The Human Gene Map for Performance and Health-Related Fitness Phenotypes: The 2005 Update

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ABSTRACT

RANKINEN, T., M. S. BRAY, J. M. HAGBERG, L. PÉRUSSE, S. M. ROTH, B. WOLFARTH, and C. BOUCHARD. The Human Gene Map for Performance and Health-Related Fitness Phenotypes: The 2005 Update. *Med. Sci. Sports Exerc.*, Vol. 38, No. 11, pp. 1863–1888, 2006. The current review presents the 2005 update of the human gene map for physical performance and health-related fitness phenotypes. It is based on peer-reviewed papers published by the end of 2005. The genes and markers with evidence of association or linkage with a performance or fitness phenotype in sedentary or active people, in adaptation to acute exercise, or for training-induced changes are positioned on the genetic map of all autosomes and the X chromosome. Negative studies are reviewed, but a gene or locus must be supported by at least one positive study before being inserted on the map. By the end of 2000, in the early version of the gene map, 29 loci were depicted. In contrast, the 2005 human gene map for physical performance and health-related phenotypes includes 165 autosomal gene entries and QTL, plus five others on the X chromosome. Moreover, there are 17 mitochondrial genes in which sequence variants have been shown to influence relevant fitness and performance phenotypes. Thus, the map is growing in complexity. Unfortunately, progress is slow in the field of genetics of fitness and performance, primarily because the number of laboratories and scientists focused on the role of genes and sequence variations in exercise-related traits continues to be quite limited. **Key Words:** CANDIDATE GENES, QUANTITATIVE TRAIT LOCI, LINKAGE, GENETIC VARIANTS, MITOCHONDRIAL GENOME, NUCLEAR GENOME, GENETICS

This paper constitutes the sixth installment in the series on the human gene map for performance and health-related fitness phenotypes published in this journal. It covers the peer-reviewed literature published by the end of December 2005. 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, performance, training, genetics, genotype, polymorphism, mutation, linkage). Other sources include personal reprint collections of the authors and documents made available to us by colleagues who are publishing in this field. The 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. The goal of the human gene map for fitness and performance is to review all genetic loci and markers 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.

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 retained are grouped under the following categories: hemodynamic traits including exercise heart rate, blood pressure and heart morphology;

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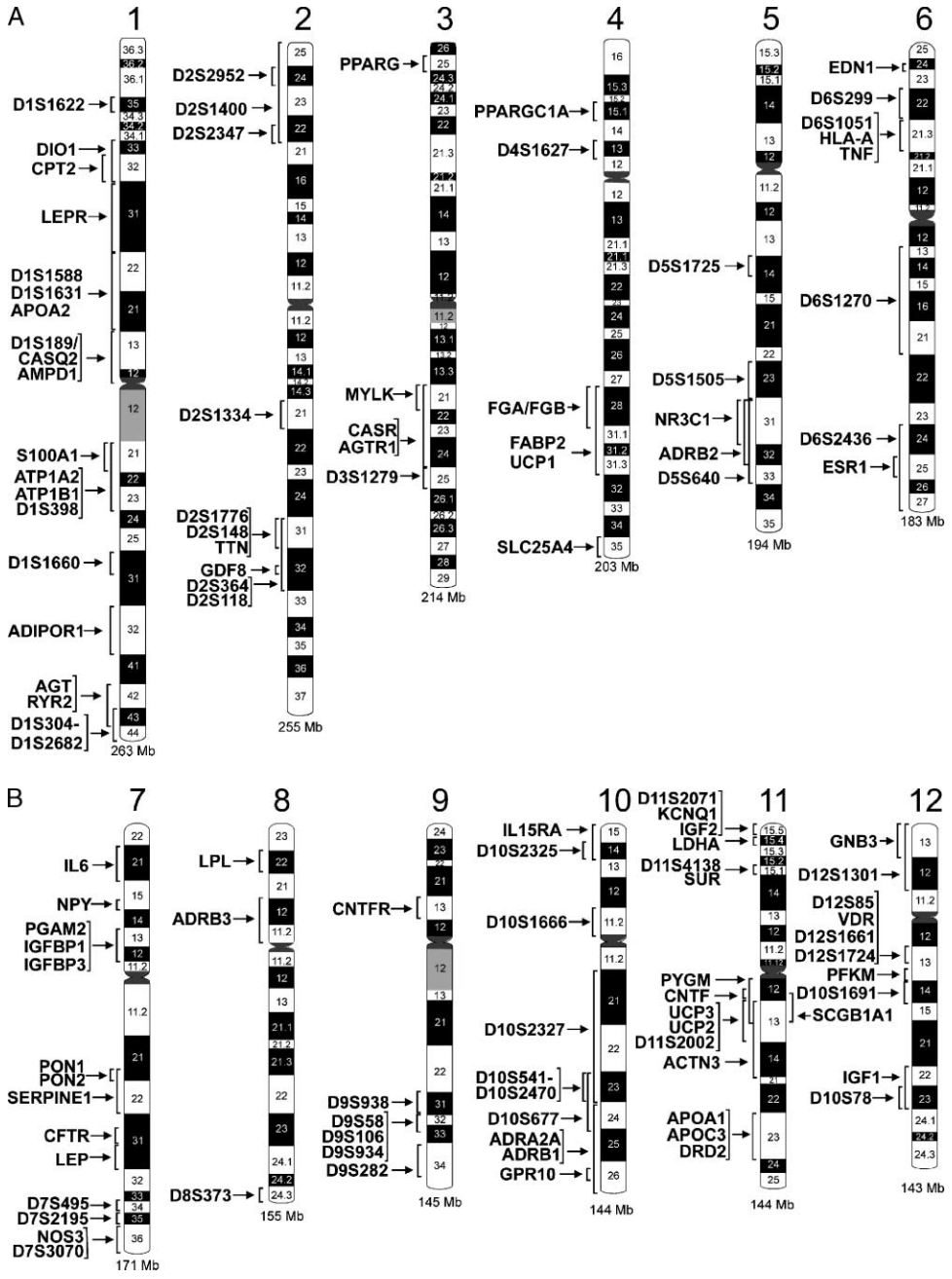

FIGURE 1—The 2005 human performance and health-related fitness gene map. The map includes all gene entries and QTL that have shown associations or linkages with exercise-related phenotypes summarized in the article. The chromosomes and their regions are from the Gene Map of the Human Genome Web site 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.

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 against controls or inactive individuals, or exercise intolerance. This is particularly important for the genetic studies that have focused on body mass index, adiposity, fat-free mass, adipose tissue distribution, and various abdominal fat phenotypes. If there were no exercise-related issues in those studies, the papers are not considered here. However, the interested reader can obtain a full summary of these other studies in one of our complementary papers published every year in *Obesity Research* under the general theme of the status of the human obesity gene map. The interested reader may also consult the following electronic version of this other map (http://obesitygene.pbrc.edu).

The studies incorporated in the review are fully referenced so that the interested reader can access the original papers. Of interest to some could be the early observations made on athletes, particularly Olympic athletes. The results of these case-control

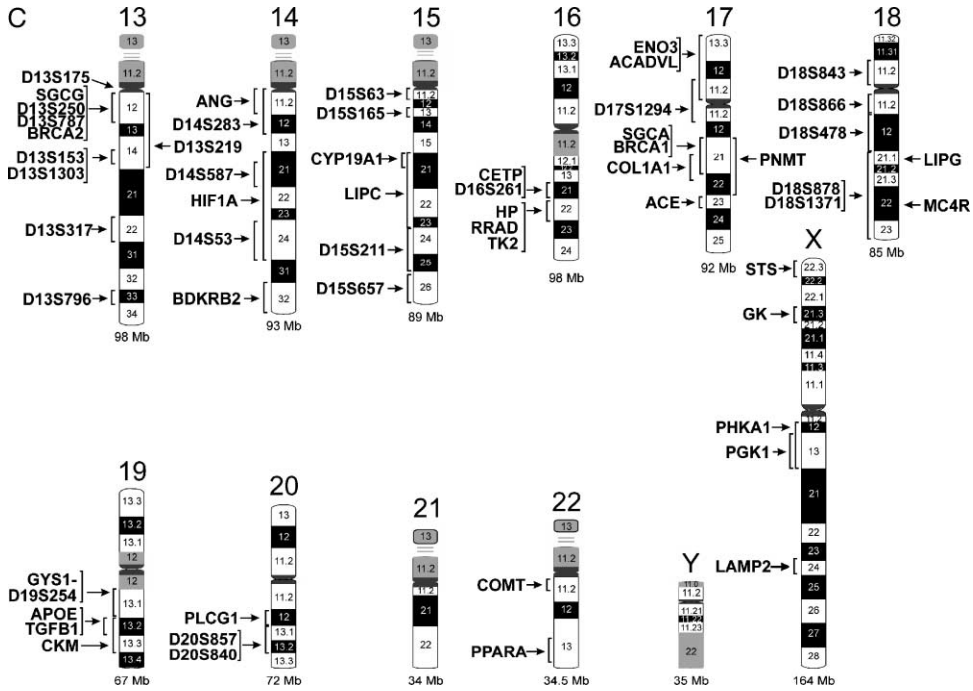

FIGURE 1—(continued).

studies based on common red blood cell 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 (164).

The 2005 synthesis of the human performance and health-related fitness gene map for the autosomes and the X chromosome is summarized in Figure 1. The 2005 update includes 26 additional gene entries and quantitative trait loci (QTL) compared with the 2004 version (255). We have also depicted in Figure 2 the gene loci in the mitochondrial DNA in which sequence variants 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.

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 the health of human beings. It is also our hope that the yearly update of the fitness and performance gene map will be useful to exercise scientists and the sports medicine community.

PERFORMANCE PHENOTYPES

Endurance Phenotypes

Case-control studies. Several new case-control studies were published in 2005 dealing with endurance performance phenotypes (Table 2). Three studies from Spain included elite cyclists and runners. The first study showed a different pattern of the angiotensin-converting enzyme (*ACE*) I/D allele distribution with a higher proportion of the D allele in cyclists (65%, $N = 50$) and controls (57.6%, $N = 119$) compared with runners (46.3%, $N = 27$, $P < 0.001$). A muscle-type creatine kinase gene (*CKM*) polymorphism showed no significant differences in allele or genotype frequencies between the same athletes and controls (109). The next two papers from the same research group included 104 cyclists and runners. The frequency of the C34T mutation of the adenosine monophosphate deaminase 1 (*AMPD1*) gene was significantly higher in 100 nonathlete controls (T: 8.5%) than in the athletes (T: 4.3%). However, because there were no genotype-dependent differences in performance traits among the athletes, the authors concluded that the *AMPD1* mutation may not significantly affect endurance performance (188). Comparing the same athletes with a group of 100 exeptional unfit controls, Lucia and coworkers found a significant difference in the *PPARGC1* (Gly482Ser) genotype distributions between the two groups. The frequency of the minor Ser482 allele was significantly lower in athletes than in the unfit controls (29.1 vs 40.0%) (108).

