Understanding Training? What Do We Learn from Genomics for Elite Sports Performance?

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Introduction

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Sitter or Rover ?

Natural Behavior Polymorphism Due to a cGMP-Dependent Protein Kinase of *Drosophila*

K. A. Osborne, A. Robichon, E. Burgess, S. Butland,*
R. A. Shaw, A. Coulthard, H. S. Pereira†, R. J. Greenspan,‡
M. B. Sokolowski§

Naturally occuring polymorphisms in behavior are difficult to map genetically and thus are refractory to molecular characterization. An exception is the *foraging* gene (*for*), a gene that has two naturally occurring variants in *Drosophila melanogaster* food-search behavior: rover and sitter. Molecular mapping placed *for* mutations in the *dg2* gene, which encodes a cyclic guanosine monophosphate (cGMP)–dependent protein kinase (PKG). Rovers had higher PKG activity than sitters, and transgenic sitters expressing a *dg2* complementary DNA from rover showed transformation of behavior to rover. Thus, PKG levels affected food-search behavior, and natural variation in PKG activity accounted for a behavioral polymorphism.

Science, 277, 1997, 834-836

"This is not something that's going to just apply to insects."
—James Truman

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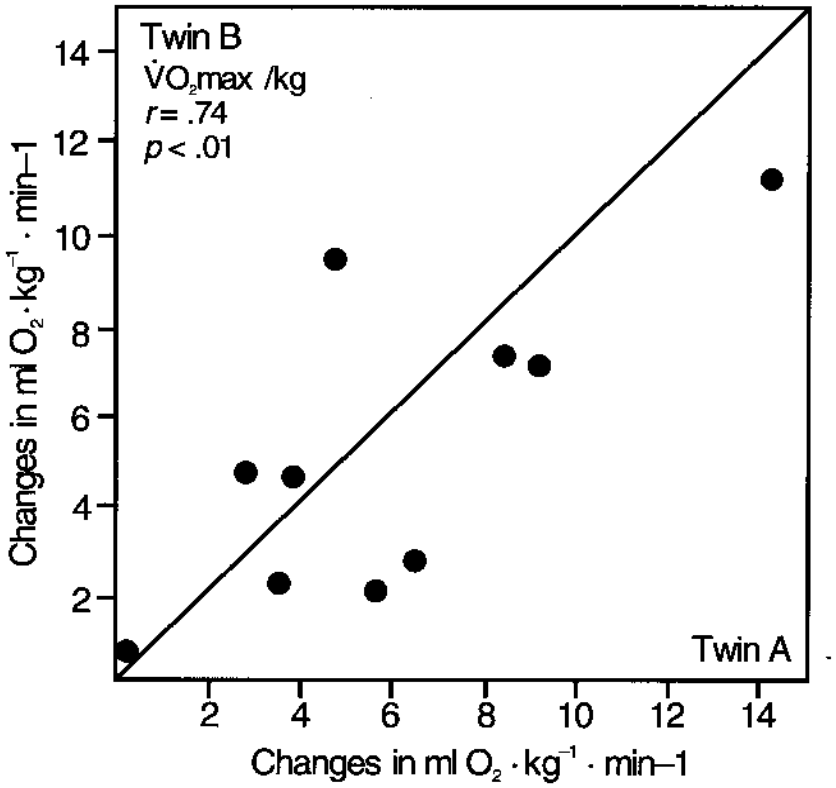
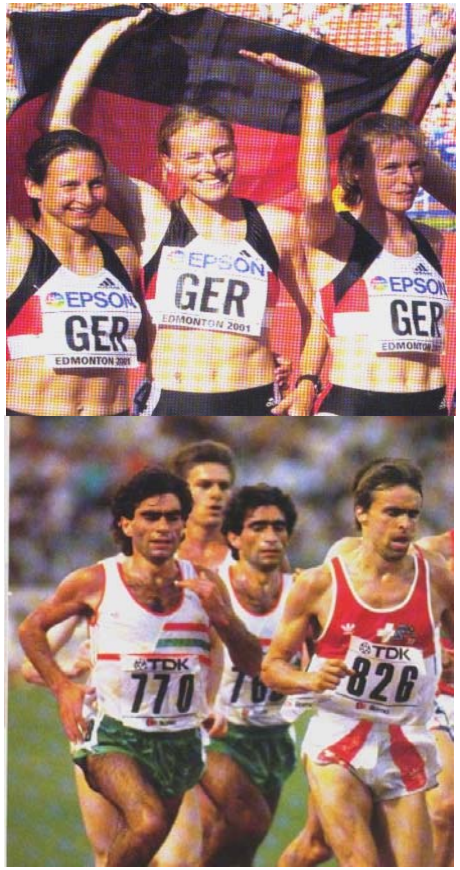
Genetics and Trainability



