Genetics of Athletic Performance

"The human body is centuries in advance of the physiologist, and can perform an integration of heart, lungs and muscles which is too complex for the scientist to analyse."

Roger Bannister (1955)

illustration by Bryan Christie

"There is likely a minimal set of physical traits or genetic makeup which facilitates achievement to a particular level of success, but I do not believe that genetics are necessarily an absolute limiter of exceptional performances."

Peter Vint (2011)

Gene 210 - Genomics and Personalized Medicine
Andrew Roos and Thomas Roos
May 15th, 2012

What is Athletic Performance?

Strength

Arnold Schwarzenegger

muscle mass
force generation
speed
agility
power

oxidative phosphorylation (ATP)
creatine phosphate usage
glycogen usage
metabolic rate

resting heart rate
max heart rate
lactate threshold
cardiac output
ventillatory rate

Endurance

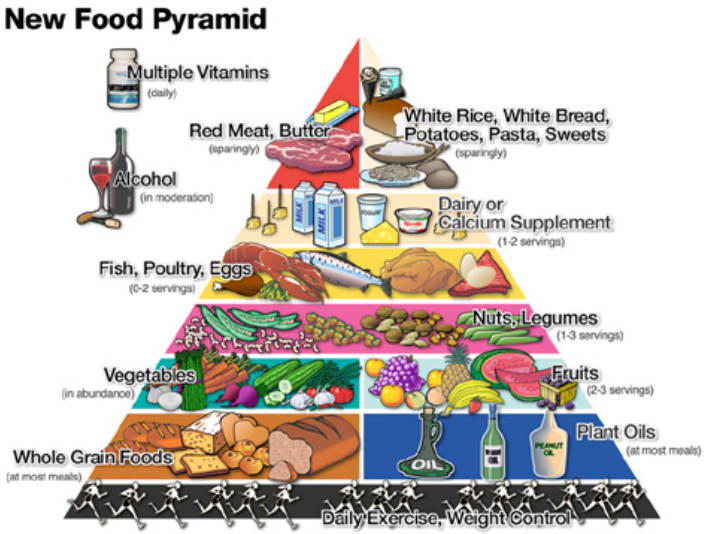
Dean Karnazes

it all depends on what you want your body to accomplish

Environmental Factors Affecting Performance

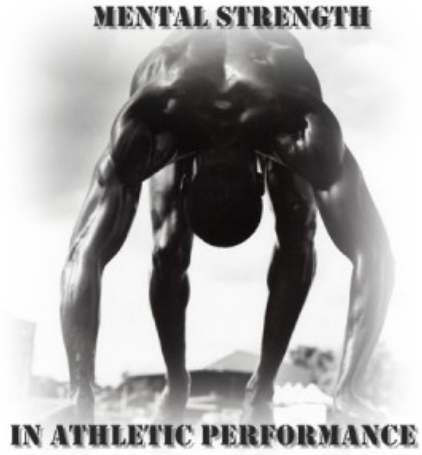
Lance Armstrong

- training/conditioning
- skill level
- age
- PED's
- climate/temperature
- altitude



US Department of Agriculture

- nutrition: food + water
- sleep
- recovery
- weight



- mental strength
- work ethic
- confidence
- focus on goals
- mental adaptation
- psychology

Genetic Factors Affecting Performance

illustration from 3dscience.com

- gender
- ancestry & ethnicity
- anatomy

Usain Bolt

- biomechanical factors
- muscle fiber types
- muscle contraction velocity
- muscle elasticity
- soft-tissue strength

- fatigue resistance
- training adaptation
- recovery
- injury resistance

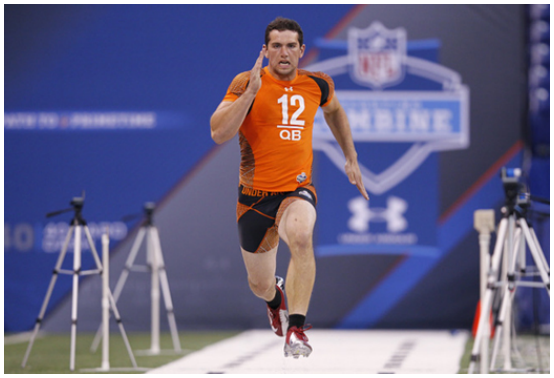
How Scientists Test "Performance"

Strength/Power

1) max weight lifted [kg]
2) max power [W/kg]
3) 100m sprint
4) vertical + horizontal jump distance