A group from Finland determined mitochondrial DNA and the alpha 3 actinin (*ACTN3*) genotypes in national elite endurance ($N = 52$) and sprint ($N = 89$) athletes. The frequency of mtDNA haplogroups differed significantly between the two groups, with some haplogroups missing totally in the endurance athletes. Moreover, they found a trend for a higher *ACTN3* X/X genotype frequency in the endurance athletes (140). In two cohorts of Ethiopian endurance runners, the investigators did not find a significant distinction for mitochondrial DNA lineages or Y chromosome haplogroups compared with the general Ethiopian population (128,199). Another study investigated two *ACE* gene polymorphisms in national- and international-level elite runners and nonathlete controls from Kenya. The

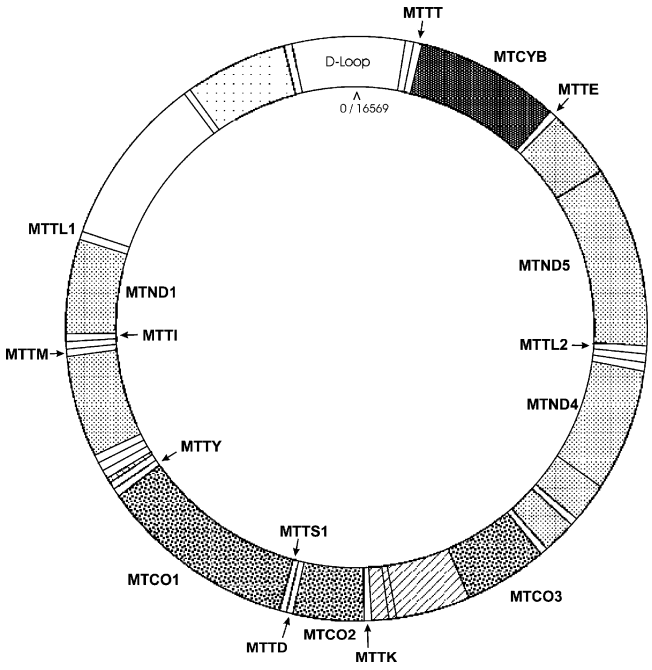

FIGURE 2—Mitochondrial genes that have been shown to be associated with exercise intolerance, fitness, or performance-related phenotypes. The location of the specific sequence variants is defined in Tables 3 and 14. The mitochondrial DNA locations are from http://www.mitomap.org.

allele and genotype frequencies did not differ between the athletes and controls (198).

Cross-sectional association studies. Three new studies reported positive findings for endurance-related phenotypes in cross-sectional association studies in 2005 (Table 3). In a study comprising 29 elite Caucasian wrestlers and 51 age-matched sedentary controls, a significant association between $\dot{V}O_{2max}$ and the *ACE* I/D genotype was found in both groups, with the D/D subjects having lower values than the I/I homozygotes. No differences were seen in genotype frequencies between the two groups (89). In a cohort of 83 patients with heart failure, peak $\dot{V}O_2$ and exercise time were significantly greater in patients homozygous for the 389R allele of the adrenergic receptor beta 1 (*ADRB1*) gene compared with the 389G homozygotes. The significant association remained after adjusting for confounding factors (age, treatment with β-blockers, LVEF) (191).

Cam et al. investigated in 88 nonelite male athletes the relationship between the *ACE* I/D genotype and middle-distance running performance measured by a 2000-m run. The *ACE* D/D genotype frequency was found to be higher in the superior group than in the poor and mediocre group based on 2000-m performance. However, no genotype-dependent differences were seen for a 60-m sprint in the same cohort (21). Another four studies showed no association between different genetic variants and $\dot{V}O_{2max}$ values in the sedentary state. These studies included NADPH oxidase p22phox gene variants in middle-aged Caucasians, the peroxisome proliferative activated receptor gamma (*PPARG*) Pro12Ala polymorphism in 139 type 2 diabetic patients, beta-adrenoceptor gene polymorphisms in patients with congestive heart failure, and *ACE* I/D variation in 18- to 35-yr-old healthy women (2,32,147,183).

Association studies with training response phenotypes. In 2005, two studies analyzed associations between training-induced changes in endurance phenotypes and genetic polymorphisms. The influence of the *PPARG* Pro12Ala genotype on training-induced changes after 6 months of endurance training was tested in 73 sedentary 50- to 75-yr-old healthy men and women. $\dot{V}O_{2max}$ values increased by almost 20% in average, but the training-induced changes did not differ between the *PPARG* genotypes (249). Similar findings were reported in 48 healthy subjects who participated in a 10-wk aerobic training program: neither baseline $\dot{V}O_{2max}$ nor $\dot{V}O_{2max}$ training response were associated with the *PPARG* Pro12Ala and the *ACE* I/D polymorphisms (143).

Linkage studies. No new linkage studies on performance-related phenotypes were published in 2005 (Table 4).

Muscle-Strength Phenotypes

Association studies. The studies reporting candidate gene associations with muscle strength or anaerobic performance phenotypes are summarized in Table 5. In 2005, six studies reported positive genetic associations with muscle strength–related phenotypes. Williams et al. (250) examined the *ACE* I/D genotype associations with quadriceps muscle strength in 81 young Caucasian men, 44 of whom completed an 8-wk strength-training program. Baseline isometric strength was significantly associated with *ACE* genotype ($P = 0.026$), with I-allele homozygotes showing the lowest strength values. No association was found with changes in strength in response to training.

Peeters and colleagues (149) reported higher isometric grip strength ($P = 0.047$) and leg-extensor strength ($P = 0.07$) in 350 predominantly Caucasian older men (> 70 yr) who carried the D1a-T allele of the type I iodothyronine deiodinase (*DIO1*) gene compared with D1a-C allele homozygotes. Kostek et al. (93) studied 67 older Caucasian men and women before and after a 10-wk unilateral strength-training program for associations between insulin- like growth factor (*IGF1*) gene polymorphisms and muscle phenotypes. Carriers of the 192 allele of the *IGF1* promoter microsatellite showed greater quadriceps-muscle strength gains compared with noncarriers ($P = 0.02$), with no differences observed for the muscle-quality response to training. Other polymorphisms in the *IGF1* gene were not associated with any muscle phenotypes. Nicklas et al. (139) examined associations between several cytokine gene markers and physical function before and after exercise training in older men and women ($\geq$ 60 yr). Stair-climb performance improved in response to training more in A-allele carriers of the A-308G polymorphism in the tumor necrosis factor alpha (*TNF*) gene compared with G/G homozygotes ($P = 0.007$).

Clarkson and colleagues (25) reported that one-repetition maximum gains in response to a 12-wk strength-training

TABLE 1. Symbols, full names, and cytogenic location of nuclear and mitochondrial genes of the 2005 Human Gene Map for Performance and Health-Related Fitness Phenotypes.

Gene or Locus	Name	Location
A B		
ACADVL	Acylcoenzyme A dehydrogenase, very long chain	17p13p11
ACE	Angiotensin I converting enzyme	17q23
ACTN3	Actinin, alpha 3	11q13q14
ADIPOR1	Adiponectin receptor 1	1q32
ADRA2A	Adrenergic, alpha2A, receptor	10q24q26
ADRB1	Adrenergic, beta1, receptor	10q24q26
ADRB2	Adrenergic, Beta2, receptor	5q31q32
ADRB3	Adrenergic, Beta3, receptor	8p12p11.2
AGT	Angiotensinogen	1q42q43
AGTR1	Angiotensin II receptor, type 1	3q21q25
AMPD1	Adenosine monophosphate deaminase 1	1p13
ANG	Angiogenin, ribonuclease, RNase A family, 5	14q11.1q11.2
APOA1	Apolipoprotein AI	11q23
APOA2	Apolipoprotein AII	1q21q23
APOC3	Apolipoprotein CIII	11q23
APOE	Apolipoprotein E	19q13.2
ATP1A2	ATPase, Na+/K+ transporting, alpha 2 (+) polypeptide	1q21q23
ATP1B1	ATPase, Na+/K+ transporting, beta 1 polypeptide	1q22q25
BDKRB2	Bradykinin receptor B2	14q32.1q32.2
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)	1p13.3p11
CASR	Calciumsensing receptor	3q21q24
CETP	Cholesteryl ester transfer protein, plasma	16q21
CFTR	Cystic fibrosis transmembrane conductance regulator, ATPbinding cassette (subfamily C, member 7)	7q31.2
CKM	Creatine kinase, muscle	19q13.2q13.3
CNTF	Ciliary neurotrophic factor	11q12.2
CNTFR	Ciliary neurotrophic factor receptor	9p13
CPT2	Carnitine palmitoyltransferase II	1p32
COL1A1	Collagen, type I, alpha 1	17q21.3q22.1
COMT	CatecholOmethyltransferase	22q11.21
CYP19A1	Cytochrome P450, family 19, subfamily A, polypeptide 1 (aromatase)	15q21.1
DIO1	Deiodinase, iodothyronine, type I	1p33p32
DRD2	Dopamine receptor D2	11q23
EDN1	Endothelin 1	6p24.1
ENO3	Enolase 3 (beta, muscle)	17pterp11
ESR1	Estrogen receptor 1	6q25.1
FABP2	Fatty acid binding protein 2, intestinal	4q28q31
FGA	Fibrinogen, A alpha polypeptide	4q28
FGB	Fibrinogen, B beta polypeptide	4q28
GDF8 (MSTN)	Growth differentiation factor 8 (myostatin)	2q32.2
GK	Glycerol kinase	Xp21.3
GNB3	Guanine nucleotide binding protein (G protein), beta polypeptide 3	12p13
GPR10	Gprotein coupled receptor 10	10q26.13
H I K L M		
HIF1A	Hypoxiainducible factor 1, alpha subunit	14q21q24
HLAA	Major histocompatibility complex, class I, A	6p21.3
HP	Haptoglobin	16q22.1
IGF1	Insulinlike growth factor 1	12q22q23
IGF2	Insulinlike growth factor 2	11p15.5
IGFBP1	Insulinlike growth factor binding protein 1	7p13p12
IGFBP3	Insulinlike growth factor binding protein 3	7p13p12
IL15RA	Interleukin 15 receptor, alpha	10p15p14
IL6	Interleukin 6	7p21
KCNQ1	Potassium voltagegated channel, KQTlike subfamily, member 1	11p15.5
LAMP2	Lysosomalassociated membrane protein 2	Xq24
LDHA	Lactate dehydrogenase A	11p15.4
LEP	Leptin	7q31.3
LEPR	Leptin receptor	1p31
LIPC	Lipase, hepatic	15q21q23
LIPG	Lipase, endothelial	18q21.1
LPL	Lipoprotein lipase	8p22
MC4R	Melanocortin 4 receptor	18q22
MTCO1	Cytochrome c oxidase subunit I	mtDNA 5904 – 7445
MTCO2	Cytochrome c oxidase subunit II	mtDNA 75868269
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 75187585
MTTE	Transfer RNA, mitochondrial, glutamic acid	mtDNA 14674 – 14742
MTTI	Transfer RNA, mitochondrial, isoleucine	mtDNA 42634331
MTTK	Transfer RNA, mitochondrial, lysine	mtDNA 8295 – 8364
MTTL1	Transfer RNA, mitochondrial, leucine 1 (UUR)	mtDNA 3230 – 3304