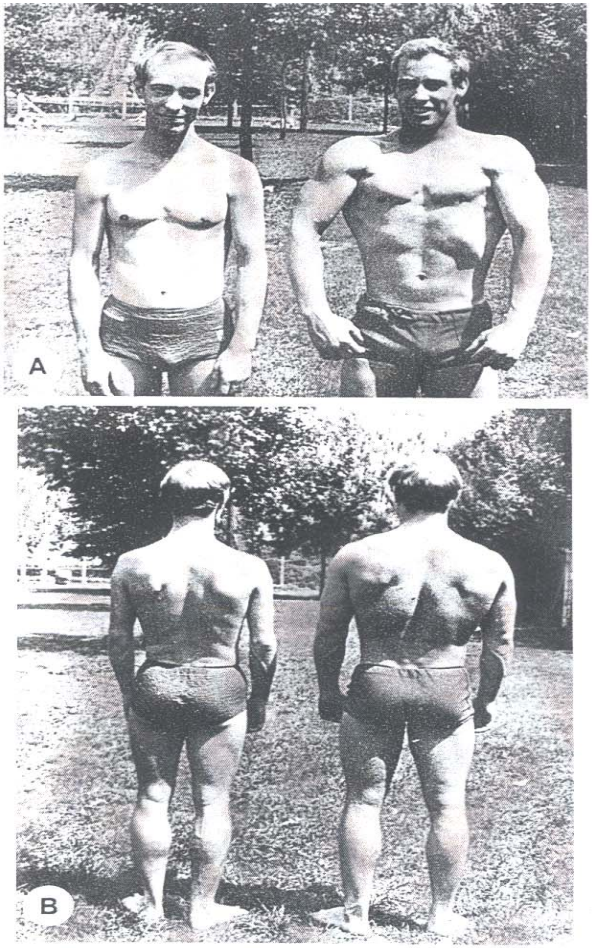


Prud´homme, D., Bouchard, C.et al.: MSSE 16:489-93;1984

Genetic Predisposition (nature)