Endurance

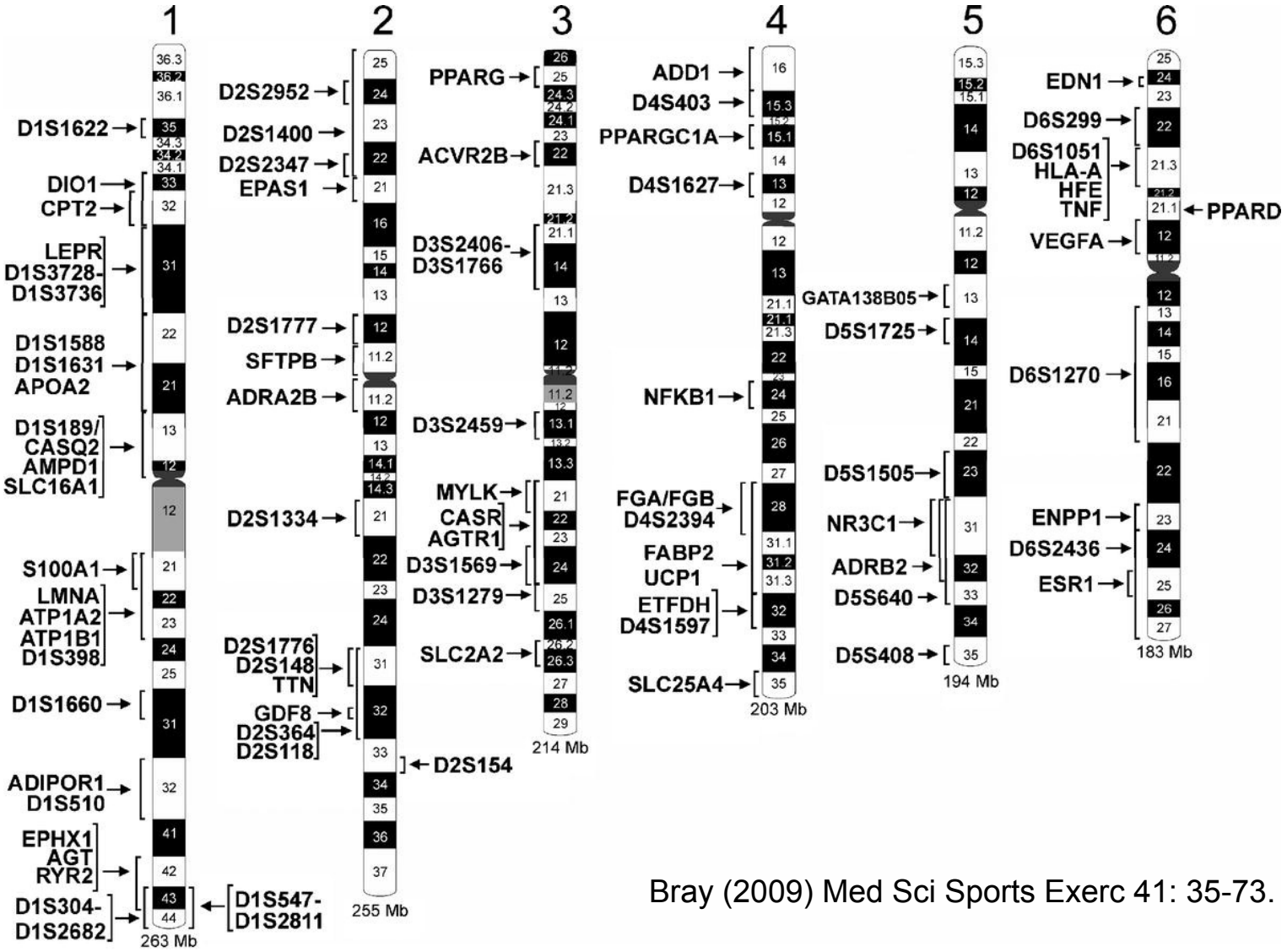
1) peak oxygen consumption (VO_2 max) [ml/min/kg]
2) running economy (RE) [ml/kg/km]
3) lactate threshold + clearance



genetics + environment

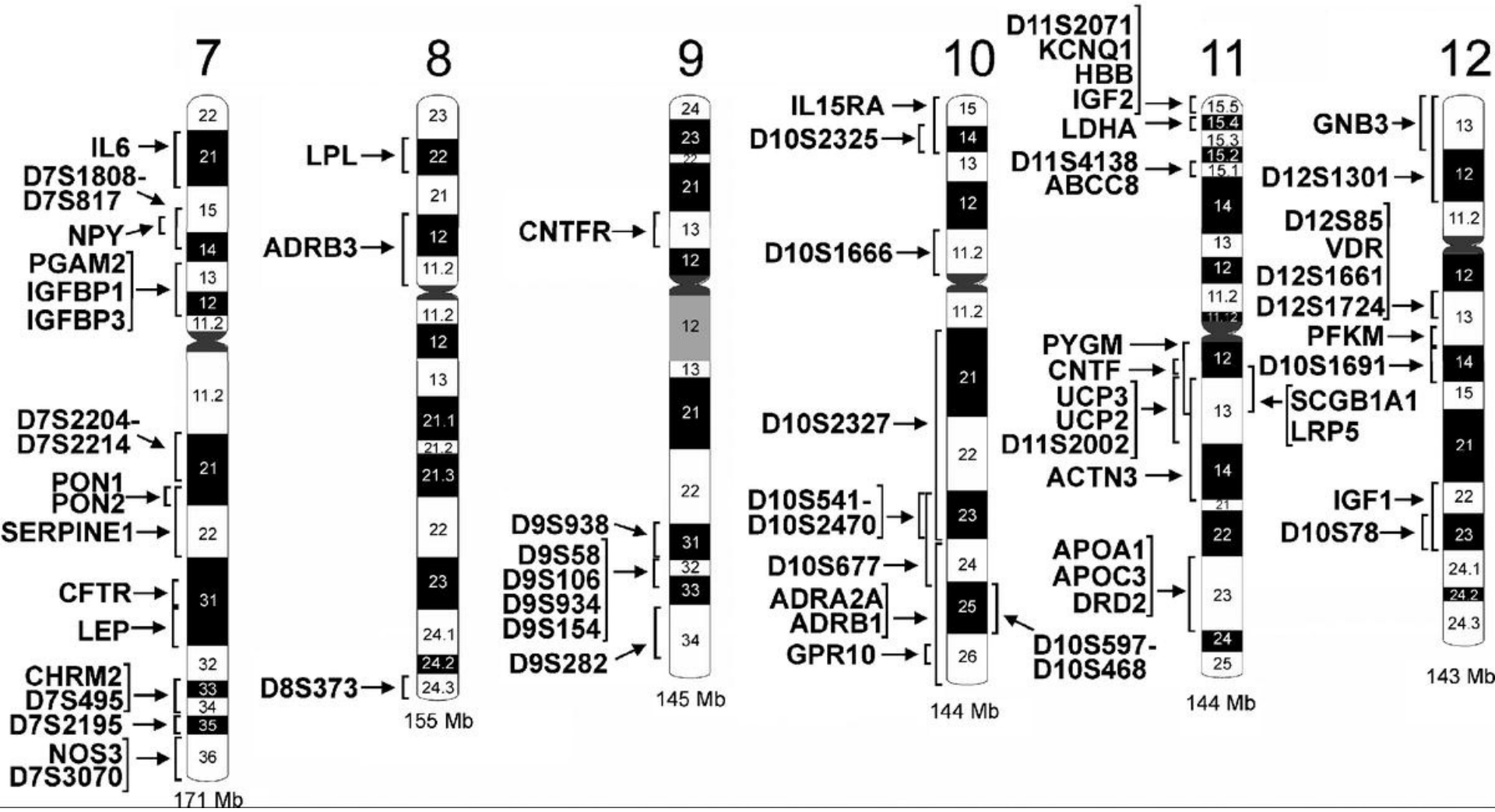
elite athletes vs controls
candidate based approach
genetic testing for SNP
data analysis

