	(206)
PGAM2	261670	7p13–p12	(88,304,310)
LDHA	150000	11p15.4	(307)
PYGM	232600	11q12–q13.2	(26,260,308)
PFKM	232800	12q13.3	(281,306,327)
SGCG	253700	13q12	(321)
TK2	188250	16q22–q23.1	(333)
ENO3	131370	17pter–p11	(40)
ACADVL	201475	17p13–p11	(271)
SGCA	600119	17q21	(176)
GYS1	138570	19q13.3	(139)
GK	307030	Xp21.3	(104)
PHKA1	311870	Xq12–q13	(27)
PGK1	311800	Xq13	(309)
GLA	301500	Xq22	(336)
LAMP2	309060	Xq24	(188)
Mitochondrial DNA			
MTTF		577–647	(43,58)
MTTL1	590050	3230–3304	(33,111,316)
MTND1	51600	3307–4262	(187)
MTTI	590045	4263–4331	(34)
MTTM	590065	4402–4469	(323)
MTTY	590100	5826–5891	(227)
MTCO1	516030	5904–7445	(130)
MTTS1	590080	7445–7516	(84,226)
MTTD	590015	7518–7585	(278)
MTCO2	516040	7586–8269	(172)
MTTK	590060	8295–8364	(19,76,186)
MTCO3	516050	9207–9990	(97,109)
MTND4	516003	10760–12137	(11)
MTTL2	590055	12266–12336	(131,324)
MTTE	590025	14674–14742	(98,169,207)
MTCYB	516020	14747–15887	(8–10,18,28,133,150,167,273)

OMIM, Online Medelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).

Spielmann et al. (287) assessed the linkage of submaximal exercise HR to chromosomal loci at baseline and after 20 wk of exercise in the black and the white participants in the HERITAGE Family Study. They found that, in whites, there was linkage evidence for HR at a 50-W work rate at baseline at 18q21.33 (LOD = 2.64, $P = 0.0002$), at 2q33.3 (LOD = 2.13, $P = 0.0009$) for the training-induced changes in HR at 50 W, and at 18q21.1 (LOD = 2.10, $P = 0.0009$) for the training-induced change in HR at 60% $\dot{V}O_{2max}$. Five markers in the chromosomal region of 10q24–q25.3 showed evidence of linkage in blacks with HR responses to exercise (Table 9). Because two putative candidate genes (*ADRB1* and *ADRA2A*) lie within this chromosomal region, the investigators performed association studies with 6 *ADRA2A* and 10 *ADRB1* SNP and found that in their black subjects, the Arg389Gly *ADRB1* SNP was significantly associated with baseline HR at 50 W in black siblings ($P = 0.02$) and in the whole cohort ($P = 0.04$).

Anthropometry and Body Composition Phenotypes

Association studies. In the past 2 yr, seven studies tested the association between candidate genes and BMI, body composition, or bone mineral density (BMD) taking into account the interaction with physical activity (PA; Table 10). A study in 1068 men from the Gothenburg Osteoporosis and Obesity Determinants study revealed that a functional polymorphism (Val158Met) in the catechol-*O*-methyltransferase (*COMT*) gene, resulting in a lowered enzyme activity, modulated the association between PA and BMD assessed by dual-energy x-ray absorptiometry (158). A significant interaction ($P < 0.0001$) was found for whole-body mineral density, and stratified analyses revealed significant differences in BMD between high (≥ 4 h·wk^{-1}) and low (< 4 h·wk^{-1}) PA groups in subjects carrying the low-activity variant (Val159Met and Met158Met subjects) compared with subjects homozygous for the high-activity allele (Val158Val subjects), suggesting that the beneficial impact of PA on BMD is greater in the former than in the latter. In a sample of 1797 unrelated subjects (868 men and 929 women) from the Framingham Offspring cohort, Kiel et al. (134) tested the hypothesis that polymorphisms in the low-density lipoprotein receptor-related protein (*LRP5*) gene could modulate the relationship between PA and BMD. Significant evidence of interaction between SNP in exon 10 (rs2306862; $P = 0.02$) and exon 18 (rs3736228; $P = 0.05$) and PA on BMD of the spine was observed in men. Another study undertaken in 190 postmenopausal women revealed evidence of interaction between a polymorphism in a transcription factor Cdx-2 binding site in the promoter of the *VDR* gene and a PA on the femoral neck and Ward's triangle BMD (81).