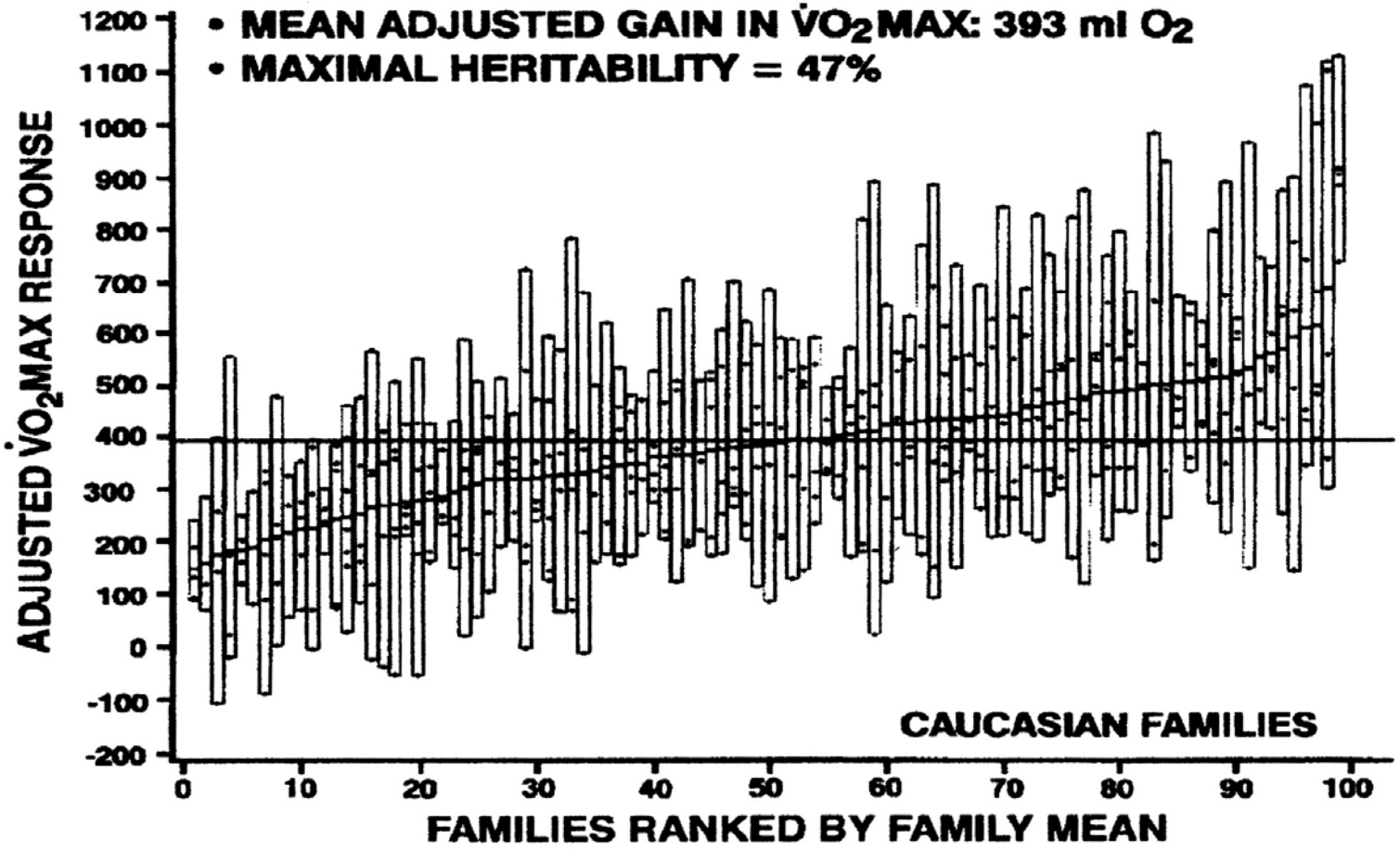
versus

Adaptation (nurture)



Circ Res, 48 162 (1981)

Genetics and Trainability



Bouchard, C. et al.: JAP 87:1003-1008 (1999)

Questions

Definition of genetic determinants of aerobic performance and trainability:

- Which genes are involved in the determination of aerobic performance and trainability?
- Is it possible to predict aerobic performance and trainability levels in humans using genetic markers?
- Are these results transferable into prognostic predictions regarding preventive or rehabilitative therapy strategies?