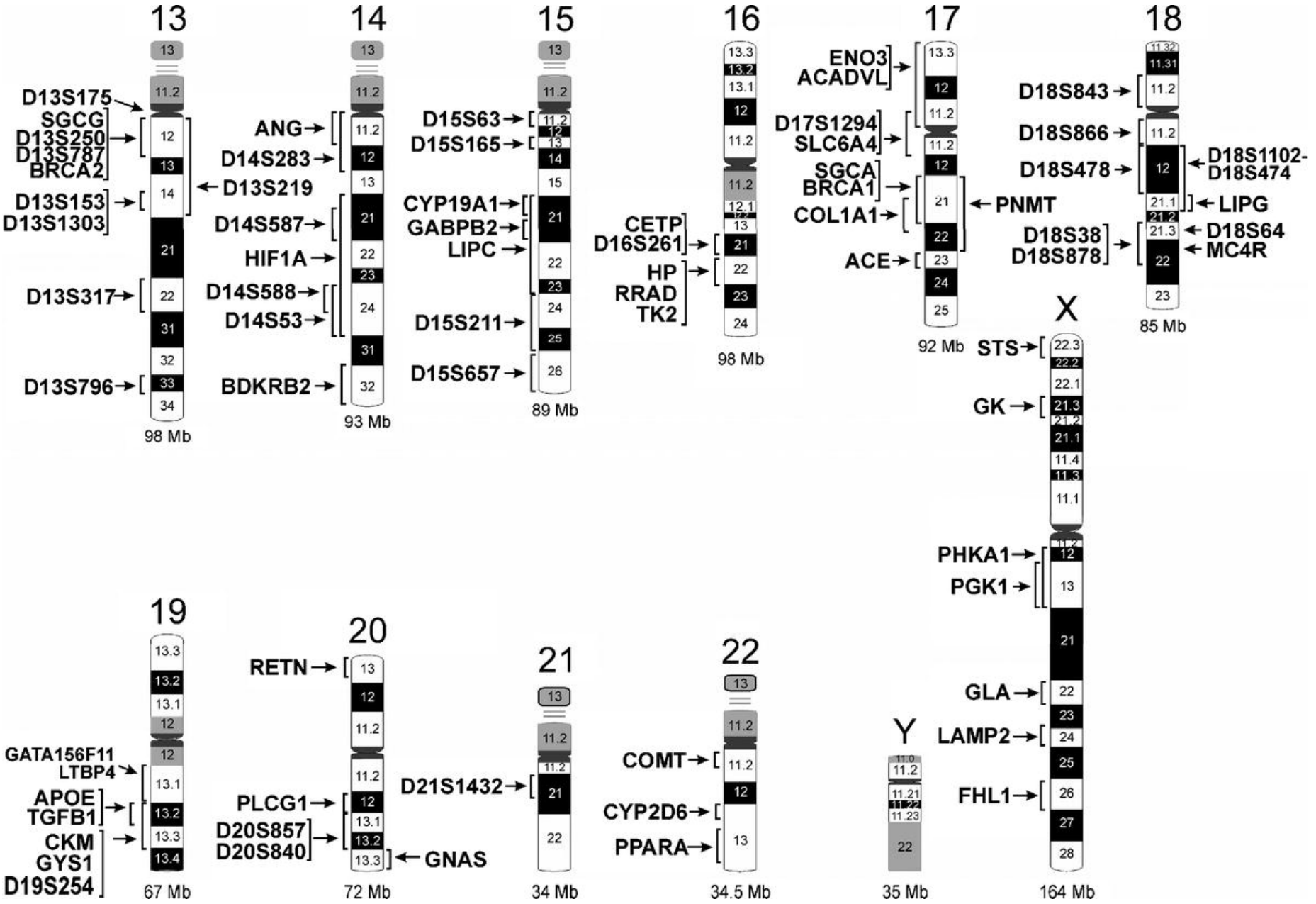
The Human Gene Map for Performance and Health-Related Fitness Phenotypes



Bray (2009) Med Sci Sports Exerc 41: 35-73.

239 gene entries: 214 autosomal; 7 on X; 18 mitochondrial




13
D13S175
SGCG
D13S250
D13S787
BRCA2
D13S153
D13S1303
D13S317
D13S796
D13S219
98 Mb
14
ANG
D14S283
D14S587
HIF1A
D14S588
D14S53
BDKRB2
93 Mb
15
D15S63
D15S165
CYP19A1
GABPB2
LIPC
D15S211
D15S657
89 Mb
16
CETP
D16S261
HP
RRAD
TK2
98 Mb
17
ENO3
ACADVL
D17S1294
SLC6A4
SGCA
BRCA1
COL1A1
ACE
PNMT
92 Mb
18
D18S843
D18S866
D18S478
D18S1102-
D18S474
LIPG
D18S38
D18S878
D18S64
MC4R
85 Mb
19
GATA156F11
LTBP4
APOE
TGFB1
CKM
GYS1
D19S254
67 Mb
20
RETN
PLCG1
D20S857
D20S840
GNAS
72 Mb
21
D21S1432
34 Mb
22
COMT
CYP2D6
PPARA
34.5 Mb
X
STS
GK
PHKA1
PGK1
GLA
LAMP2
FHL1
164 Mb
Y
35 Mb

ACE

- **ACE**: angiotensin converting enzyme
  1) converts inactive angiotensin I to active angiotensin II in liver
  2) degrades bradykinin & other vasodilator peptides
- functions= vasoconstriction, salt/water balance, inflammation, RBC synthesis, tissue oxygenation, muscle efficiency.

- I allele: 287bp insertion; lower ACE activity
  I/I genotype -> increased endurance performance [p=0.009]
  increased metabolic response from training, metabolic efficiency

- D allele: deletion variant; higher ACE activity
  D/D genotype -> increased power performance [p=0.004]
  increased strength gain from training, L ventricle mass, VO_2 max

- many studies w/ conflicting results on ACE & athletic performance
  8 show positive association & 5 show no association
  different sports, different criteria for cases/ct's, different methods

Gayagay (1998) Hum Genet 103:48–50; Montgomery (1998) Nature 393:221–22; Montgomery (1999) Lancet 353:541–45; Myerson (1999) J Appl Physiol 87:1313–16; Tsiano (2004) Eur J Appl Physiol 92:360–62; Thompson (2007) High Alt Med Biol 8:278–85.