In a large sample of 10,988 whites and 3728 blacks, Grove et al. (85) tested the interaction between the *GNB3* 825 C > T polymorphism and the PA level in relation to obesity. No significant evidence of interaction was found in

whites, but a significant ($P < 0.001$) interaction was observed in blacks; the T-allele being associated with an increased risk of obesity in subjects with low PA level and a decreased risk in subjects with high PA level (85). In a study conducted in 899 women and 902 men aged between 30 and 75 yr, the *PPARGC1A* Gly482Ser polymorphism was found to be associated with an increased risk of obesity but only in physically inactive (< 2 h·wk^{-1}) males aged ≥50 yr (248). However, the interaction between the polymorphism and the PA level was not statistically significant, and this result is this considered as a negative finding and, consequently, is not reported in Table 10. In other studies involving the *PPARG* Pro12Ala (195) polymorphism and polymorphisms in the *PPARGC1A* gene (194), no evidence of gene–PA interaction could be found for obesity-related phenotypes.

Response to exercise. We found seven studies that tested association with candidate genes and adiposity phenotypes in response to exercise and five reported positive findings (Table 10). In the first study, the effects of several SNP in the resistin (*RETN*) gene were tested for association with changes in upper arm subcutaneous fat and cortical bone volumes measured by magnetic resonance imaging before and after 12 wk of a resistance training program of the nondominant arm in 120 men and 203 women (221). No evidence of association was found with changes in subcutaneous fat, but two *RETN* SNP were associated with changes in the cortical bone volume in women (398 C > T and 980 C > G) and in men (980 C > G). In the second study, 84 Korean women with abdominal obesity were tested before and after 12 wk of aerobic (walking) exercise, and changes in body fat were found to be associated with a polymorphism (K121Q) in the gene ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*) encoding the plasma cell membrane glycoprotein PC-1 (211). Women homozygotes for the K-allele exhibited greater reductions in body weight ($P = 0.002$) and BMI ($P = 0.03$) compared with women carrying the Q-allele.

The third study tested the association of body weight changes during ironman triathlons with polymorphisms in the *ACE*, *BDKRB2*, *NOS3*, and solute carrier family 6 (neurotransmitter transporter, and serotonin) member 4 (*SLC6A4*) genes in 428 triathletes (265). Two functional polymorphisms in the *BDKRB2* and the *SLC6A4* genes were found to be associated with larger weight losses in the triathletes. The fourth study investigated the association between the *PPARA* L162V polymorphism and the upper arm subcutaneous fat in response to resistance training in 610 young men and women (315). Increases in the fat volume of the untrained arm were observed in male ($n = 146$) carriers of the V-allele after exercise training compared with a decrease in subjects with the LL genotype. According to the authors, this finding is a consequence of the 78% increase in triglycerides found in the V-allele carriers compared with the homozygous genotype (315). In the fifth study, CT-assessed changes in intermuscular fat in response to 10 wk of single-leg strength training were examined in relation to polymorphisms in the *ADRB2* and the *ADRA2B* genes in 98 men and women (352). Decreases in intermuscular fat were found to be significantly different between carriers and noncarriers of the *ADRA2B* Glu(9) polymorphism.

Two other studies provided negative findings. In one of these, the influence of the *ADRB3* Trp64Arg polymorphism on weight loss after a 3-month lifestyle modification

TABLE 16. Association and linkage studies for PA phenotypes.