Current studies

Authors	Study	Design	Subjects	Intervention
Bouchard et al.	HERITAGE	Prospective Training Study Family Study	app. 100 white families app. 200 Afro-American families	20 weeks controlled endurance training
Defoor et al.	CAREGENE	Prospective Training Study	1095 men and women with coronary artery disease	3 months graded exercise with achieving evident exhaustion
Hagberg et al.	GERS	Prospective Training Study	225 sedentary, healthy men and women (50-75 yrs)	24 weeks endurance training
Bouchard, Wolfarth et al.	GENATHLETE	Case-control-study, elite endurance athletes ($\dot{V}O_2$ max > 75ml/kg) vs. untrained controls ($\dot{V}O_2$ max < 50ml/kg)	app. 300 endurance athletes app. 300 untrained controls	
Ahmetov et al.	Elite Russian athlete	Case-control study, elite athletes from mixed sport's disciplines vs. healthy controls	786 elite Russian endurance athletes 1242 healthy controls	
Scott et al.	Elite East African athlete	Case-control study	291 elite Kenyan endurance athletes	
Yang et al.	Elite Australian athlete	Case-control study, elite athletes from different sports vs. controls	429 elite Australian athletes, 436 unrelated controls	
Montgomery et al.	British military recruit	Prospective Training Study	app. 140 army recruits	10 weeks standardized physical fitness program
Cerit et al.	Turkish military recruit	Prospective Training Study	186 Caucasian men	6 months training program
He et al.	Chinese military recruit	Prospective Training Study	102 healthy and untrained military personnel	18 weeks exercise training program

Genathlete

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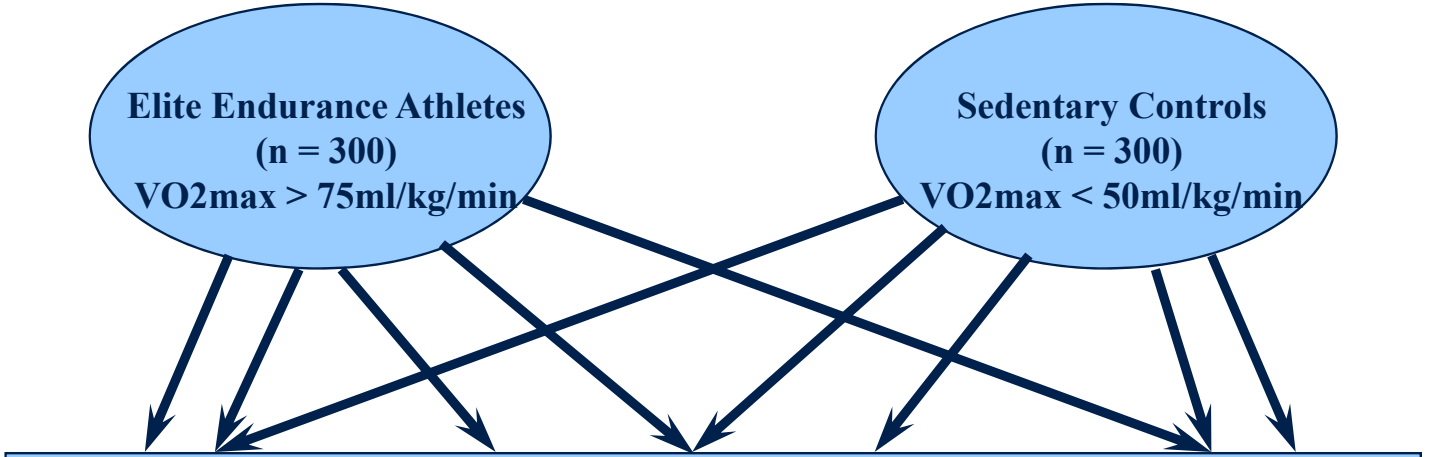
Genathlete