ACE

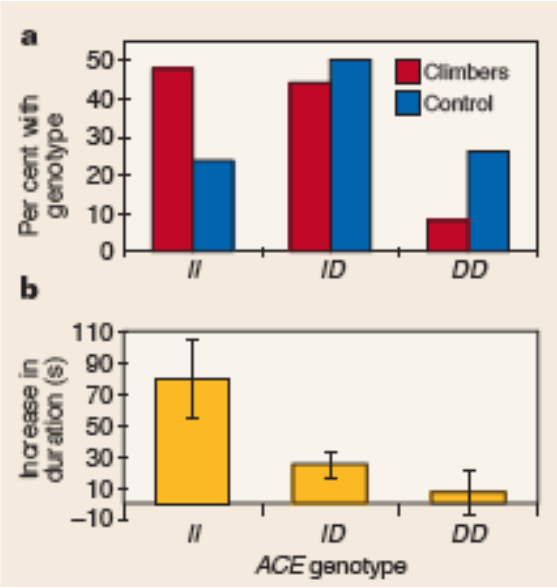


Table 1. By ACE I/D Genotype and Mean Maximum Altitude Achieved

ACE genotype	*Maximum altitude achieved (m)*
II	8559 ± 565
ID	8107 ± 653
DD	8079 ± 947

Table 2. ACE I/D Genotype and Success in Ascent to 8000 m

	Group A (climbed >8000 m)	*Group B (never climbed >8000 m)*	*Total*
II	30 (32.6%)	3 (6.4%)	33 (23.7%)
ID	41 (44.6%)	28 (59.6%)	69 (49.6%)
DD	21 (22.8%)	16 (34.0%)	37 (26.6%)
I-allele frequency	0.55	0.36	0.49
D-allele frequency	0.45	0.64	0.51

Table 3. Logistic Regression Analysis of the Categorical Variables Influencing Success in Ascent to 8000 m

	Significance
Age	0.620
Sex	0.184
Race	0.118
Smoker	0.187
ACE I-allele	0.002

	II		D+		p*		Adjusted mean change†		Adjusted p‡
	n	Mean (SD) change	n	Mean (SD) change	II	D+	II	D+	
Total mass									
Bioimpedance (kg)	19	1·97 (2·57)	61	−0·10 (3·32)	0·03	0·54	2·14	−0·10	0·001
Skinfold assessment (kg)	14	1·88 (2·59)	13	−0·57 (1·85)	0·01	0·28	1·78	−0·47	0·01
MRI volume (cm³)	16	9·96 (10·15)	14	0·15 (7·20)	0·001	0·98	9·27	0·83	0·01
Fat mass									
Bioimpedance (kg)	19	0·73 (1·69)	57	−0·26 (1·54)	0·07	0·21	0·55	−0·20	0·04
Skinfold assessment (kg)	14	−0·13 (1·23)	13	−1·66 (1·60)	0·67	0·004	−0·36	−1·35	0·05
MRI volume (cm³)	16	0·59 (6·35)	14	−3·34 (5·12)	0·70	0·08	0·16	−2·86	0·20
Non-fat mass									
Bioimpedance (kg)	19	1·09 (1·59)	57	−0·08 (2·61)	0·007	0·82	1·31	−0·15	0·01
Skinfold assessment (kg)	14	2·01 (1·83)	13	1·03 (1·19)	0·002	0·01	2·00	1·03	0·11
MRI volume (cm³)	16	9·57 (7·21)	14	3·61 (4·25)	0·0001	0·01	9·32	3·88	0·02

Montgomery (1998) Nature 393:221–22; Montgomery (1999) Lancet 353:541–45; Thompson (2007) High Alt Med Biol 8:278–85.

ACTN3

- alpha-actinin-3: crosslinks actin thin filaments in skeletal muscle type 2 (fast) fibers; thought to play a role in maintaining ordered fiber arrays and coordinating contraction

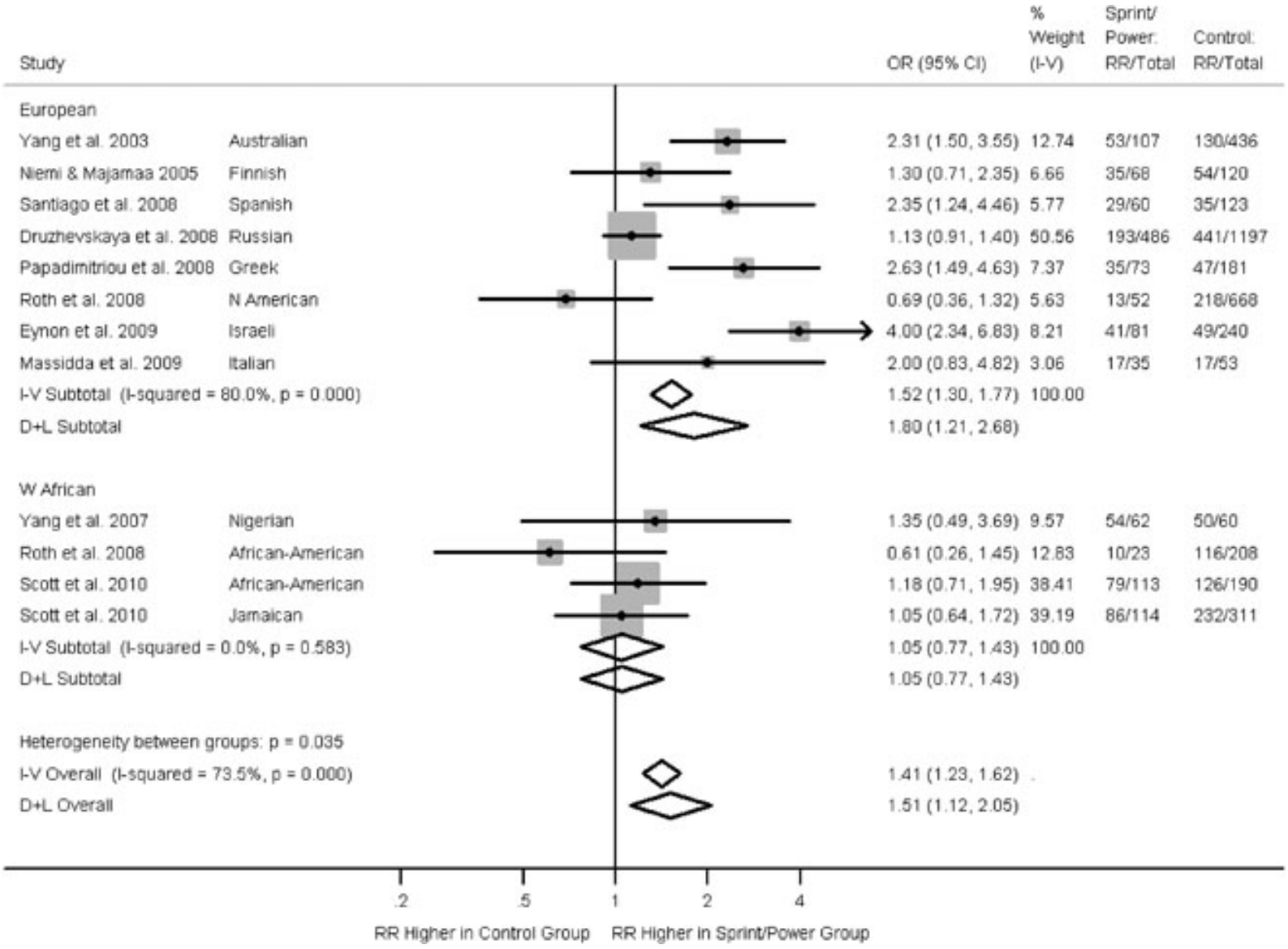
- R577X: rs1815739; C->T; 25% Asian, 18% European, 1% African