Gene/Marker	Location	No. Subjects/Sib-pairs	Phenotype	*P* Value	Reference
Associations					
LEPR	1p31	268	Total PA (24-h EE/sleeping EE)	0.008	(290)
		222 boys (7 yr old)	Total PA	0.016	(245)
CASR	3q21–q24	97	Weight-bearing PA	0.01	(159)
DRD2	11q23	402 white women	PA	0.016	(283)
		256 white women	Sports index	0.023	(283)
			Work index	0.004	
CYP19A1	15q21.1	331	PA	0.039	(263)
ACE	17q23	355	Sedentary vs active	0.001	(343)
MC4R	18q22	669	Moderate-to-strenuous activity	0.005	(156)
			Inactivity	0.01	
Linkage					
D2S2347	2p22.3	309	Inactivity	0.0012	(284)
D3S1569	3q24	700	Participation in competitive sports	LOD = 2.35 ($P = 0.0005$)	(50)
UCP1	4q28–q31	309	Moderate to strenuous activity	0.005	(284)
D4S1597	4q32.3	700	Participation in competitive sports	LOD = 1.87 ($P = 0.0017$)	(50)
IGFBP1	7p13–p12	308	Inactivity	0.0046	(284)
		308	Moderate to strenuous activity	0.006	(284)
D9S938	9q31	308	Moderate to strenuous activity	0.0028	(284)
C11P15_3	11p15	329	Total activity (previous year)	0.0089	(284)
D13S317	13q22	308	Total activity	0.0029	(284)
		308	Moderate to strenuous activity	0.0067	(284)
D15S165	15q13	329	Total activity (previous year)	0.009	(284)
D18S1102–D18S474	18q12.1–18q21.1	1030 children from 319 families	Sedentary activities	LOD = 4.07	(30)
			Light activities	LOD = 2.79	
D18S64	18q21.32	1030 children from 319 families	Total activity	LOD = 2.28	(30)
			Moderate activities	LOD = 2.2	
PLCG1	20q12	308	Inactivity	0.0074	(284)

program was investigated in 65 obese patients (47). The program consisted of a hypocaloric diet combined with three sessions (60 min each) of aerobic exercise per week. Significant reductions of body weight, BMI, fat mass, and waist circumference were observed in both carriers and noncarriers of the Arg64 allele. Although the authors reported that carriers of the Arg64 allele had a different response than noncarriers, no evidence could be found in the data presented that the response was statistically different between the two genotype groups, as only differences between pre- and postvalues within each genotype group were reported (47). For that reason, and despite the claim of the authors, the results of this study are considered as negative. In another study using the same cohort and lifestyle modification program, de Luis et al. (48) investigated the influence of the *LEPR* Lys656Asn polymorphism on weight loss and leptin changes. As in the previous study, they reported a different response between body weight, BMI, and leptin levels between Lys656Lys subjects and carriers of the *Asn* allele, but no formal tests of the differences between the two genotype groups were reported.

Linkage studies. No new linkage studies on anthropometry and body composition-related phenotypes were published in 2006–2007 (Table 11).

Insulin and Glucose Metabolism Phenotypes

Gene–PA interaction. In a study undertaken in 566 subjects, a significant interaction ($P = 0.02$) between PA and *PPARG* Pro12Ala polymorphism on the risk of T2DM was reported in subjects from families with T2DM (196). The authors found that the Pro12 allele was associated with an increased risk of T2DM (OR = 2.37), but only in subjects with low PA (Table 12).