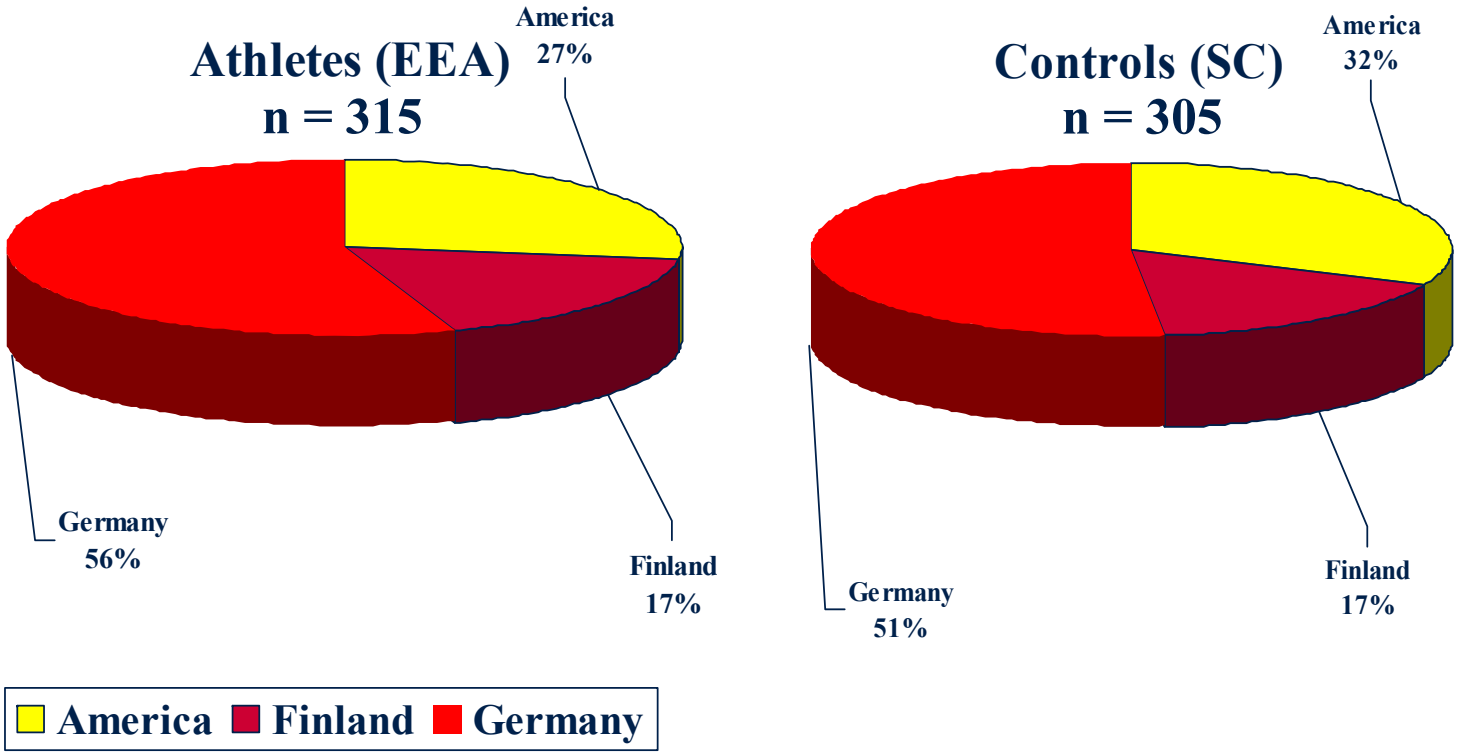


Aim of the study

Panel of genetic markers to characterise genetic determinants of aerobic performance and trainability