(continued on next page)

TABLE 1. (*continued*)

Gene or Locus	Name	Location
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		
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)	7p13p12
PGK1	Phosphoglycerate kinase 1	Xq13
PHKA1	Phosphorylase kinase, alpha 1 (muscle)	Xq12q13
PLCG1	Phospholipase C, gamma 1	20q12q13.1
PNMT	Phenylethanolamine Nmethyltransferase	17q21q22
PON1	Paraoxonase 1	7q21.3
PON2	Paraoxonase 2	7q21.3
PPARA	Peroxisome proliferative activated receptor, alpha	22q13.31
PPARG	Peroxisome proliferative activated receptor, gamma	3p25
PPARGC1A	Peroxisome proliferative activated receptor, gamma, coactivator 1, alpha	4p15.1
PYGM	Phosphorylase, glycogen, muscle	11q12q13.2
RYR2	Ryanodine receptor 2 (cardiac)	1q42.1q43
S100A1	S100 calcium binding protein A1	1q21
SCGB1A1	Secretoglobin, family 1A, member 1	11q12.3q13.1
SERPINE1	Serine (or cysteine) proteinase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1	7q21.3q22
SGCA	Sarcoglycan, alpha (50 kDa dystrophinassociated glycoprotein)	17q21
SGCG	Sarcoglycan, gamma (35 kDA dystrophinassociated glycoprotein)	13q12
SLC25A4	Solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 4	4q35
STS	Steroid sulfatase (microsomal)	Xp22.32
SUR	Sulfonylurea receptor	11p15.1
TGFB1	Transforming growth factor, beta 1	19q13.1
TK2	Thymidine kinase 2, mitochondrial	16q22q23.1
TNF	Tumor necrosis factor (TNF superfamily, member 2)	6p21.3
TTN	Titin	2q31
UCP1	Uncoupling protein 1	4q28q31
UCP2	Uncoupling protein 2	11q13
UCP3	Uncoupling protein 3	11q13
VDR	Vitamin D (1,25 –dihydroxyvitamin D3) receptor	12q13.11

The gene symbols, names, and cytogenetic locations are from the Locus Link Web site (http://www.ncbi.nlm.nih.gov/LocusLink) available from the National Center for Biotechnology Information (NCBI). For mitochondrial DNA, locations are from the human mitochondrial genome database (http://www.mitomap.org).

program were greatest in women homozygous for the X-allele of the (*ACTN3*) gene compared with the R-allele homozygotes ($P < 0.05$). In contrast, the X/X women had lower baseline isometric strength than the R/R women ($P < 0.05$). No association was observed between the *ACTN3* R577X polymorphism and muscle phenotypes in men. In an examination of genotypes in the *ACTN3* and myosin light-chain kinase (*MYLK*) genes, Clarkson et al. (26) studied associations with exertional muscle damage in 157 predominantly Caucasian men and women. Subjects performed eccentric contraction of the elbow flexors, with creatine kinase, myoglobin, and isometric strength tested before and after the exercise bout. Although *ACTN3* genotype was associated with baseline creatine kinase levels, no associations were observed for any other phenotypes before or after exercise. Polymorphisms in the *MYLK* gene were associated with baseline muscle strength and with creatine kinase and myoglobin responses and strength loss after the eccentric exercise bout.

In 2005, three studies reported negative genetic associations with muscle strength–related phenotypes. Grundberg et al. (56) reported no association between a TA-repeat polymorphism in the estrogen-receptor alpha (*ESR1*) gene and several muscle-strength measures in 175 Swedish women (20–39 yr). Walsh and colleagues (245) found no association between muscle strength and an androgen-receptor (*AR*) gene CAG–repeat polymorphism in two cohorts of older men and women, despite finding significant genotype associations with fat-free mass in the men of both cohorts. Finally, Walston and coworkers (246) examined individual polymorphisms and haplotypes in the interleukin-6 (*IL6*) gene for association with several muscle-strength measures. They reported no associations for any *IL6* genotypes with any strength or related phenotypes in a study of 463 older women (70–79 yr).

Linkage studies. In 2005, one investigation provided linkage data relevant to muscle-strength phenotypes (Table 4). Huygens et al. (73) performed a linkage analysis in 367 young Caucasian male siblings from 145 families with markers in the general vicinity of nine genes involved in the myostatin signaling pathway and various measures of muscle strength. Significant linkages were reported on four chromosomal regions with knee muscle-strength measures: chromosome 13q21 (D13S1303), chromosome 12p12–p11 (D12S1042), chromosome 12q12–q13.1 (D12S85), and chromosome 12q23.3–q24.1 (D12S78). These findings represent an expansion of an earlier linkage study reported by the same group in 2004 (71).

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

		Athletes			Controls			
Gene	**Location**	***N***	**Sports**	**Frequency**	***N***	**Frequency**	***P***	**Reference**
AMPD1	1p13	104	endurance	C: 0.045 T: 0.955	100	C: 0.085 T: 0.915	< 0.05	188
PPARGC1A	4p15.1	104	Endurance	Ser: 0.29 Gly: 0.71	100	Ser: 0.40 Gly: 0.60	0.01	108
ADRA2A	10q24q26	140	Endurance	6.7/6.7: 0.77 6.7/6.3: 0.21 6.3/6.3: 0.02	141	6.7/6.7: 0.62 6.7/6.3: 0.34 6.3/6.3: 0.04	0.037	256
				6.7: 0.88 6.3: 0.12		6.7: 0.8 6.3: 0.2	0.011	
ACTN3	11q13q14	107	Sprinters	RR: 0.49 RX: 0.45 XX: 0.06	436	RR: 0.30 RX: 0.52 XX: 0.18	< 0.001	261
				R: 0.72 X: 0.28		R: 0.56 X: 0.44		
ACE	17q23	64	Endurance	II: 0.30 ID: 0.55 DD: 0.16	118	II: 0.18 ID: 0.51 DD: 0.32	0.03	51
				I: 0.57 D: 0.43		I: 0.43 D: 0.57	0.02	
		79	Running	I: 0.57 D: 0.43	Ref. Pop.	I: 0.49 D: 0.51	0.039	135
		25	Mountaineering	n.a.	Ref. Pop.	n.a.	0.02 0.003	126
		60	Elite athletes (cycling, running, handball)	II: 0.25 ID: 0.58 DD: 0.17	Ref. Pop.	II: 0.16 ID: 0.45 DD: 0.39	0.0009	3
				I: 0.54 D: 0.46		I: 0.38 D: 0.62		
		56	Elite swimmers (subsample of 103 swimmers)	II: 0.15 ID: 0.39 DD: 0.46	1248	II: 0.24 ID: 0.49 DD: 0.27	0.004	258
				I: 0.34 D: 0.66		I: 0.48 D: 0.52		
		30	Short-distance athletes	II: 0.07 ID: 0.43 DD: 0.50	449	II: 0.23 ID: 0.52 DD: 0.24	0.001	138
				I: 0.28 D: 0.72		I: 0.5 D: 0.5		
		35	Middle-distance athletes (subsample of 217 Russian athletes)	II: 0.37 ID: 0.51 DD: 0.12			0.032	
				I: 0.63 D: 0.37				
		33	Olympic aerobic athletes	II: 0.30 ID: 0.30 DD: 0.39	152	II: 0.13 ID: 0.43 DD: 0.44	0.05	193
				I: 0.45 D: 0.55		I: 0.34 D: 0.66		
		80	University athletes	II: 0.14 ID: 0.36 DD: 0.5	80	II: 0.11 ID: 0.19 DD: 0.70	0.026	232
				I: 0.32 D: 0.68		I: 0.21 D: 0.79		
		100	Triathlon	I: 0.52 D: 0.48	166	I: 0.42 D: 0.58	0.036	27
		50	Cyclists	I: 0.35 D: 0.65	119	I: 0.42 D: 0.58	< 0.001	109
		27	Runners	I: 0.54 D: 0.46				
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**	140
		89	Sprint	H: 0.47 V: 0.079 U: 0.15 K: 0.09				

(continued on next page)

TABLE 2. (*continued*)

Gene	Location	Athletes N	Athletes Sports	Athletes Frequency	Controls N	Controls Frequency	P	Reference
				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.

HEALTH-RELATED FITNESS PHENOTYPES

Hemodynamic Phenotypes

Acute exercise. In 2005, three groups published results relative to the impact of common genetic variations on exercise-related hemodynamic phenotypes (Table 6). Eisenach and coworkers found that men and women homozygous for the Gly16 allele of the adrenergic receptor beta 2 (*ADBR2*) gene had larger heart rate responses (60 ± 4 vs 45 ± 4%, $P = 0.03$) and a higher cardiac output (7.6 ± 0.3 vs 6.5 ± 0.3 $L \cdot min^{-1}$, $P = 0.03$) during isometric handgrip exercise than otherwise similar individuals homozygous for the Arg16 allele (38). However, the decrease in systemic vascular resistance during handgrip exercise did not achieve statistical significance between the two homozygous genotype groups ($P = 0.09$).

Trombetta et al. found in women that the Gly16 and Glu27 genotypes at the *ADRB2* gene locus affected the forearm blood flow (FBF), but not conductance, responses to isometric handgrip exercise (225). Whereas all genotype groups increased their FBP during handgrip exercise, women homozygous for both the Gly16 and the Glu27 alleles had a significantly greater FBF increase than those homozygous for the other combinations of these alleles.

Roltsch and coworkers found that the *ACE* I/D genotype did not significantly influence any hemodynamic responses to submaximal or maximal exercise in a cohort of 77 young healthy women (183). The hemodynamic responses assessed in this study included heart rate, systolic and diastolic BP, cardiac output, stroke volume, total peripheral resistance, and a-$\dot{V}O_2$ difference.