Response to exercise. Using data from 481 participants of the Finnish Diabetes Prevention Study followed-up for an average of 4.1 yr, Laaksonen et al. (143) found an interaction ($P = 0.03$) between the *ADRA2B* 12Glu9 polymorphism, which consists of a deletion of 9 bp encoding three glutamic acid residues, and the changes in PA on the risk of developing T2DM. Increased PA was associated with a reduced risk of T2DM but only in subjects with the Glu12/12 (RR = 0.12) and Glu12/9 (RR = 0.30) genotypes. In another study based on data from the same cohort (135), the association of polymorphisms in the solute carrier family 2 (facilitated glucose transporter), member 2 (*SLC2A2*), ATP-binding cassette, subfamily C (CFTR/MRP), member 8 (*ABCC8*), and potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*) genes with the conversion from impaired glucose tolerance (IGT) to T2DM according to changes in PA level was studied in 479 subjects. Three polymorphisms in the *SLC2A2* gene as well as one polymorphism in the *ABCC8* gene provided significant evidence of interaction with changes in moderate-to-vigorous PA (≥3.5 METs) in predicting the conversion from IGT to T2DM. In all cases, increased moderate-to-vigorous PA, independent of the changes in diet and body weight, was associated with a reduced risk of T2DM, but only in carriers of the common homozygous genotypes (135). The impact of lifestyle modification (dietary counseling and endurance exercise

TABLE 17. Evolution in the status of the human gene map for performance and health-related fitness phenotypes.

Phenotypes	2000	2001	2002	2003	2004	2005	2006–2007
Endurance							
No. articles	20	24	29	39	47	53	72
No. loci	22	23	25	31	37	37	47
Strength + anaerobic							
No. articles	2	6	8	9	16	23	40
No. loci	2	5	7	8	13	20	26
Hemodynamics							
No. articles	12	18	28	35	40	44	67
No. loci	7	31	45	46	47	48	80
Familial cardiac arrhythmias							
No. articles	—	—	6	6	6	6	6
No. loci	—	—	5	5	5	5	5
Anthropometry + body composition							
No. articles	7	15	25	30	33	37	44
No. loci	7	21	28	31	34	34	39
Insulin + glucose metabolism							
No. articles	1	2	4	7	11	16	21
No. loci	1	1	3	11	15	25	30
Lipids, inflammation + hemostatics							
No. articles	8	11	16	20	25	32	38
No. loci	5	7	8	11	14	21	25
Chronic disease							
No. articles	—	—	—	3	4	7	7
No. loci	—	—	—	4	5	7	7
Exercise intolerance							
No. articles	—	30	36	39	43	52	66
No. loci	—	20	22	23	27	31	37
PA							
No. articles	—	—	—	—	5	6	9
No. loci	—	—	—	—	13	14	18

for 9 months) on changes in insulin sensitivity measured in 139 subjects was tested for association with polymorphisms in the *PPARD* (three SNP) and *PPARGC1A* (one SNP) genes (289). Two polymorphisms in the *PPARD* gene were associated with changes in fasting insulin and insulin sensitivity, whereas no association was found with the *PPARGC1A* gene. The associations between three polymorphisms in the 4.5 LIM domain 1 (*FHL1*) gene and insulin responses to endurance training were investigated in participants from the HERITAGE Family Study (298). In white men ($n = 221$), two polymorphisms in the FHL1 gene were associated with fasting insulin, the disposition index and the glucose disappearance index responses to exercise training. In white women ($n = 207$), one polymorphism was associated with the glucose disappearance index training response. In the study of de Luis et al. (47) described in the Response to exercise section, significant improvements of glucose levels and insulin sensitivity in response to the lifestyle modification program were reported in subjects with the *ADRB3* Trp64Trp genotype compared with no improvements in carriers of the Arg64 allele. However, as explained above, in the absence of a statistical test showing a difference between the two genotype groups, we treated this result as a negative finding.

Linkage studies. No new linkage studies were published in 2006–2007 (Table 13).