Source of subjects

n = 620



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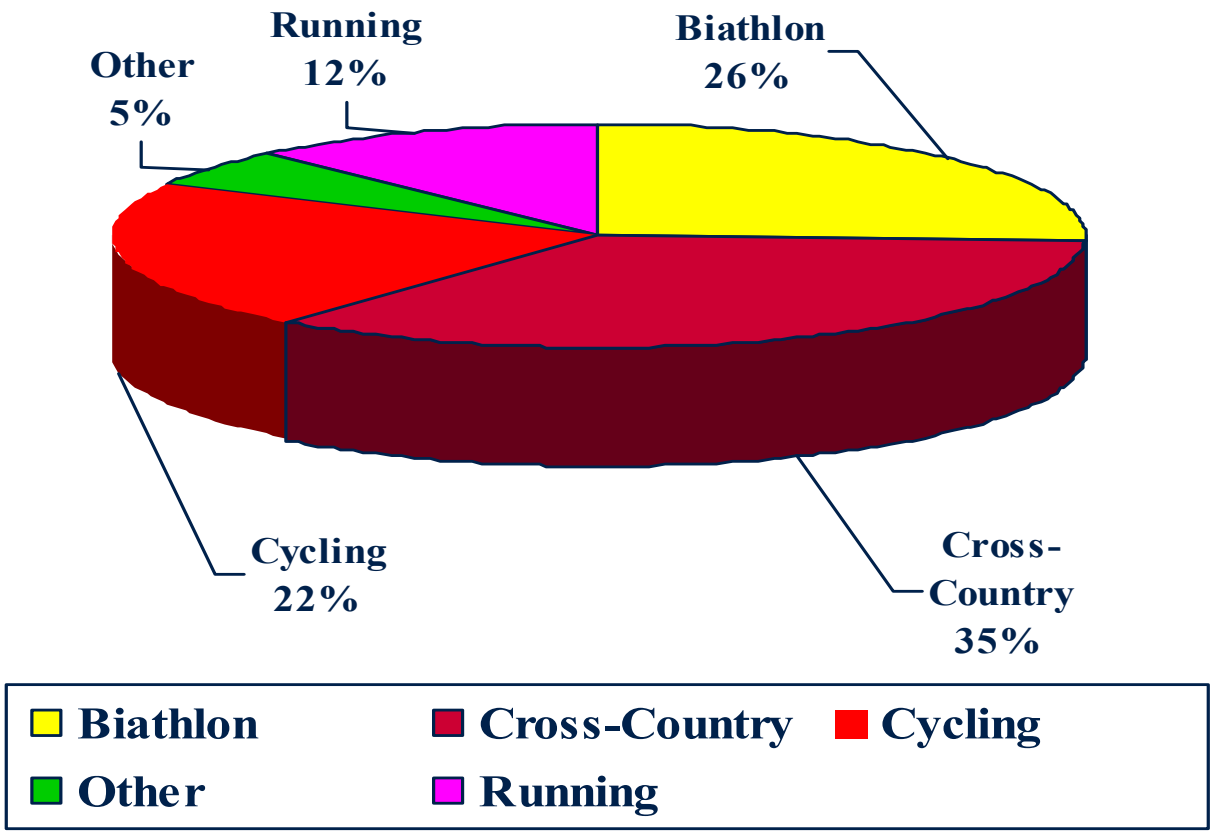
Sports of athletes



Descriptives

		Age (years)	Height (cm)	Weight (kg)	VO2maxkg (ml/kg/min)
EEA (n=315)	number	315	315	315	315
	mean	22,2	178,8	69,7	79,11
	SD	5,9	6,11	7,2	3,52
SC (n=305)	number	305	305	305	305
	mean	29,52	177,5	76	39,23
	SD	12,5	7,34	11,39	7,2

Candidate Genes

- Hormones (EPO, EPO-R, ß-ADR, a-ADR, ANG)
- Muscle (CK, mtDNA, FABP3, CPT2)
- Lipoprotein Metabolism (LPL, LIPE, LDLR)
- Growth Factors (IGF, TGF, GH)
- Cellular Mediators (FOS, JUN, SKI)
- Other (HIF1α, TNF-α, ACE, NOS3)