Gene–physical activity interactions. In 2005, two studies assessed the interactive effect of common genetic polymorphisms and physical activity levels on hemodynamic phenotypes (Table 6). Roltsch and coworkers found that the *ACE* I/D genotype did not interact with habitual level of physical activity, ranging from sedentary to endurance trained, to significantly alter hemodynamic responses (heart rate, systolic and diastolic BP, cardiac output, stroke volume, total peripheral resistance, and a-$\dot{V}O_2$ difference) to submaximal or maximal exercise in young women (183).

Tanriverdi and coworkers found in a group of predominantly male athletes (middle-distance runners, soccer players) that flow-mediated dilation (FMD) was significantly greater in those with the *ACE* I/I genotype (10.5 ± 1.6%) compared with those with the I/D (8.4 ± 2.3%) or D/D (7.0 ± 1.2%) genotypes (217). No *ACE* genotype–dependent FMD relationships were evident in the untrained individuals they studied.

Training response. Delmonico and coworkers reported that the angiotensinogen (*AGT*) A-20C genotype affected the resting systolic BP reductions, whereas the angiotensin II receptor type 1 (*AGTR1*) A1166C genotype affected the resting diastolic BP reductions resulting from 23 wk of resistive training in 52- to 81-yr-old sedentary men and women (34). However, the *AGT* M235T genotype did not affect the degree to which these men and women reduced their resting systolic or diastolic BP with resistive training (Table 7).

Linkage studies. No new linkage studies were published in 2005 (Table 8).

Anthropometry and Body-Composition Phenotypes

Association studies. In 2005, four studies (10,94, 129,143) tested associations between candidate genes and body fat in response to exercise or in interaction with physical activity, and three of them reported positive findings (Table 9). In a 10-yr follow-up study of obese and nonobese Danish men, interactions between leisure-time physical activity and polymorphisms in the uncoupling protein 2 (*UCP2*) and 3 (*UCP3*) genes were examined in relation to changes in body mass index (BMI), but no evidence of interaction between the UCP genes and physical activity on the changes in BMI was uncovered (10). The second study (129) examined the interactions between the *ACE* I/D polymorphism and physical activity on adiposity in adolescent (11–18 yr old) males ($N = 535$) and females ($N = 481$). Strong evidence of association was found between the *ACE* I/D polymorphism and triceps ($P = 0.012$) and subscapular ($P = 0.001$) skinfolds, but only in inactive ($N = 207$) females. The polymorphism accounted for 4.3 and 6.5% of the variance in the triceps and subscapular skinfolds, respectively (129).

Another study involving the *ACE* I/D polymorphism genotype in more than 3000 adult subjects aged 70–79 yr found higher values of percent body fat and intermuscular thigh fat (assessed by CT scan) in subjects with the I/I genotype compared with those with the I/D or D/D genotype, but the association was observed only among physically active subjects (94). Ostergard and coworkers reported that in a small group of offspring of type 2 diabetics, the Ala12 allele carriers of the *PPARG* Pro12Ala polymorphism showed a greater weight loss compared with

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

Gene	Location	Subjects	Phenotype	*P*	Reference
Acute exercise					
AMPD1	1p13	400 whites	RPE	0.0002	174
PPARGC1A	4p15.1	599 healthy subjects	PAEE/$\dot{V}O_{2max,\ pred}$	0.009	45
ADRB2	5q31q32	232 HF patients	$\dot{V}O_{2peak}$	0.0001	243
		63 PM women	$\dot{V}O_{2max}$	< 0.05	127
		62 PM women	$\dot{V}O_{2max}$	< 0.05	116
		62 PM women	Max $avDo_2$	0.006	
			Submax $avDo_2$	0.004	
HLAA	6p21.3	8 MZ and 8 DZ twin pairs	$\dot{V}O_{2max}$	0.001	182
IL6	7p21	479 young smokers	PWC_{max}	0.002	142
CFTR	7q31.2	97 CF patients	$\dot{V}O_{2peak}$	< 0.05	201
ADRB1	10q24q26	263 cardiomyopathy patients	$\dot{V}O_{2peak}$	< 0.05	244
			Exercise time	< 0.05	
			$\dot{V}_E/\dot{V}CO_2$	< 0.05	
		83 heart failure patients	$\dot{V}O_{2peak}$	< 0.05	191
			Exercise time	< 0.05	
SCGB1A1	11q12.3q13.1	96 asthmatic children	FEV_1 after exercise	< 0.04	203
UCP2	11q13	16 healthy subjects	Exercise efficiency (gross)	0.02	20
			Exercise efficiency (incremental)	0.03	
HIF1A	14q21q24	125 whites	$\dot{V}O_{2max}$ (age interaction)	NS (55 yr)	154
				0.012 (60 yr)	
				0.005 (65 yr)	
		29 blacks	$\dot{V}O_{2max}$	0.033	
BDKRB2	14q32.1q32.2	73 male Army recruits	Muscle efficiency	0.003	251
		42 female sedentary Caucasians			
HP	16q22.1	96 PAOD patients	Walking distance	< 0.05	33
ACE	17q23	58 PM women	$\dot{V}O_{2max}$	< 0.05	61
		47 PM women	Max $avDo_2$	< 0.05	
		91 (79 Caucasians)	Running distance	0.009	135
		57 cardiomyopathy patients	$\dot{V}O_{2peak}$	0.05	1
			Exercise time	0.04	
		62 PM women	$\dot{V}O_{2max}$	< 0.05	62
		36 COPD patients	Postexercise lactate	< 0.0001	82,83
		43 COPD patients	Postexercise lactate	0.01	
		60	$\dot{V}_E$ during hypoxia	0.008	148
		67 Chinese men	$\dot{V}O_{2max}$	0.04	263
		33 COPD patients	DO_2	< 0.05	86
		88 nonelite athletes	Middle-distance running performance	0.026	21
		51 untrained Caucasians	$\dot{V}O_{2max}$	< 0.001	89
		29 strength-trained athletes		< 0.001	
CKM	19q13.2q13.3	160 white parents	$\dot{V}O_{2max}$	0.007	178
		80 white offspring	$\dot{V}O_{2max}$	NS	
MTND5	12337–14148*	46	$\dot{V}O_{2max}$	< 0.05	37
MTTT	15888–15953*	46	$\dot{V}O_{2max}$	< 0.05	37
Training responses:					
AMPD1	1p13	400 whites	$\dot{V}O_{2max}$	0.006	174
			$\dot{V}E_{max}$	0.006	
ATP1A2	1q21q23	472 whites	$\dot{V}O_{2max}$	0.018	162
		294 white offspring	$\dot{V}O_{2max}$	0.017	
HIF1A	14q21q24	101 whites	$\dot{V}O_{2max}$ (age interaction)	NS (55 yr)	154
				0.005 (60 yr)	
				0.006 (65 yr)	
ACE	17q23	294 white offspring	$\dot{V}O_{2max}$	0.008–0.150	163
			Power output	0.0001–0.003	
		78 Army recruits	Maximum duration for repetitive elbow flexion with 15 kg	0.001	126
		58 Army recruits	Muscle efficiency	< 0.025	252
		58 Army recruits (24II, 26DD)	Exercise efficiency	0.02	260
		95 COPD patients	Maximal workload	0.04	53
APOE	19q13.2	51	$\dot{V}O_{2max}$	< 0.05	60
		120	$\dot{V}O_{2max}$	< 0.001	220
CKM	19q13.2q13.3	160 white parents	$\dot{V}O_{2max}$	0.004	178
		80 white offspring	$\dot{V}O_{2max}$	< 0.025	
MTND5	12337–14148*	46	$\dot{V}O_{2max}$	< 0.05	37

* Mitochondrial DNA. $\dot{V}O_{2max}$, maximal oxygen uptake; $\dot{V}_E/\dot{V}CO_2$, ratio of ventilation to carbon dioxide consumption; Wmax, maximal power output; $a\text{-}vDo_2$, arterial–venous oxygen difference; PM, postmenopausal; HF, heart failure; MZ, monozygous; DZ, dizygous; CAD, coronary artery disease; CF, cystic fibrosis; exercise efficiency, decrease in oxygen consumption on given workloads; PAOD, peripheral arterial occlusive disease; $\dot{V}_E$, ventilation; RPE, rating of perceived exertion; PWC, physical working capacity; FEV, forced expiratory volume; DO_2, oxygen delivery.

the Pro12Pro homozygotes in response to 10 wk of endurance training (143).

In 2005, one study tested association between candidate genes and bone mineral density (BMD) responses to exercise training. Rabon-Stith and colleagues examined the response of BMD to both aerobic and strength training in 206 total older men and women in relation to two polymorphisms in the vitamin D–receptor gene (*VDR*) (158). The FokI polymorphism was significantly associated with the femoral neck BMD response to strength training.

TABLE 4. Linkage studies with endurance and strength phenotypes.

Gene	Marker	Location	No. of Pairs	Phenotype	*P*	Reference
QTL	LEPR	1p31	90 black	$\Delta\dot{V}O_{2max}$	0.0017	175
			102 black	$\dot{V}O_{2max}$	0.01	
ATP1A2		1q21q23	309 white	$\Delta\dot{V}O_{2max}$	0.054	162
				ΔW_{max}	0.003	
QTL	S100STU1	1q21	316 white	ΔW_{max}	0.0091	175
QTL	D1S398	1q22	90 black	ΔW_{max}	0.0033	175
QTL	D2S118	2q32.2	204 white	Knee extension	0.0002	71
				Knee flexion	0.004	
QTL	D4S1627	4p13	315 white	ΔW_{max}	0.0062	175
QTL	FABP2	4q28q31	315 white	$\Delta\dot{V}O_{2max}$	0.009	15,175
OTL	D5S1505	5q23	315 white	ΔW_{max}	0.002	175
QTL	D6S1051	6p21.3	204 white	Knee extension	0.009	71
				Knee flexion	0.004	
QTL	LEP	7q32	102 black	$\dot{V}O_{2max}$	0.0068	175
QTL	D7S495	7q34	315 white	$\Delta\dot{V}O_{2max}$	0.0089	175
QTL	NOS3	7q36	102 black	$\dot{V}O_{2max}$	0.003	175
OTL	D10S677	10q23	315 white	W_{max}	0.0014	175
QTL	D11S4138	11p15	204 white	Knee extension	0.004	71
				Knee flexion	0.002	
QTL	SUR	11p15.1	315 white	$\dot{V}O_{2max}$	0.0014	15,175
QTL	D12S1042	12p11	367 white	Multiple knee-strength measures	< 0.05	73
QTL	D12S85	12q13	367 white	Multiple knee-strength measures	< 0.05	73
QTL	D12S78	12q23	367 white	Multiple knee-strength measures	< 0.05	73
QTL	D13S153	13q14.2	204 white	Trunk flexion	0.0002	72
QTL	D13S1303	13q21	367 white	Multiple knee-strength measures	< 0.05	73
QTL	D13S175	13q11	90 black	ΔW_{max}	0.0055	175
QTL	D13S787	13q12	315 white	$\Delta\dot{V}O_{2max}$	0.0087	175
QTL	D13S796	13q33	351 white	W_{max}	0.0098	175
QTL	RADI	16q22	90 black	$\Delta\dot{V}O_{2max}$	0.0041	175
QTL	D18S478	18q12	351 white	W_{max}	0.0064	175
CKM		19q13.2	260 white	$\Delta\dot{V}O_{2max}$	0.04	181
QTL	D20S857	20q13.1	90 black	$\Delta\dot{V}O_{2max}$	0.0028	175

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

TABLE 5. Muscular strength and anaerobic phenotypes and association studies with candidate genes.