Blood Lipid and Lipoprotein Phenotypes

A total of six new articles were published in 2006/2007 that analyzed genetic association or linkage for lipid responses to acute or chronic exercise and/or PA (Table 14). Seip et al. (276) investigated the effect of *APOE* genotype on lipoprotein subclass concentrations in response to 6 months of submaximal aerobic exercise training. LDL particle fractions changed significantly after exercise training as a function of genotype, with medium LDL cholesterol (LDL-C) increasing in *APOE*3/3 homozygotes and decreasing significantly differently from the *APOE*3/3 genotype class ($P < 0.01$) in individuals with *APOE*2/3 or *APOE*3/4 genotypes. Conversely, small LDL-C increased in *APOE*2/3 and *APOE*3/4 heterozygotes and decreased in subjects with the *APOE*3/3 genotype class, which was significantly different from *APOE*2/3 and *APOE*3/4. Although other lipid fractions (all VLDL fractions, large LDL, and small and large HDL) were altered by exercise training, these alterations were not different by *APOE* genotype (276). In a separate intervention study, participants underwent a lifestyle modification program that consisted of a hypocaloric diet combined with aerobic exercise three times per week for 12 wk (46). Levels of LDL-C were significantly lower by genotype at the Ala54Thr variant in the *FABP2* gene after the intervention. Ala54/Ala54 homozygotes had significantly lower LDL levels after exercise/diet intervention, whereas no significant differences were observed in carriers of the Thr54 allele (46).

Hautala et al. (99) investigated two variants (exon 4 + 15 C/T and exon 7 + 65 A/G) in the *PPARD* gene for associations with blood lipid responses to 20 wk of aerobic exercise training in white and black men and women from the HERITAGE Family Study. In white subjects, both variants were associated with increases in HDL cholesterol (HDL-C) and HDL-C subfractions (HDL_2-C and HDL_3-C), with exon 4 + 15 C homozygotes and exon 7 + 65 G homozygotes experiencing the largest increases in HDL-C after exercise training. Haplotypes of the two variants were also associated with HDL-C and HDL_2-C training response in white subjects (99). In black subjects, HDL-C fractions were not different by genotype, but increases in ApoA1 levels after exercise training were associated with the exon 4 + 15 C/T (but not the exon 7 +65 A/G) polymorphism, with C/C homozygotes having the largest increases in this measure (99). In a separate study of the HERITAGE participants, changes in total HDL-C, HDL-C subfractions, and ApoA1 levels after exercise training were investigated for associations with multiple variants in the *CETP* gene (286). None of the variants were robustly associated with alterations in blood lipids after exercise training in black subjects. Nevertheless, the −1337C > T and −629C > A variants were both associated with changes in HDL_3-C and ApoA1 but only in whites (286). A significant Sex × Genotype interaction was observed for the −629C > A polymorphism for HDL_3-C and ApoA1 training response levels. Women with the A/A genotype had significantly higher levels of HDL_3-C and ApoA1 after exercise training, whereas no differences in levels of either variable by −629C > A genotype were observed for men (286).

In investigating gene–exercise interactions, Naito et al. (191) reported a significant interaction ($P < 0.05$) between exercise frequency and genotype for the *PPARA* V227A polymorphism in predicting HDL-C. Homozygotes for the V227 allele who exercised more than three times per week had significantly higher HDL-C compared with those who exercised two or fewer times per week. No significant differences were observed for HDL-C between exercise frequency groups for the A227 carriers (191).

Only one investigation provided linkage data relevant to blood lipid phenotypes. Feitosa et al. (66) performed a linkage analysis in 99 white and 101 black families, with 654 markers covering the human genome. Significant linkage was observed on chromosome 12q23–q24 for baseline values of HDL-C and TG in white families but not in black families. Weak but nonsignificant signals for HDL-C after exercise training were found for whites but not for blacks (66).

Hemostatic Factors, Inflammation Phenotypes, and Plasma Hormone Levels

One association study investigated the effect of the *TNFA* G308A polymorphism on levels of C-reactive protein (CRP) before and after a 20-wk exercise intervention in

456 white and 232 black men and women (147). Both black and white men and black women who were homozygous for the 308A allele had significantly higher baseline levels of CRP than carriers of the 308G allele. After exercise training, the significant association between the *TNFA* G308A variant and the CRP levels remained in white men and black women only, with 308A/308A homozygotes again having the highest levels of CRP compared with other genotypes (147).