The „ACE story“

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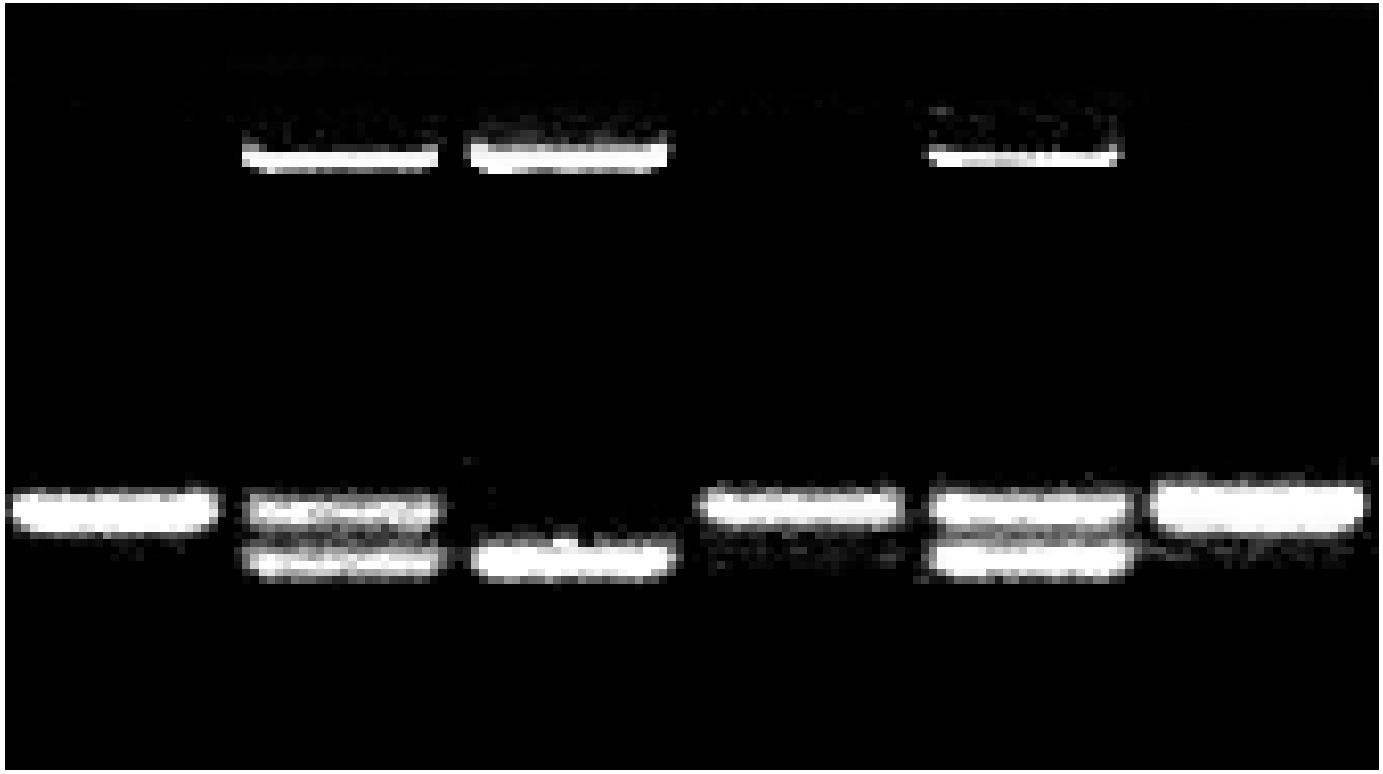
Angiotensin I-Converting Enzyme I/D-Polymorphism

- Rigat, B. et al., NAR 20: 1433, 1992
- Insertion/Deletion-polymorphism in intron 16 of the angiotensin I-converting enzyme (ACE) gene
- ACE ID genotype was determined by polymerase chain reaction. PCR products were subjected to electrophoresis in 2% agarose gels, DNA was visualised by ethidium bromide
- Chromosome 17q23