Yang (2003)
- CC [RR] genotype associated with increased strength (OR=2.31; p=0.0001)
- TT [XX] genotype associated with increased endurance (OR=1.38; p=0.148)

Controversial
- 10 studies showing association between RR and strength/power
- 2 studies showing no association between RR and strength/power
- 1 study showing association between XX and endurance
- 7 studies showing no association between XX and endurance

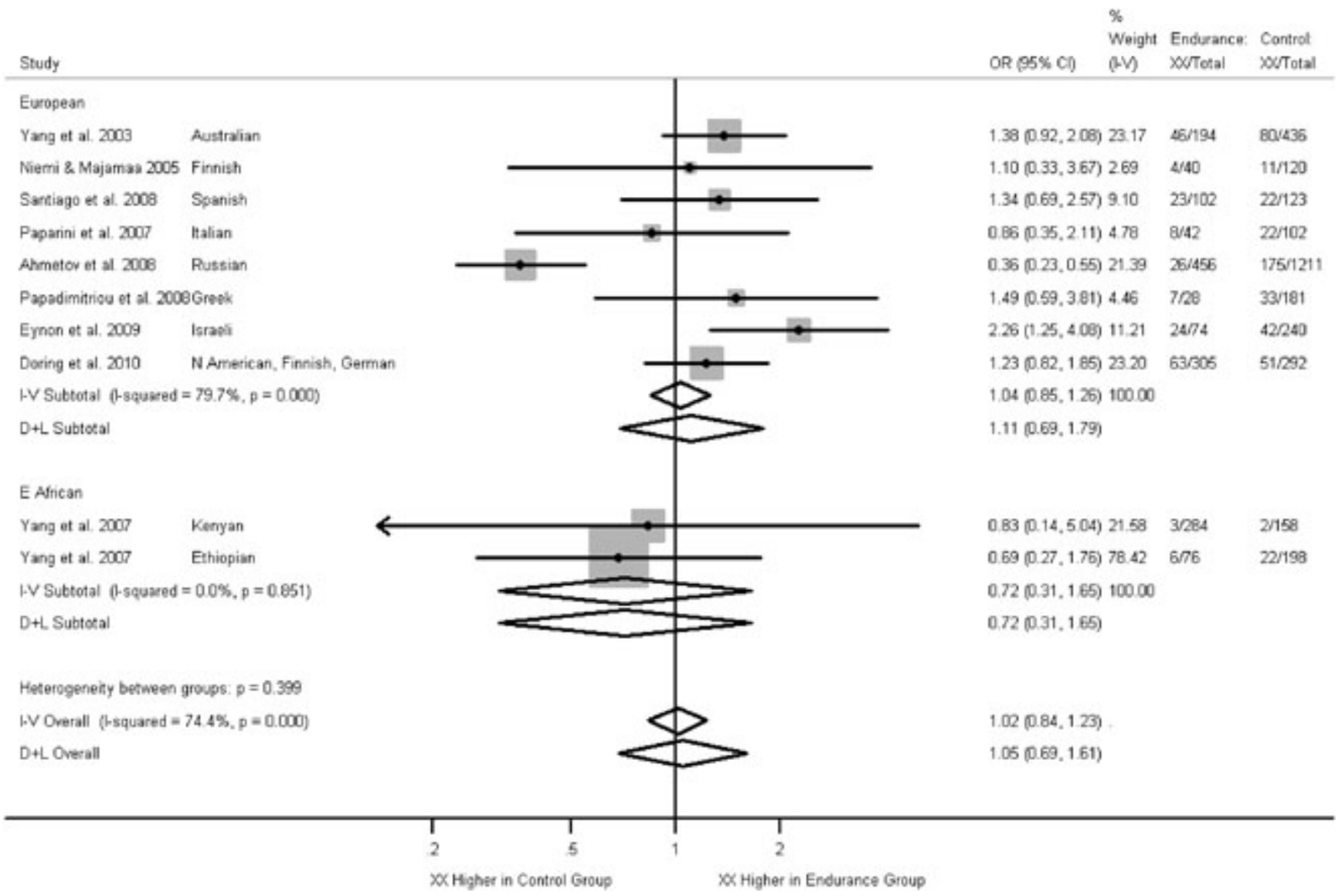
Yang (2003) Am J Hum Genet 73: 627-631.
Alfred (2011) Hum Mut 32: 1008-1018.

ACTN3



Alfred (2011) Hum Mut 32: 1008-1018.

ACTN3



Alfred (2011) Hum Mut 32: 1008-1018.