Exercise Intolerance

Fourteen studies related to exercise intolerance were published in 2006–2007 (Table 15). Seven of the studies reported mutations in six nuclear genes, whereas another seven studies dealt with four mitochondrial genes. Wang et al. (336) investigated a cohort of 44 women diagnosed with Fabry disease. A total of 23 missense and 18 nonsense mutations in the alpha galactosidase (*GLA*) gene were detected, and 83% of the women were affected by exercise intolerance (336). Gempel et al. (80) reported seven isolated myopathic coenzyme Q10 deficiency patients, who also exhibited exercise intolerance. Other symptoms included fatigue, proximal myopathy, and high serum creatine kinase levels. Mutation screening of electron-transferring flavoprotein dehydrogenase (*ETFDH*) gene revealed four missense mutations (80).

Kollberg et al. (139) reported three siblings with major skeletal muscle and heart glycogen deficiencies. The two oldest siblings also exhibited exercise intolerance that manifested as difficulty to keep up with physical activities of other children. However, there were no muscle cramps or pain after exercise. Resequencing of the muscle glycogen synthase (*GYS1*) gene revealed that all three siblings were homozygotes for a mutation in exon 11, which replaced an arginine residue with a premature stop codon at residue 462 (139). Two studies reported mutation screening of the muscle glycogen phosphorylase (*PYGM*) gene in McArdle disease patients. Rubio et al. (260) reported three patients who were compound heterozygotes of a known Arg50Stop mutation and a novel c.13_14delCT mutation in exon 1. The new exon 1 mutation induces a frameshift and a premature stop codon 21 amino acids downstream from the mutation site. Bruno et al. (26) identified 30 PYGM mutations in 68 Italian McArdle disease patients, including 19 novel variants. However, none of the novel mutations correlated directly with the clinical phenotype of the patients.

Exercise-induced hyperinsulinism (EIHI) is a dominantly inherited disorder that features a paradoxical increase in insulin secretion during anaerobic exercise resulting in hypoglycemia. Otonkoski et al. (205) mapped a QTL for EIHI on chromosome 1 (LOD = 3.6) in two families with 10 EIHI patients. The strongest candidate gene located under the linkage peak was *SLC16A1*, which encodes monocarboxylate transporter 1. Mutation screening of SLC16A1 revealed promoter mutations in all investigated EIHI patients. Functional studies revealed that the promoter mutations induced a marked transcriptional stimulation of the gene in pancreatic beta cells, where *SLC16A1* expression is normally very low. When lactate and pyruvate levels increase during exercise, the abnormally high expression of *SLC16A1* in EIHI patients facilitates pyruvate uptake in beta cells and leads to pyruvate-stimulated insulin release although blood glucose level is normal or even low. Finally, Liang et al. (154) reported a novel mutation in codon 520 of the lamin A/C (*LMNA*) gene in an exercise intolerance patient diagnosed with Emery–Dreifuss muscular dystrophy.

Seven studies reported mutations in four mitochondrial genes in exercise intolerance patients. Additional exercise intolerance patients were reported with a 3243A > G mutation in the *MTTL1* locus (316) and novel mutations in the *MTTK* (19,76) and the MTTE loci (169,207). A new mitochondrial gene entry to the fitness gene map is *MTTF* that encodes phenylalanine transfer RNA. Darin et al. (43) reported an *MTTF* 583G > A mutation in a 17-yr-old girl with mitochondrial myopathy and exercise intolerance, whereas a 622G > A mutation was identified in a 66-yr-old woman with a late-onset neuromuscular disease and exercise intolerance (58).