Gene	Location	Subjects	Phenotype	*P*	Reference
DIO1	1p32p33	350 men, > 70 yr	Grip strength	0.047	149
GDF8	2q32.2	286 women	Hip flexion	0.01	200
		55 AA women (subsample of 286)	Overall strength	< 0.01	200
			Hip flexion	< 0.01	
			Knee flexion	< 0.01	
MYLK	3q21	157 men and women	Isometric strength	0.019	26
			Δ elbow-flexor strength after ecc exercise	< 0.05	
NR3C1	5q31	158 men, 13–36 yr	Arm strength	< 0.05	236
			Leg strength	< 0.05	
TNF	6p21.3	214 men and women, ≥ 60 yr	Δ Stairclimb time	0.007	139
CFTR	7q31.2	97 CF patients	Peak anaerobic power	< 0.05	201
CNTFR	9p13	465	KE ecc, sv	< 0.05	184
			KE ecc, fv	< 0.05	
IGF2	11p15.5	397 men, aged 64–74	Grip strength	0.05	192
		239 women, 20–94 yr	Arm peak torque con	< 0.05	195
			Arm peak torque ecc	< 0.05	
			Leg peak torque con sv	< 0.05	
			Leg peak torque con fv	< 0.05	
CNTF	11q12.2	494	KE con, fv	< 0.05	185
			KE ecc, sv	< 0.05	
			KF con, sv	< 0.05	
			KF con, fv	< 0.05	
			KF ecc, sv	< 0.05	
ACTN3	11q13q14	355 women, < 40 yr	Baseline isometric strength	< 0.05	25
			Δ onerepetition maximum	< 0.05	
VDR	12q13.11	501 PM women	Grip and quadriceps strength	< 0.01	52
		175 women, 20–39 yr	Knee flexion	< 0.05	55
		302 men, > 50 yr	Knee-extensor isometric torque	< 0.05	186
IGF1	12q22q23	67 men and women	KE onerepetition maximum	0.02	93
COL1A1	17q21.3q22.1	273 men, 71–86 yr	Grip strength	0.03	235
			Biceps strength	0.04	
ACE	17q23	33	Δ muscle strength	< 0.05	44
		83 PM women	Specific muscle strength of adductor pollicis	0.017	259
		103 COPD patients	KE maximal strength	< 0.05	68
			KE twitch force	< 0.05	
		81 men	KE isometric strength	0.026	250

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.

TABLE 6. Summary of the association studies between candidate gene markers and acute exercise-related hemodynamic phenotypes as well as gene-physical activity interactions on hemodynamic traits. Genes causing exercise-related familial cardiac arrhythmias* are listed at the end of the table.

Gene	Location	Subjects	Phenotype	*P*	Reference
AMPD1	1p13	400 whites	Maximal exercise SBP	0.003	174
AGT	1q42q43	25	Submaximal exercise DBP	< 0.01	95
		190 sedentary white men	DBPmax	0.007	161
		61 PM women	HRmax	0.008	115
ADRB2	5q31q32	232 HF patients	Exercise cardiac index	< 0.05	243
			Exercise systemic vascular resistance	< 0.05	
			Exercise stroke volume	< 0.05	
		12 obese women	Exercise DBP	0.01	110
		31	HR during handgrip exercise	0.001	39
		64 women	Handgrip exercise FBF	< 0.05	225
		47 men and women	Handgrip exercise HR and cardiac output	0.03	38
EDN1	6p24.1	873	SBPmax	0.03	221
		372 with BMI > 26	SBPmax	< 0.0001	
GNB3	12p13	437 whites	SBP at 50 W	0.036	166
ANG	14q11.1q11.2	257 blacks	SBP at 60% and 80% $\dot{V}O_{2max}$	< 0.05	179
			SBPmax	< 0.05	
ACE	17q23	58	Max heart rate	< 0.05	61
		66	DBPmax	0.010	47
		96	Exercise ANP	0.043	48
		19 COPD patients	Exercise Ppa	0.008	84
			Exercise Rpv	< 0.05	
		39 COPD patients	Postexercise Ppa	< 0.01	85
		62 PM women	Submaximal exercise heart rate	0.04	62
		37 COPD patients	Postexercise Ppa	< 0.01	82
		43 COPD patients	Postexercise Rpv	< 0.01	83
		33 COPD	Exercise mPAP	< 0.05	86
			Exercise Rpv	0.001	
TGFB1	19q13.2	480 whites	SBP at 50 W, 60% $\dot{V}O_{2max}$	< 0.05	180
			SBPmax	< 0.05	
Gene–physical activity interactions:					
ADRB2	5q31q32	62 PM women	Submaximal exercise $avDO_2$	0.05	116
NOS3	7q36	63	FBF	0.03	31
			FVR	0.0003	
		832	Resting SBP	0.0062	91
GPR10	10q26.13	687 men and women	Resting DBP	0.006	46
			Resting SBP	0.008	
ACE	17q23	56 male and female athletes	FMD	0.0001	217
Familial cardiac arrhythmias*					
CASQ2	1p13.3p11	41	ARFPVT	Coseg**	97
		29	ARFPVT	Coseg**	153
RYR2	1q42.1q43	26	ADFPVT	Coseg**	98
		24	AD FPVT	Coseg**	155
KCNQ1	11p15.5		Long QT syndrome 1	Coseg**	197,248

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; Q, cardiac output; FBF, forearm blood flow; FVR, forearm vascular resistance; AR, autosomal recessive; AD, autosomal dominant; FPVT, familial polymorphic ventricular tachycardia.

* Only familial cardiac arrythmias where acute exercise has been shown to trigger cardiac event have been listed.

** Mutations cosegregate with the phenotype in affected families.

There was no association between either VDR polymorphism with the BMD response to aerobic training.

Linkage studies. No linkage studies pertaining to training-induced changes in body-composition phenotypes (Table 10) were reported in 2005.

Insulin and Glucose Metabolism Phenotypes

Five studies in the past year investigated associations with insulin and glucose metabolism phenotypes in response to exercise (Table 11). The first study investigated associations between the *PPARG* Pro12Ala polymorphism and improvements in insulin action in response to endurance training in sedentary men (N = 32) and women (N = 41). Subjects underwent an oral glucose-tolerance test before and after 6 months of endurance training. Results showed that decreases in fasting insulin and insulin area under the curve in response to training were about fourfold greater in the Pro12Ala heterozygous men compared with Pro12 homozygous men. No genotype-specific effects of exercise training were found in women (249). The second study evaluated the impact of the *PPARG* Pro12Ala and the *ACE* I/D polymorphisms on insulin sensitivity (measured by the hyperinsulinemic euglycemic clamp technique) in response to 10 wk of endurance training in 29 offspring of type 2 diabetic patients and 17 control subjects (143). Improvements in insulin sensitivity were not associated with the *PPARG* and *ACE* genotypes.

The third study examined associations between the hepatic lipase (*LIPC*)-514 C>T polymorphism and changes in insulin sensitivity in response to endurance training in 219 black adults and 443 white adults of the HERITAGE Family Study (219). In the sedentary state, the insulin sensitivity, assessed by an intravenous glucose-tolerance test, did not differ between the *LIPC*-514 genotypes.

TABLE 7. Summary of the association studies between candidate gene markers and hemodynamic phenotype training responses.

Gene	Location	Cases	Phenotype	*P*	Reference
AMPD1	1p13	400 whites	DBP at max	0.03	174
AGT	1q42q43	226 white males	DBP at 50 W	0.016	161
		70 older men and women	Resting SBP	0.05	34
		120 males	Resting SBP	< 0.01	168
			Resting DBP	< 0.01	
TTN	2q31		SV and Q at 50 W	0.005	165
AGTR1	3q21q25	70 older men and women	Resting DBP	0.05	34
NOS3	7q36	471 whites	DBP at 50 W	0.0005	167
			HR at 50 W	0.077	
			RPP at 50 W	0.013	
		67 CAD patients	APV response to acetylcholine	< 0.05	40
LPL	8p22	18	Resting SBP	< 0.05	59
			Resting DBP	< 0.05	
GNB3	12p13	163 black women	Resting SBP	0.0058	166
			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	14q32.1q32.2	109 white Army recruits	LV mass	0.009	16
ACE	17q23	28 male soccer players	LV mass	0.02	41
		140 white Army recruits	Septal thickness	0.0001	124
			Posterior wall thickenss	0.0001	
			Enddiastolic diameter	0.02	
			LV mass	0.0001	
			LV mass index	0.0001	
		49 white Army recruits	BNP	< 0.05	
		18	Resting DBP	0.005	59
		294 white offspring	HR at 50 W	0.0006	161
		144 white army recruits	LV mass	0.002	136
		64 hypertensives	Resting DBP	< 0.05	262
			Resting MAP	< 0.05	
APOE	19q13.2	18	Resting SBP	< 0.05	59
PPARA	22q13.31	144 white Army recruits	LV mass	0.009	76

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

However, the training-induced improvements in insulin sensitivity, after adjustment for age, sex, BMI, and baseline values, were found to be greater in both black ($P = 0.008$) and white ($P = 0.002$) C/C homozygotes ($+1.25 \pm 0.2$ and $+0.22 \pm 0.2$ $\mu U \cdot min^{-1} \cdot mL^{-1}$) than in the T/T homozygotes ($+0.27 \pm 0.3$ and -0.97 ± 0.3 $\mu U \cdot min^{-1} \cdot mL^{-1}$). The fourth

TABLE 8. Exercise-related hemodynamic phenotypes and linkage studies.