ADRB1, ADRB2, ADRB3

- beta-adrenergic receptors 1/2/3: G-protein coupled receptors in cardiac and adipose tissue that regulate cardiac function and metabolism
- cardiac tissue: activated receptor -> increased cardiac output
- adipose tissue: activated receptor -> increased lipid mobilization for energy production

ADRB1: rs1801253; Arg389Gly; C->G
- C allele associates with increased VO_2 max and exercise time/endurance (p=0.002)
- G allele associates with decreased VO_2 max (p=0.006)

ADRB2: rs1042713; Arg16Gly; G->A
- G allele associates with elite endurance performance in males (p=0.03)
- A allele associates with increased BMI and decreased VO_2 max (p<.001)

ADRB2: rs1042714; Gln27Glu; C->G
- C allele associates with elite distance running in middle age women (p=0.05)
- G allele associates with increased BMI and decreased VO_2 max (p=0.0001)

Wagoner (2002) Am Heart J 144.
Wolfarth (2007) Met Clin Exp 56: 1649-1651.
Moore (2001) Metabolism 50: 1391-1392.

ADRB1, ADRB2, ADRB3

ADRB3: rs4994;Trp64Arg; T->C
- C allele associates with elite endurance performance (p=0.0008)

- study: elite Spanish athletes for endurance or strength sports
- TT genotype: no association in endurance or strength vs controls
- TC genotype: association in endurance vs controls but not strength vs controls
- CC genotype: very rare; association in strength vs controls

Santiago (2011) Br J Sports Med 45: 147-149.

COL5A1 and COL6A1

- alpha1 chain of type V and type VI collagen
- extracellular matrix (ECM) structural component of musculoskeletal soft tissue
- known mutations involved in various clinical muscle diseases (cause hyper-elasticity in the muscles -> decreased function)
- biomechanics: stiffer connective tissue (inflexibility) -> enhanced storage/return of energy -> increased running economy -> increased endurance performance

COL5A1
- BstUI RFLP: T/C
- TT genotype (vs CT + CC) associated with increased endurance performance (faster Ironman Triathlon run time) [p=0.020]

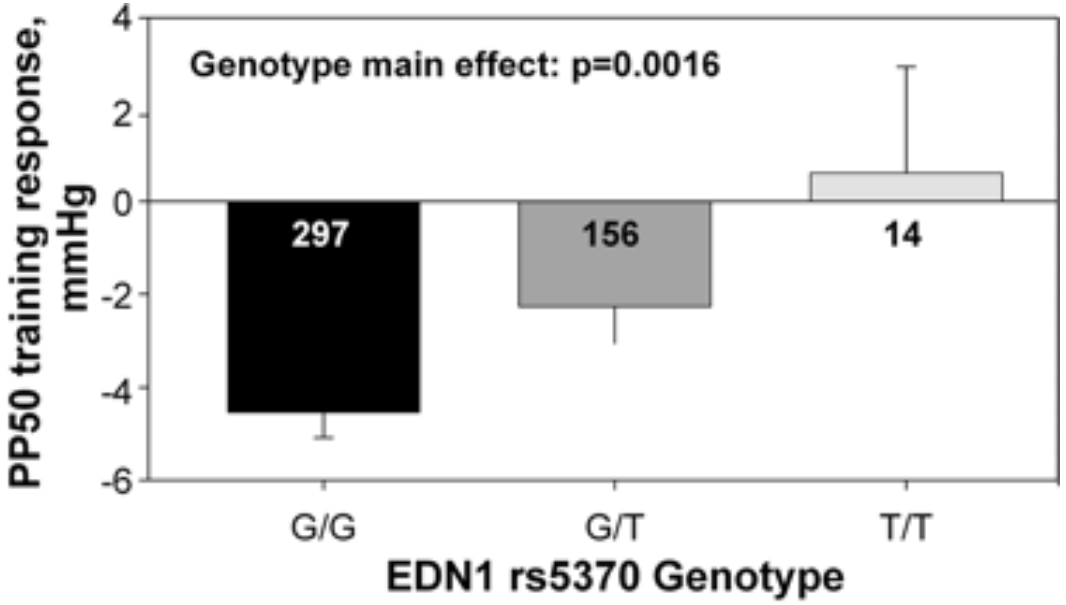
COL6A1
- rs35796750: intron 32, T/C, T= ancestral allele
- CC genotype (vs CT + TT) associated with multiple muscle diseases
- TT genotype (vs CT + CC) associated with increased endurance performance (faster Ironman Triathlon finish time) [p=0.030]

Posthumus (2011) Med Sci Sports Exerc 43: 584-9.
O'Connell (2011) Int J Sports Med 32: 896-901.

EDN1

- endothelin 1: expressed in vascular endothelium; acts as a vasoconstrictor to regulate blood pressure

rs5370: Lys198Asn; G->T
- G allele associates with increased cardiorespiratory fitness (OR=1.95; p=0.00025)
- T allele associates with increased hypertension (p=.0003)
    - for Caucasians only and not African Americans
- T allele decreases the VO_2 max and pulse pressure response to training



Rankinen (2007) Hypertension 50: 1120-1125.

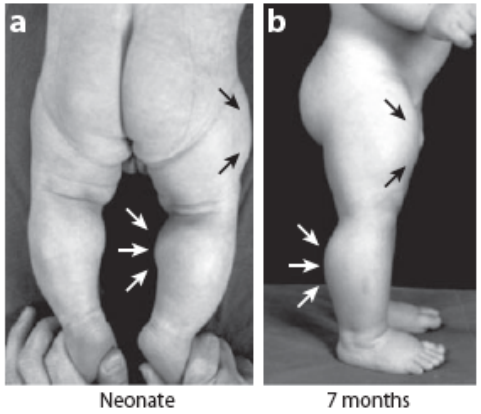
MSTN

- **MSTN**: myostatin (TGF-B family member)
  negative regulator of skeletal muscle growth

- homozygous mutation in MSTN -> inactivation
  human patient 1-4.5yrs old w/ increased muscle mass

- protein truncation deletion removing C-term domain MSTN -> catalytically dead
  increased muscle mass in livestock (cattle, pigs)

- *Mstn* k/o mouse model -> increased muscle mass & # muscle fibers
  overall more fast glycolytic type II muscle fibers than ct



Schuelke (2004) N. Engl. J. Med. 350:2682–88; Marchitelli (2003) Mamm. Genome 14:392–95; McPherron (1997) Nature 387:83–90; Girgenrath (2005) Muscle Nerve 31:34–40.