Physical Activity

During 2006 and 2007, three studies dealing with DNA sequence variation and PA-related traits were published (Table 16). Richert et al. (245) investigated associations between Gln223Arg polymorphism in the leptin receptor (*LEPR*) gene and total PA in 222 prepubertal boys. PA level was assessed twice, first at the age of 7 yr and a second time 2 yr later when boys were 9 yr old. Activity level was assessed using questionnaires, and total activity was expressed as PA energy expenditure. The *LEPR* Arg223Arg homozygotes had a significantly lower PA level than the other two genotypes at baseline (7 yr old), but the difference had disappeared 2 yr later (245).

Cai et al. (30) performed a genome-wide linkage scan for PA phenotypes in 1030 Hispanic children (average age = 11.0 yr) from 319 families. The maximal heritabilities for total PA, sedentary activity, and light and moderate activities (derived from 3-d accelerometer recordings) varied from 46% to 57%. The linkage analysis revealed QTL on chromosome 18q12.2–q21.1 for sedentary and light activities with logarithm of odds (LOD) scores of 4.07 and 2.79, respectively. Maximum LOD scores of 2.28 and 2.2 for total and moderate activities, respectively, were detected about 20 cM downstream at 18q21.32, near the melanocortin 4 receptor (*MC4R*) locus.

A genome-wide linkage scan for participation in competitive sports was performed in 700 female dizygotic twins (50). Participation history (athlete status) was obtained by asking if the subjects had ever participated in competitive sports and at what level they had competed. A heritability

estimate of 66% was derived for athlete status. The genome-wide linkage scan using 1946 markers (736 microsatellites, 1210 SNP) revealed two suggestive QTL on chromosomes 3q22–q24 (LOD = 2.35) and 4q31–q34 (LOD = 1.87) (50).

SUMMARY AND CONCLUSIONS

In this current version of the performance and health-related fitness gene map, we report 27 new autosomal or X-linked genes, one mitochondrial variant, and 24 QTL identified as being associated with fitness or performance traits or exhibiting gene–PA or gene–exercise training interactions since the previous version of the map. A total of 221 autosomal and X-linked genes and 18 mitochondrial markers have been shown to be associated with a relevant phenotype in at least one study, whereas 119 QTL have been reported for exercise- or PA-related traits. Table 17 provides an overview of the evolution of the interest in genetics of fitness and performance traits by family of phenotypes or endophenotypes since the first version of the map in 2000. The *ACE* gene continues to be by far the most extensively studied of any gene, with at least 58 articles examining the effect of an insertion/deletion polymorphism on fitness and performance traits. The conflicting findings among the many studies for the *ACE* gene exemplify the complexity of genetic studies of 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. This is primarily, but not exclusively, due to the fact that studies are almost universally underpowered and because an unknown number of negative studies remain unpublished. In addition to *ACE*, several other genes are characterized by at least five positive findings; they are *ADRB2* (17 studies), *VDR* (15 articles), *APOE* (9 studies), *MTCYB* (9 studies), *NOS3* (9 studies), *PPARG* (6 studies), and *ACTN3*, *ADRB1*, *AGT*, *AMPD1*, *BDKRB2*, *CPT2*, and *IGF1* each with five positive articles.

Although the fitness and performance gene map is exhaustive for published accounts in four languages, many other genes have not been investigated yet for their potential contributions to human variation in fitness or performance or trainability. The role of regular PA in reducing the risk for common, chronic diseases such as CV disease, type 2 diabetes, or obesity is generally considered as well established, but the interactions between the specific genes and the benefits accrued from a physically active lifestyle in terms of health outcomes have not received much attention thus far. The same is true for the individual differences in the risk level associated with a sedentary lifestyle. We do not know whether specific genes confer a higher risk or conversely some protection from being chronically sedentary and inactive. Addressing the latter questions is extremely important if we are going to make progress in our understanding of the true role of regular exercise or PA in the prevention of common chronic disease and of physical inactivity in the risk of premature death. Much research is also needed on the genetic basis of a sedentary lifestyle and on the propensity to engage in regular PA. For such a research enterprise to be successful, it is of the utmost importance that it be of very high quality, a requirement that can be attained only through data sharing, collaborative effort, and multicenter studies.

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