Gene	Marker	Location	No. of pairs	Phenotype	*P*	Reference
QTL	D1S1588, D1S1631	1p21.3	102 black	SV at 50 W	0.005	159
QTL	D1S189, CASQ2	1p13p21	42 members from 7 families	ARFPVT	LOD = 8.24	96,97
QTL	D2S2952	2p24	344 white	SBP at 80% $\dot{V}O_{2max}$	0.0026	160
QTL	D2S1400	2p22p25	102 black	DBP at 50 W	0.0044	160
QTL	D2S1334	2q21	344 white	SBP at 80% $\dot{V}O_{2max}$	0.0031	160
QTL	D2S148, D2S384 (TTN)	2q31	328 white	ΔSV and ΔQ at 50 W	0.0002	165
QTL	D2S364	2q31q32	52 members from 2 families (14 affected)	Abnormal PASP response to exercise	LOD = 4.4	57
QTL	D5S640	5q31q33	344 white	ΔDBP at 50 W	0.0046	160
QTL	D6S1270	6q13q21	344 white	DBP at 80% $\dot{V}O_{2max}$	0.0037	160
QTL	D6S2436	6q24q27	344 white	DBP at 50 W	0.0041	160
QTL	D7S2195	7q35	102 black	SBP at 80% $\dot{V}O_{2max}$	0.0046	160
QTL	D8S373	8q24.3	344 white	ΔSBP at 50 W	0.0005	160
QTL	D9S58, 106, 934	9q32q33.3	328 white	SV at 50 W	0.003–0.006	159
QTL	D10S2325	10p14	102 black	Q at 50 W	0.0045	159
QTL	D10S1666	10p11.2	328 white	ΔSV at 50 W	0.00005	159
QTL	D10S2327	10q21q23	102 black	ΔDBP at 80% $\dot{V}O_{2max}$	0.0019	160
QTL	D10S677	10q23q24	344 white	SBP at 80% $\dot{V}O_{2max}$	0.0018	160
QTL	D11S2071	11p15.5	102 black	DBP at 50 W	0.0042	160
QTL	UCP3	11q13	102 black	DBP at 80% $\dot{V}O_{2max}$	0.0023	160
QTL	D12S1301	12p12p13	102 black	SBP at 80% $\dot{V}O_{2max}$	0.005	160
QTL	D12S1724	12q13.2	102 black	SV at 50 W	0.0038	159
QTL	D13S250	13q12	91 black	Resting ΔSBP	0.004	173
QTL	D14S283	14q11.1q12	344 white	SBP at 80% $\dot{V}O_{2max}$	0.0034	160
QTL	D14S53	14q31.1	328 white	SV at 50 W	0.0019	159
QTL	D15S211	15q24q25	344 white	DBP at 80% $\dot{V}O_{2max}$	0.0024	160
QTL	D15S657	15q26	102 black	SBP at 80% $\dot{V}O_{2max}$	0.0035	160
QTL	D16S261	16q21	344 white	SBP at 80% $\dot{V}O_{2max}$	0.0026	160
QTL	D17S1294	17p11q11	102 black	SBP at 80% $\dot{V}O_{2max}$	0.0031	160
QTL	D18S843	18p11.2	102 black	DBP at 50 W	0.0012	160
QTL	D18S866	18q11.2	102 black	Q at 50 W	0.0022	159

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; Q, cardiac output.

TABLE 9. Evidence for the presence of associations between candidate genes and the response of BMI, body composition, or fat distribution phenotypes to habitual physical activity or regular exercise.

Gene	Location	No. of Cases	Phenotype	*P*	Reference
Interactions with exercise/physical activity					
GDF8 (MSTN)	2q32.2	18 men and 14 women	Leg muscle volume	NS (all) 0.067 (women)	75
ADRB2	5q31q32	420 men	Weight	0.0001	119
			BMI	0.0001	
			Waist circumference	0.0001	
			Hip circumference	0.0007	
			WHR	0.02	
		252 women	Obesity, BMI	$0.005 < P < 0.05$	29
NPY	7p15.1	9 Leu7/Leu7 and 9 Leu7/Pro7	Plasma NPY during exercise	< 0.05	80,81
			Plasma GH during exercise	< 0.05	
ADRB3	8p12p11.2	61 obese diabetic women	Weight	< 0.001	189
			BMI	< 0.001	
			WHR	< 0.001	
UCP3	11q13	368 obese patients	BMI	0.015	144
VDR	12q13.11	33 women	Bone mineral density	0.03	231
		120 girls	Bone mineral density	0.04	92
		99 girls	Bone mineral density	0.02	107
		575 PM women	Bone mineral density	0.04	13
		44 male athletes; 44 controls	Bone mineral content; bone mineral volume	< 0.02	137
ACE	17q23	481 teenage girls	Subscapular and triceps skinfolds	< 0.012	129
		3075 subjects, aged 70–79 yr	%FAT, intermuscular thigh fat	0.02	94
Training responses or acute exercise					
PPARG	3p25	490 subjects	Body weight	0.04	104
		29 healthy offspring of type 2 diabetics	Body weight	0.05	143
ADRB2	5q31q32	12 obese women	RER	< 0.05	110
		482 men and women	BMI, FM, %FAT, subcutaneous fat	$0.0003 < P < 0.03$	50
		70 men and women	Percent body fat, trunk fat	< 0.02	151
ESR1	6q25.1	140 men	Bone mineral density	0.007	171
LPL	8p22	249 white women	BMI, fat mass, percent body fat	$0.01 < P < 0.05$	49
		171 black women	Abdominal visceral fat	0.05	
ADRB3	8p12p11.2	106 men	Leptin	< 0.05	79
		76 women	Body weight, BMI, waist circumference	$0.001 < P < 0.02$	206
		70 men and women	Fat mass, percent body fat, trunk fat	< 0.05	151
IL6	7p21	130 men	Cortical bone area	0.007	36
IL15RA	10p15p14	153 men and women	Lean mass	< 0.05	176
			Arm circumference	< 0.05	
			Leg circumference	< 0.05	
UCP3	11q13	503 whites	Subcutaneous fat	0.0006	102
GNB3	12p13	255 blacks	FM	0.012	166
			%FAT	0.006	
VDR	12q13.11	20 men	1,25 dihydroxyvitamin D_3 plasma level	< 0.05	216
		83 older men and women	Femoral neck bone mineral density	< 0.05	158
IGF1	12q22q23	502 men and women	Fat-free mass	0.005	213
CYP19A1	15q21.1	173 women	BMI, fat mass, percent body fat	< 0.05	233
PNMT	17q21q22	149 women	Body weight	0.002	150
ACE	17q23	81 men	Body weight	0.001	123
			Fat mass	0.04	
			Fat-free mass	0.01	
COMT	22q11.21q11.23	173 women	Percent body fat	< 0.05	233

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

study examined the effects of the *PPARG* Pro12Ala polymorphism on changes in glucose homeostasis and body-composition variables in 139 sedentary type 2 diabetic patients who completed 3 months of supervised exercise training (2). Although exercise training resulted in significant improvements in glucose homeostasis and body-composition variables, there were no significant differences between carriers and noncarriers of the Ala allele in response to exercise, except for fasting plasma glucose levels, which showed greater reductions ($P = 0.03$) in the Ala carriers (-2.02 ± 0.70) than in Pro12Pro homozygotes (-0.86 ± 0.32). In the fifth study, a polymorphism in the adiponectin receptor 1 (*ADIPOR1*) gene was found to be associated with lower insulin sensitivity in a follow-up study of 45 subjects (average follow-up of 9.8 months) who received diet counselling and increased their physical activity to at least 3 $h \cdot wk^{-1}$ of sports (211).

The only linkage study pertaining to glucose and insulin metabolism phenotypes reported in 2005 was a genome-wide linkage analysis of prediabetes phenotypes in response to 20 wk of endurance training in subjects from the HERITAGE Family Study (Table 12). Training-induced changes in insulin sensitivity, acute insulin response to glucose, disposition index, and glucose effectiveness were assessed in 441 subjects from 98 white families and 187 subjects from black families, adjusted for the effect of age, sex, BMI, and the respective baseline phenotypic values and tested for linkage with a total of 654 markers (4). In

TABLE 10. Summary of linkage studies with training-induced changes in body-composition phenotypes.

Gene	Marker	Location	No. of Pairs	Phenotype	*P*	Reference
QTL	S100A1	1q21	291 white	FFM	0.0001	24
	ATP1A2	1q21q23	291 white	%FAT	0.001	24
QTL	S100A1, ATP1A2, ATP1B1	1q21q23	72 black	ATF	< 0.01	172
QTL	D1S1660	1q31.1	291 white	FM, %FAT	0.0007	24
QTL	D5S1725	5q14.1	291 white	BMI	0.0004	24
QTL	D7S3070	7q36	72 black	ATF	0.00032	172
QTL	D9S282	9q34.11	291 white	FM, %FAT, Sum of skinfolds	$0.001 < P < 0.04$	24
QTL	ADRA2A	10q24q26	72 black	ASF	< 0.01	172
QTL	IGF2	11p15.5	72 black	ATF	< 0.01	172
QTL	UCP2	11q13	291 white	%FAT	0.0008	24,102
				FM	0.004	
IGF1		12q22q23	308 white	FFM	0.0002	213
QTL	IGF1	12q22q23	291 white	FFM	0.0001	24
QTL	D18S878, 1371	18q21q23	291 white	FM, %FAT	$0.001 < P < 0.04$	24

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.

whites, suggestive ($P \leq 0.01$ or LOD ≥ 1.17) evidence of linkage with disposition index (a measure of overall glucose homeostasis) was found on chromosomes 1p35.1, 3q25.2, 6p22.1, and 7q21.3. In blacks, suggestive linkages with glucose effectiveness were found on chromosomes 1q44, 2p22.1-p21, 10q23.1–q23.2, 12q13.11–q13.13, and 19q13.33–q13.43.

Blood Lipid and Lipoprotein Phenotypes

Seven new papers were published in 2005 analyzing genetic association or linkage for lipid responses to acute or chronic exercise and/or physical activity (Table 13). Ruano et al. investigated the effect of a promoter region variant (-75G>A) polymorphism in the apolipoprotein A1 gene (*APOA1*) on high-density lipoprotein (HDL) cholesterol after 6 months of aerobic exercise training (187). Although *APOA1* genotype was not associated with either total HDL or subfractions of HDL at baseline or after exercise training, the ratio of large HDL subfraction (HDL_3 + HDL_4 + HDL_5) to small HDL subfraction (HDL_1 + HDL_2) was significantly different by genotype after exercise training. Homozygotes for the -75G allele had increased amounts of the large HDL subfractions and decreased amounts of the small HDL subfraction compared with carriers of the -75A allele, suggesting that *APOA1* genotype is associated with HDL subfraction redistribution after exercise (187).

Halverstadt and colleagues investigated the association between variation in the *IL6* gene and HDL-C in elderly men and women undergoing 24 wk of aerobic exercise training (64). Sixty-five subjects were genotyped for the *IL6* 174G > C variant and measured for total HDL-C as well as HDL-C subfractions before and after training. Although the *IL6* 174G > C polymorphism not associated with any measure of HDL-C at baseline, this variant was significantly associated with changes in total HDL-C, HDL_3-C, integrated $HDL_{4,5}$-C (as measured by nuclear magnetic resonance spectroscopy), and HDL_{size}, with homozygotes of the 174C allele having greater increases after exercise training for each of these measures compared with those carrying the 174G allele (64).