NRF1, NRF2

- **NRF1**: nuclear respiratory factor 1
  role in exercise adaptation: mitochondrial biogenesis, heme biosynthesis

- rs240790
  CC gentotype associated w/ increased VO_2 max + RE w/ training [p=0.004]
- rs6949152
  AA gentotype associated w/ increased VO_2 max w/ training [p=0.047]

- **NRF2/NFE2L2**: nuclear regulatory factor 2
  tranxs factor activating oxidative stress response & antioxidants

- rs12594986, rs8031031, rs7181866
  A/T/G haplotype associated w/ 57% higher training response [p=0.006]

He (2008) Br. J. Sports Med. 42:361–66.

PPARGC1A

- **PPARGC1A**: peroxisome proliferators-activated receptor g coactivator 1a
  activator of ox phos genes that control glucose & lipid metabolism
  skeletal muscle fiber-type formation
  mitochondrial biogenesis

- rs8192678: G -> A; Gly482Ser
  AA genotype associated w/ higher VO_2 max in European men [$p<0.0001$]
  not associated w/ better VO_2 max or RE in Chinese men

- rs6821591: A -> G; 3' UTR
  GG genotype associated w/ higher VO_2 max & RE in Chinese men

Lucia (2005) J. Appl. Physiol. 99:344–48.
Saunders (2004) Sports Med. 34:465–85.

Other Reported Performance Enhancing Polymorphisms (PEPs)

- 2 validated markers w/ multiple positive associations: ACE, ACTN3
- 4 other markers w/ positive associations: ADRB2, AMPD1, APOE, BDKRB2

- physiological categories influenced by human PEPs
  - cardiac function
  - circulatory system
  - respiratory system
  - muscle structure
  - adrenergic receptors
  - mitochondrial function (oxidative phosphorylation)
  - mitochondrial DNA

- 239 total reported PEPs but very few validated
- potential limitations of studies
  - studied only specific populations only specific gender
  - too few subjects
  - different criteria for cases vs controls
  - significant p-values (?)

Daily Health Advice - Genetics in Sports

Ostrander (2009) Annu Rev Genomics Hum Genet 10:407-429.

Athletic performance is determined by a combination of factors

- measure: Ironman Triathlon finish times

    no significant difference in training time/volume between "fast" and "slow" groups

age + weight explain 14% of variance

COL6A1 genotype (TT vs TC/CC) explains 8% of variance

    BDKRB2 +9/+9 & NOS3 GG genotypes associate w/ significantly slower times [p=0.001]

- measure: endurance (VO_2 max + LT) + efficient muscle contraction

    ACE-I/BDKRB2-9 haplotype significantly associated in Olympic athletes vs ct's [p=0.003]

- heritability of beneficial endurance traits is ~50% (VO_2 max, RE, LT)
- heritability of athletic status in women is ~66% (recreational vs elite competition)
    positive associations for SLC9A9, FABP2, UCP1

- can we identify other factors?

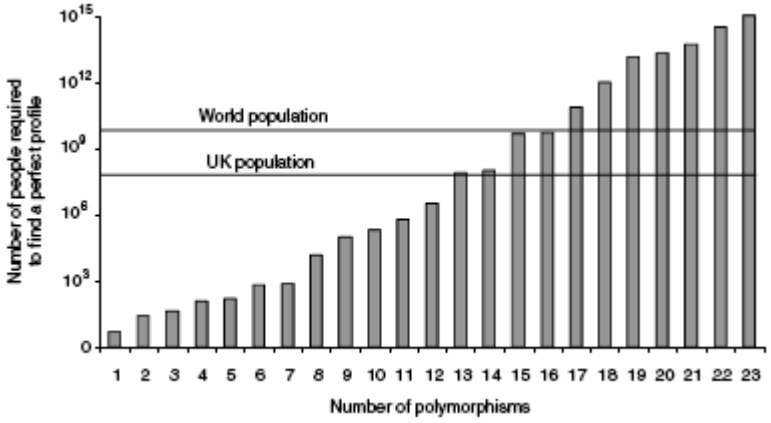
Williams (2004) J. Appl. Physiol. 96:938–42.
Saunders (2006) Hum. Mol. Genet. 15:979–87.
De Moor (2007) Twin Res. Hum. Genet. 10:812–20.

Can There be a Perfect Endurance Athlete? - Population Distribution of Genetic Potential

Table 1. Probability of perfect genetic profile by number of polymorphisms

Number of polymorphisms influencing endurance performance	New gene included at each stage	Typical frequency of optimal genotype (%)	Probability of possessing a 'perfect' profile	
			% chance	Approximate odds ratio
1	*ACE*	21	21.0	1 : 5
2	*ACTN3*	18	3.78	1 : 25
3	*ADRA2*	62	2.34	1 : 40
4	*ADRB2*	35	0.82	1 : 120
5	*AMPD1*	80	0.66	1 : 150
6	*APOE*	24	0.16	1 : 600
7	*ATP1A2**	81	0.13	1 : 800
8	*ATP1A2*	5	6.4×10^{-3}	1 : 16 000
9	*BDKRB2*	15	9.6×10^{-4}	1 : 100 000
10	*CKM*	49	4.7×10^{-4}	1 : 200 000
11	*EPAS1**	33	1.5×10^{-4}	1 : 600 000
12	*EPAS1*	19	2.9×10^{-5}	1 : 3 million
13	*HFE*	4	1.2×10^{-6}	1 : 85 million
14	*HIF1A*	77	9.1×10^{-7}	1 : 110 million
15	*HLA-A*	2	1.8×10^{-8}	1 : 5.5 billion
16	*MT-ND5**	93	1.7×10^{-8}	1 : 6 billion
17	*MT-ND5*	7	1.2×10^{-9}	1 : 85 billion
18	*MT-ND5*	7	8.3×10^{-11}	1 : 1.2 trillion
19	*MT-TT*	7	5.8×10^{-12}	1 : 17 trillion
20	*PPARA*	70	4.0×10^{-12}	1 : 25 trillion
21	*PPARGC1A*	40	1.6×10^{-12}	1 : 62 trillion
22	*UCP2*	17	2.7×10^{-13}	1 : 364 trillion
23	*VEGFA*	30	8.2×10^{-14}	1 : 1212 trillion

Williams (2008) J Physiol 586(1):113-21.