The -514C>T polymorphism within the *LIPC* gene was investigated for association to lipid-related measures

TABLE 11. Evidence for the presence of associations between candidate genes and the responses of glucose and insulin metabolism phenotypes to habitual physical activity or regular exercise.

Gene	Location	Subjects	Phenotype	*P*	Reference
Interactions with exercise/physical activity					
VDR	12q13.11	1539	Fasting glucose	< 0.001	141
Training responses or acute exercise:					
ADIPOR1	1p36.1q41	45	Insulin sensitivity	0.03	211
PPARG	3p25	123 men	Fasting insulin, HOMA	$0.02 < P < 0.05$	78
		139 men	Fasting glucose	0.03	2
		32 men	Fasting insulin, insulin AUC	0.003	249
UCP1	4q28q31	106 men	Fasting glucose	< 0.01	79
ADRB2	5q31q32	19 obese women	Insulin to glucose ratio	< 0.05	111
		124 men	Fructosamine	0.0005	77
ADRB3	8p12p11.2	106 men	Fasting glucose, glycosylated hemoglobin levels	< 0.05	189
LEPR		397 men and women	Insulin sensitivity, glucose tolerance, pancreatic Bcell compensation for insulin resistance	$0.01 < P < 0.05$	99
LEP		397 men and women	Fasting insulin	0.02	99
IL6	7p21	56 men and women	Glucose tolerance	0.02	118
LIPC	15q21q23	522 subjects	Incidence of type 2 diabetes	0.001	222
		219 blacks	Insulin sensitivity	0.008	219
		443 whites	Insulin sensitivity	0.002	219
ACE	17q23	35 men	Insulin sensitivity	< 0.05	35

AUC, area under the curve.

before and after exercise in black and white families from the HERITAGE study. Individuals from this study underwent 20 wk of aerobic exercise training and were measured for a lipid panel that included triglycerides (TG), low-density and very-low-density lipoprotein (LDL and VLDL, respectively), HDL, HDL_2, HDL_3, Apo-A1, and apolipoprotein B (apoB) (219). In addition, the subjects were also measured for postheparin hepatic lipase and lipoprotein-lipase activity. Homozygotes for the -514C allele had significantly higher postheparin hepatic lipase activity at baseline and after exercise training ($P < 0.0001$ for both) in both black and white subjects compared with those with the T/T genotype. The -514C allele was also associated with lower postheparin lipoprotein lipase in blacks and whites before and after exercise training compared with -514T homozygotes (219). The LIPC -514C>T polymorphism was significantly associated with baseline TG, VLDL, LDL, HDL, ApoA1, and ApoB in whites and with pretraining HDL, HDL_3, and ApoA-1 in blacks. The only posttraining variable associated with the *LIPC* -514C>T variant was the training response measure of apoB in blacks. All other pre- and postexercise lipid measures were unrelated to the -514C>T polymorphism (219).

Two studies assessed the effects of genetic variation in response to diet/lifestyle/behavior interventions that included exercise. Coronary artery disease patients (N = 307) underwent a cardiac rehabilitation intervention that included diet, eduction, psychosocial, and smoking cessation counseling, in addition to twice-weekly aerobic exercise for 16 wk. Three gene variants were measured in these patients: the cholesterol-ester transfer protein (*CETP*) *TaqI*B polymorphism, the *LIPC* -514C>T variant, and the apolipoprotein E (*APOE*) epsilon variant. Although the cardiac rehabilitation intervention resulted in significant improvements in all measures assessed (total cholesterol (TC), LDL-C, HDL-C, TG, TC/HDL-C, BMI, and exercise capacity), results of this study for genetic association were primarily negative. Of all measures tested, the only significant result was for TC and the *CETP TaqI*B polymorphism ($P < 0.048$), with B1/B1 homozygotes experiencing decreased TC levels and B2 carriers having little or no change in TC after the lifestyle/exercise intervention (9). In another study, men and women underwent a diet and physical activity intervention designed to reduce insulin resistance, and the -8503G>A polymorphism within the *ADIPOR1* was investigated for association to measures of insulin sensitivity and hepatic lipids (211). The dietary therapy was aimed at reducing fat intake, whereas the physical activity intervention involved a minimum of 3 $h \cdot wk^{-1}$ of sports participation. After exercise and diet therapy, homozygotes for the -8503G allele had significantly lower hepatic lipid content (as measured by proton magnetic resonance spectroscopy) compared with subjects carrying the -8503A allele (211).

Two linkage studies for lipid-related phenotypes in the context of exercise training were reported in 2005 (Table 12). In a study of black and white families from the HERITAGE Family Study, Feitosa and colleagues reported evidence of QTL on chromosomes 13q and 14q for triglyceride subfractions (low-density lipoprotein (LDL-TG) and HDL-TG) at baseline and after 20 wk of exercise training (43). The highest LOD score reported was for baseline HDL-TG (LOD = 3.8) on 13q12–q14, and suggestive evidence for linkage was found in this same region for LDL-TG training response (LOD = 2.2) in whites only. For baseline LDL-TG in whites, significant or suggestive evidence of linkage was found on 14q31 (LOD = 3.2), 10p14 (LOD = 2.9), and 19p13 (LOD = 2.2). For HDL-TG in whites, suggestive evidence of linkage was found on 12q24 (LOD = 2.7) for baseline measures and on 10q23 (LOD = 2.2) for measures performed after 20 wk of exercise training. No evidence of linkage was found for any measure of total triglycerides, and no linkage was observed in the black families from this study (43).

In a second linkage scan for apoB and LDL-C in the same family sample from the HERITAGE study, suggestive linkages were observed for training responses in LDL-C on 12q14.1 (LOD = 2.1) and in LDL-apoB on 20q13 (LOD =

TABLE 12. Linkage studies for insulin and glucose metabolism, and lipid and lipoprotein training response phenotypes.

Gene	Markers	Location	No. of pairs	Phenotype	*P* Value/LOD	Reference
QTL	D1S1622	1p35.1	280 white	DI	1.2	4
QTL	D1S304D1S2682	1q43q44	72 black	S_G	1.1–1.7	4
QTL	D2S2247D2S2374	2p22.1p21	72 black	S_G	1.3–1.5	4
QTL	D2S1776	2q31	300 white	finsulin	0.0042	100
QTL	D3S1279	3q25.2	280 white	DI	1.2	4
QTL	D6S299	6p22.1	280 white	DI	1.2	4
QTL	PON2	7q21	300 white	finsulin	0.0035	100
QTL	PON1D7S821	7q21.3	280 white	DI	1.2–1.4	4
QTL	LEP	7q31	300 white	finsulin	0.0004	100
QTL	D10S541D10S2470	10q23.1q23.2	72 black	S_G	1.0–1.4	4
QTL	D10S2470	10q23.2	286 white	HDLTG	2.2	43
QTL	D12S1661D12S1604	12q13.11q13.13	72 black	S_G	1.0–1.3	4
QTL	D12S1691	12q14.1	286 white	LDLC	2.1	42
QTL	D13S219	13q12q14	286 white	LDLTG	2.2	43
QTL	D15S63	15q11	72 black	finsulin	0.0059	100
QTL	GYS1D19S254	19q13.33q13.43	72 black	S_G	1.8–3.1	4
QTL	D20S840	20q13	286 white	LDLapoB	2.2	42

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

Gene	Location	Subjects	Phenotype	*P*	Reference
Acute exercise					
FGB	4q28	149	Fibrinogen	0.01	125
ADRB2	5q31q32	15 obese women	Lipolysis, fat oxidation	< 0.05	112
		19 obese women	Fat oxidation	0.024	111
NPY	7p15.1	18	Serum FFA	< 0.05	80
APOC3	11q23.1q23.2	100 Korean men	Triglycerides	0.042	257
STS	Xp22.32	62 men, 58 women	DHEA	0.006	177
Exercise training					
APOA1	11q23q24	75 subjects	Large HDL fraction	0.0005	187
			Small HDL fraction	0.005	
IL6		41 women, 24 men	Total HDLC change	0.003	64
			HDL_3C 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	15q21q23	219 blacks, 443 whites	ApoB levels	0.04 (blacks only)	219
			LIPC activity	0.0001 (whites and blacks)	
			LPL activity	0.009 (whites and blacks)	
ADIPOR1	1p36.1q41	45 subjects	Hepatic lipid content	0.008	211
FGA	4q28	125	Fibrinogen	0.002	170
FGB	4q28	250	Fibrinogen	0.001	17
SERPINE1	7q21.3q22	132	Plasminogen activator inhibitor, type1	0.025	234
LPL	8p22	18	HDLcholesterol	< 0.05	59
			HDL_2cholesterol	< 0.05	
CETP	16q21	32	$HDL_{3\ 5NMR}$cholesterol	< 0.05	253
		307 men and women	Total cholesterol	0.048	9
LIPG	18q21.1	83	HDLcholesterol	0.04	63
APOE	19q13.2	51	HDLcholesterol	< 0.03	60
			HDL_2 cholesterol	< 0.01	
		252 white women	LDLcholesterol	0.022	103
			HDLcholesterol	0.0062	103
			HDL2cholesterol	0.013	103
			HDL3cholesterol	0.013	103
			VLDLcholesterol	< 0.0001	103
			Triglycerides	0.0024	103
			apoAI	< 0.0001	103
		241 white men	Total cholesterol	< 0.0001	103
			LDLcholesterol	< 0.0001	103
			HDLcholesterol	0.05	103
			Triglycerides	0.011	103
			apoB	0.005	103
		177 black women	apoAI	0.043	103
		89 black men	LDLcholesterol	0.017	103
		120 men and women	TC/HDL ratio	0.033	220
			LDL/HDL	0.015	220
			ApoB/AI	0.046	220
		60 women	LPLA	0.032	220
STS	Xp22.32	62 men, 58 women	DHEA	0.005	177
			DHEA:DHEAS	0.022	
Exercise–genotype interactions					
APOA2	1q21q23	200	Serum triglycerides	< 0.05	152
FGA	4q28	159	Fibrinogen	0.024	169
ADRB2	5q31q32	604	Nonesterified FFA	0.05	120
PON1	7q21.3	256	Serum triglycerides	0.017	204
			HDL cholesterol	0.018	
		17	PON1 activity	< 0.001	223
			Oxidized LDL	0.018	
LPL	8p22	379	Serum cholesterol	0.003	14
			Apolipoprotein B	0.003	
			HDLcholesterol	0.03	
LIPC	15q21q23	200	HDLcholesterol	< 0.01	152
			Apolipoprotein A1	< 0.01	
CETP	16q21	52 male CAD cases	HDLcholesterol	0.007	131
		15 female CAD cases	HDLcholesterol	0.029	131
APOE	19q13.2	713	Serum cholesterol	0.014	215
			LDLcholesterol	0.0082	
			HDL/serum cholesterol	0.0004	
		338	HDL cholesterol	0.001	30
		1708	HDLcholesterol	$0.001 < P < 0.008$	11
			Triglycerides	0.03	
		200	LDLcholesterol	< 0.01	152
			Apolipoprotein B	< 0.01	

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

2.2) (42). Significant or suggestive evidence for linkage was found on 1q41-q44 for baseline measures of LDL-apoB (LOD = 3.7), apoB (LOD = 2.9), and LDL-cholesterol (LOD = 2.1) in blacks. In whites, baseline measures of LDL-chol, LDL-apoB, and apoB were significantly or suggestively linked to chromosomal region 8q24 (LOD = 3.6, 3.3, and 2.5, respectively).