Results = "Using probability calculations, we found only a 0.0005% chance of a single individual in the world having the 'preferable' form of all 23 polymorphisms."

the human body works as a "system": if one factor is sub-par, then the whole system loses the capacity to function at optimal performance

What Will the Future Hold for Genetics and Athletics?

- all athletes competing at recreational to elite levels have complicated genetic profiles & environmental histories
    - many factors influence potential athletic ability
    - actual performance & success is hard to predict

- genetic engineering ("gene doping") to enhance athletic performance
    - many new PEP targets will be validated in the near future
    - delivery methods are available to allow beneficial "gene therapy"
    - will detection ever be able to keep up with "cheating"?

- scientist viewpoint= global perspective to understand how certain alleles beneficial to performance arose & how they have spread geographically

- athlete viewpoint= develop training program to maximize individual genetic endowment for optimal performance

Ostrander (2009) Annu Rev Genomics Hum Genet 10:407-429.

Direct-to-consumer testing for athletic performance

Atlas Sports Genetics
2008
"Atlas First SportGene Test"

AIBioTech
June 2011
"Sports X Factor"

http://www.sportsxfactor.com/Home.aspx

Sports X Factor

601 Biotech Drive
Richmond, VA 23235
804.648.3820 Fax 804.648.2641

Dr. Anyone A. Jones
Anywhere Laboratory
123 A Street Suite 000
Anywhere, VA 12345
1.804.456.7890

Name: John Smith
Date of Birth: 01/02/85
Sex: Male
Age: 16
Phone: 1-123-456-7890

Date Collected: 02/03/11
Date Received: 02/05/11
Date Reported: 02/10/11

SXF12-3456-1234567

PERFORMANCE INDICATORS

Gene	Genotype	Reynolds Score	
DIO1	The Type I iodothyronine deiodinase (DIO1) protein encoded by this gene is involved in thyroid hormone activation. Higher isometric grip strength and leg-extensor strength has been associated with theD1a-T allele of this gene..	**Power Score (0-3)** 2.0	
NOS3	The NOS3 gene encodes nitric oxide synthase 3, and is also known as eNOS. A small change (NOS3 -786 T>C polymorphism) in this gene has been studied and found to be associated with elite power sports performance.	**Power Score (0-4)** 2.0	
IL6	Interleukin-6 (IL-6) gene encodes a multifunctional cytokine expressed in many tissues involved in inflammatory processes and may additionally modify the regulation of energy balance. One small change in this gene (the IL6 -174 G/C polymorphism) is associated with sprint/power sports performance, with the GG genotype exerting a favorable effect. CC genotypes have been associated with obesity in some studies.	**Power Score (0-3)** 3.0	
ACE	Sequence variants in the angiotensin I converting enzyme gene (ACE) have been shown in studies to have positive effects on athletic performance. This test detects the I and D variants of ACE with the D variant favoring improved endurance ability, the I allele promotes more power-orientated events.	**Power Score (0-3)** 2.0	**Endurance Score (0-3)** 0
$ACTN_3$	The actinin, a-3 (ACTN3) gene encodes for the synthesis of a-actinin-3, a protein necessary for producing fast contractions, in Type II skeletal-muscle fibers. This polymorphism is associated with elite power/sprint performance. Conversely homozygous X/X indicates only slow twitch muscle fibers present. Studies have shown highly significant associations between ACTN3 genotype and athletic performance.	**Power Score (0-6)** 3.0	**Endurance Score (0-6)** 3.0
PPARGC	The peroxisome proliferator-activated receptor gamma coactivator-1α (PPARGC) gene function is associated with cellular energy metabolism. Two genotypes associated with this gene have been positively associated with endurance. The Gly482Ser genotype is associated with endurance athletes. The Pro12Ala genotype has only been shown so far to have a favorable impact on males.	**Endurance Score (0-5)** 2.5	
VEGFR	Vascular endothelial growth factor receptor 2 (VEGFR2) is essential to induce the full spectrum of VEGF angiogenic responses to aerobic training. One allele associated with this gene (His472Gln polymorphism) has been associated with elite athlete status, endurance performance and muscle fiber type composition in females.	*Females Only*	

RISK FACTOR ASSESSMENT

Condition	Description	Present - Absent
Concussion Marker*	Athletes with the concussion risk factor variant gene who were studied were tested for recovery time after a concussion and found they are more likely to recover slower than non-variant carriers. It is not entirely clear how the marker affects brain recovery, but the gene is involved in the inflammatory response of the brain after injury, and people with the variant appear to take longer to clear their brains of a particular protein called amyloid, which floods in following head trauma.	Absent
Heart Screen*	Hypertrophic cardiomyopathy (HCM)- A disease of the muscle of the heart in which a portion of the heart is thickened without any obvious cause. We screen for risk factors in 3 Genes which represent 80% of known risk factors for HCM.	Absent
Acquired Arrhythmia*	This test detects the risk of acquired arrhythmia by detecting a variant of the cardiac sodium channel gene SCN5A which is associated with arrhythmia in African Americans.	Absent

SUMMARY

Gene	Description	Reynold's Score (Percentile)	
Performance	Total performance score is calculated for both endurance and strength. The score is based on the summary of the results from the genetic markers tested by AIB on the sample received. This score is weighted and calculated based on several factors including the genotype reported and frequency in the general population. VEGFR marker is for females only while one of the two PPARGC genotypes tested is for males only. The score is a guide to help the individual to maximize fitness focusing on strength, endurance and muscle growth (Please refer to individual workout page for instructions on how to obtain a tailor made workout based on performance results). Your results will be provided as a numerical value for each genetic marker and in the summary as the total score calculated for both endurance and power. Included with your total score for each area will the percentile your score achieved in relation to the database of individuals who have been previously tested with Sport X Factor. An average score will be one that is in the 50th percentile.	**Power** 10.0 90th Percentile	**Endurance** 5.5 69th Percentile

Direct-to-consumer testing for athletic performance