Hemostatic Factors, Inflammation Phenotypes and Plasma Hormone Levels

No new studies were published in 2005.

Chronic Diseases

A significant interaction between physical activity and genotype ($P < 0.01$) was demonstrated in an analysis of the *IGF1* gene on colon cancer outcomes. Homozygotes for a CA repeat polymorphism within the *IGF1* gene ("192/192") who reported no habitual physical activity were almost 50% more likely to develop colon cancer (OR = 1.46, 95% CI = 1.08, 2.05), whereas active individuals with the 192/192 genotype experienced decreased risk for colon cancer (OR = 0.57, 95% CI = 0.39, 0.83) compared with active individuals not carrying the 192 allele (209). Similarly, for a single nucleotide polymorphism resulting in an amino acid change from glycine to alanine at codon 32 (Gly32Ala) within the insulin-like growth factor binding protein 3 (*IGFBP3*) gene, the protective effect of physical activity on colon cancer was only observed in male carriers of the Ala32 allele ($P < 0.01$) (130).

In a sample of 1577 colon cancer patients (1971 controls) and 794 rectal cancer patients (1001 controls), Slattery and colleagues reported no significant interactions between the Pro12Ala variant in the *PPARG* gene and energy expenditure (a surrogate of physical activity) in predicting cancer risk (210). In a sample of 4248 elderly white women, Modugno et al. also reported no association between risk for breast cancer and either the catechol-*O*-methyltransferase (*COMT*) Val158Met polymorphism or an isoleucine to valine variant at codon 462 in the *CYP1A1* gene, a gene also involved in hydroxylation of free estrogen. There was no significant interaction when stratifying by physical activity (walking for exercise) (121).

Exercise Intolerance

Nine studies related to exercise intolerance were published in 2005 (Table 14). These studies reported mutations in four nuclear and five mitochondrial genes. Palmieri and coworkers reported a patient with exercise intolerance, lactic acidosis, and hypertrophic cardiomyopathy. A skeletal muscle biopsy revealed presence of ragged-red fibers and multiple deletions of muscle mitochondrial DNA. A mutation screening of muscle-specific adenine nucleotide translocator gene (*SLC25A4*) revealed a homozygous C to A transversion at nucleotide 368, which changed a highly conserved alanine residue to an aspartic acid at codon 123 (145).

TABLE 14. Genes encoded by nuclear and mitochondrial DNA in which mutations have been reported in patients with exercise intolerance.

Gene	OMIM No.	Location	Reference
Nuclear DNA			
CPT2	255110	1p32	114, 214, 218, 240, 241
AMPD1	102770	1p13	74, 146
SLC25A4	103220	4q35	145
PGAM2	261670	7p13p12	58, 224, 230
LDHA	150000	11p15.4	227
PYGM	232600	11q12q13.2	228
PFKM	232800	12q13.3	205, 226, 242
SGCG	253700	13q12	237
TK2	188250	16q22q23.1	247
ENO3	131370	17pterp11	28
ACADVL	201475	17p13p11	194
SGCA	600119	17q21	122
GK	307030	Xp21.3	67
PHKA1	311870	Xq12q13	18
PGK1	311800	Xq13	229
LAMP2	309060	Xq24	134
Mitochondrial DNA			
MTTL1	590050	3230–3304	22, 70
MTND1	51600	3307–4262	133
MTTI	590045	4263–4331	23
MTTM	590065	4402–4469	238
MTTY	590100	5826–5891	157
MTCO1	516030	5904–7445	87
MTTS1	590080	7445–7516	54, 156
MTTD	590015	7518–7585	202
MTCO2	516040	7586–8269	117
MTTK	590060	8295–8364	132
MTCO3	516050	9207–9990	65, 69
MTND4	516003	10760–12137	8
MTTL2	590055	12266–12336	88, 239
MTTE	590025	14674–14742	66
MTCYB	516020	14747–15887	5, 6, 7,12,19,90,101,113,196

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

Isackson et al. reported two Caucasian brothers with exercise intolerance and myoadenylate deaminase deficiency (74). Interestingly, neither brother carried the common Q12X nonsense mutation. Instead, they were compound heterozygotes for a K287I mutation in exon 7 and a novel CTTT deletion in intron 2. The K287I mutation is fairly frequent in general population, whereas the intron 2 mutation, which affects the splicing machinery, was found only in these patients. Skeletal muscle mRNA analysis revealed several alternatively spliced *AMPD1* transcripts, with either partial or complete deletions of either exon 3 or exons 3 and 4. Moreover, the deletion seems to activate a cryptic splice site that results in an extension of the 5 end of exon 4 (74).

A Danon disease patient with persistent hyperCKemia, exercise intolerance, and hypertrophic cardiomyopathy but with no muscle weakness or mental impairment was described by Musumeci et al (134). Skeletal muscle samples showed a vacuolar myopathy and a lysosome-associated membrane protein 2 (lamp2) deficiency. The lamp2 protein deficiency was caused by a novel T/C substitution at position 961 in exon 8 of the *LAMP2* gene (134). Wang et al. reported an exercise-intolerant patient with severe mitochondrial myoptahy and 92% reduction in skeletal-muscle mitochondrial DNA content. The patient was a compound heterozygote for a T77M and R161K mutations in the thymidine kinase 2 (*TK2*) gene (247).

TABLE 15. Association and linkage studies for physical activity phenotypes.

Gene/Marker	Location	Subjects/Sibling Pairs	Phenotype	*P*	Reference
Associations					
LEPR	1p31	268	Total physical activity (24h EE/sleeping EE)	0.008	212
CASR	3q21q24	97	Weightbearing physical activity	0.01	106
DRD2	11q23	402 white women	Physical activity	0.016	207
		256 white women	Sports index	0.023	207
			Work index	0.004	
CYP19A1	15q21.1	331	Physical activity	0.039	190
ACE	17q23	355	Sedentary vs active	0.001	254
MC4R	18q22	669	Moderate to strenuous activity	0.005	105
			Inactivity	0.01	
Linkage					
D2S2347	2p22.3	309	Inactivity	0.0012	208
UCP1	4q28q31	309	Moderate to strenuous activity	0.005	208
IGFBP1	7p13p12	308	Inactivity	0.0046	208
		308	Moderate to strenuous activity	0.006	208
D9S938	9q31	308	Moderate to strenuous activity	0.0028	208
C11P15-3	11p15	329	Total activity (previous year)	0.0089	208
D13S317	13q22	308	Total activity	0.0029	208
		308	Moderate to strenuous activity	0.0067	208
D15S165	15q13	329	Total activity (previous year)	0.009	208
PLCG1	20q12	308	Inactivity	0.0074	208

Mutations in five mitochondrial DNA genes were reported in exercise-intolerant patients. The only new gene to be introduced in the map was the mitochondrial transfer RNA aspartate (*MTTD*) gene. An A to G transition at position 7526 was identified in a young girl with pronounced exercise intolerance, decreased anaerobic threshold and $\dot{V}O_{2max}$, and decreased complex I and IV enzyme activity (202). A heteroplasmic T/C mutation at position 9789 in the mitochondrial cytochrome c oxidase subunit III (*MTCO3*) gene introducing a S195P change was found in skeletal muscle of a 22-yr-old exercise-intolerant patient (69). Blakely et al. reported a novel mutation in the mitochondrial cytochrome b (*MTCYB*) gene introducing an Arg318Pro substitution and a severe reduction of both complexes I and III in skeletal muscle (12).

Four new patients were reported carrying an A3302G mutation in the mitochondrial transfer RNA leucine (UUR) (*MTTL1*) gene. All patients had a mitochondrial myopathy, exercise intolerance, and proximal muscle weakness (70). Finally, Pulkes and colleagues reported a patient with isolated myopathy and exercise intolerance who carried both a C-insertion and a homoplasmic A to C transition at nucleotide position 7472 in the mitochondrial transfer RNA serine (UCN) (*MTTS1*) gene (156).

Physical Activity

Association studies. One new study on the associations between candidate gene markers and physical activity–related phenotypes was published in 2005 (Table 15). Loos

TABLE 16. Evolution of the status of the Human Gene Map for Performance and Health-Related Fitness Phenotypes.

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

and colleagues reported significant associations between a C/T polymorphism located 2745 base pairs upstream of the melanocortin 4 receptor (*MC4R*) gene start codon and physical activity phenotypes. Homozygotes for the rare T-allele had significantly lower moderate-to-strenuous physical activity levels and higher inactivity score than the other genotypes (105).

Linkage studies. No new linkage studies were published in 2005.

SUMMARY AND CONCLUSIONS

This review provides a compendium of all genes and markers that have been associated with performance and health-related fitness phenotypes in scientific papers published by the end of 2005. Little progress has been made in the last 12 months with respect to the genetic basis of human variation in performance and health-related fitness. Indeed, although a growing number of genes are being identified, only a handful of them have been investigated with a view to assess whether DNA sequence variation in such genes play a role in the biological basis of human individuality.

The 2005 map includes 165 autosomal entries, five X chromosome assignments, and 17 mitochondrial DNA markers. There are 25 more nuclear markers and one more mitochondrial genome marker than in 2004. Given the complexity of the performance- and health-related fitness phenotypes, it should be obvious that we have a long way to go before we have a satisfactory understanding of the role of genetic inheritance on exercise-related traits and in the adaptation to a physically active lifestyle. Given the growing prevalence in obesity, type 2 diabetes, cardiovascular disease, and other chronic diseases associated with physical inactivity, an increased understanding of how the genetic susceptibilities that lead to these diseases may interact with exercise and physical activity interventions is urgently needed.

There is a growing number of genes with at least a minimum of evidence supporting their involvement in fitness- and performance-related phenotypes. This is illustrated by the trends in the number of loci from 2000 to 2005 for the families of phenotypes as defined in this review. Table 16 presents this synthesis for the 10 classes of phenotypes considered here. In each case, the number of genes or markers has increased slowly but steadily since the topic was first reviewed in 2000.

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