Plasma ACE activity
+ ACE genotype



ID II DD

Plasma ACE activity + ACE genotype

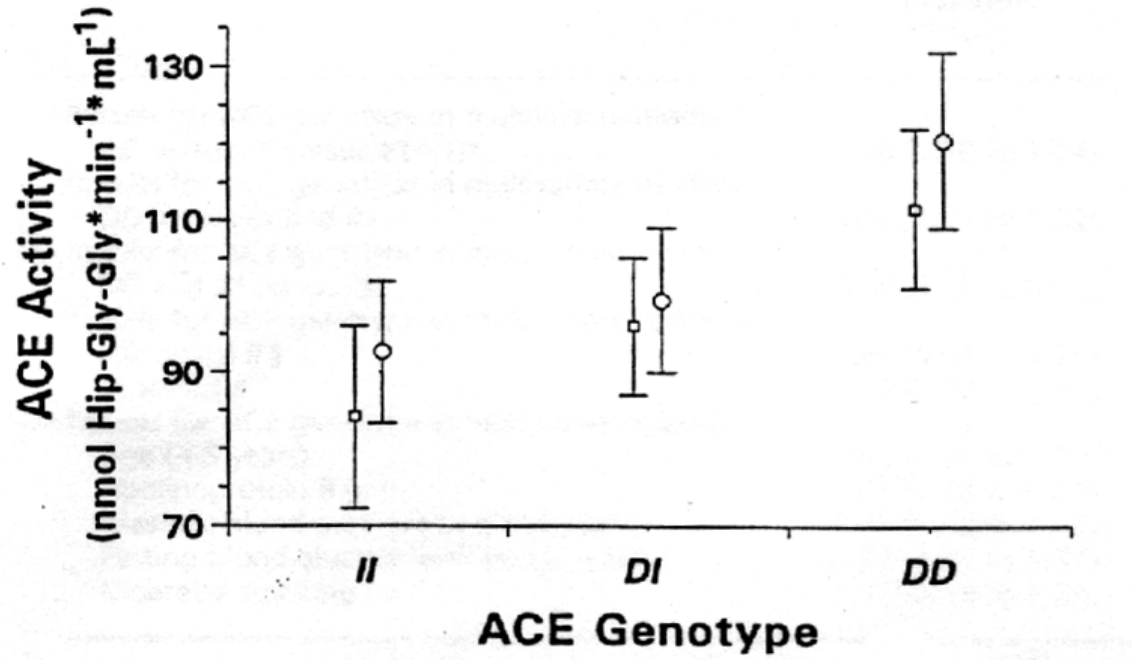
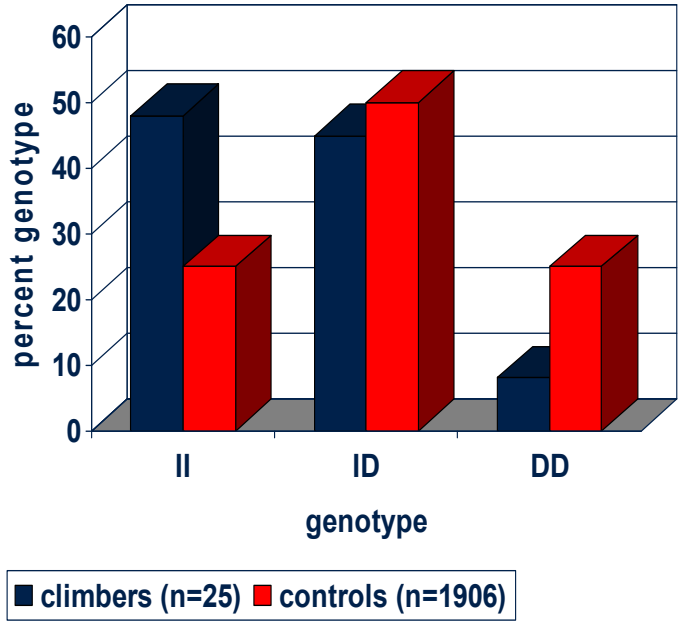


Figure 1. Plasma angiotensin I–converting enzyme (*ACE*) activity in patients with coronary artery disease (*squares*) and controls (*circles*) not treated with an ACE inhibitor. In each patient group, ACE activity differed significantly depending on ACE genotype ($P < 0.001$). Values are expressed as means with 95% CIs.

(adapted from Winkelmann et al., Ann.Intern.Med., 124:19-25, 1996)

A gene for physical performance !?

- 25 unrelated British mountaineers with ascendings beyond 7000metres without supplementary oxygen
- Control group 1906 British males free from cardiovascular disease
- results: different genotype distribution (p 0,02) and allelic frequency (p 0,003), favouring the I allele in mountaineers
- furthermore in 15 climbers who had ascended 8000metres without oxygen 6 II, 9 ID and none DD genotype.



from Montgomery H.E. et al, Nature, 393: 221 (21 May 1998)

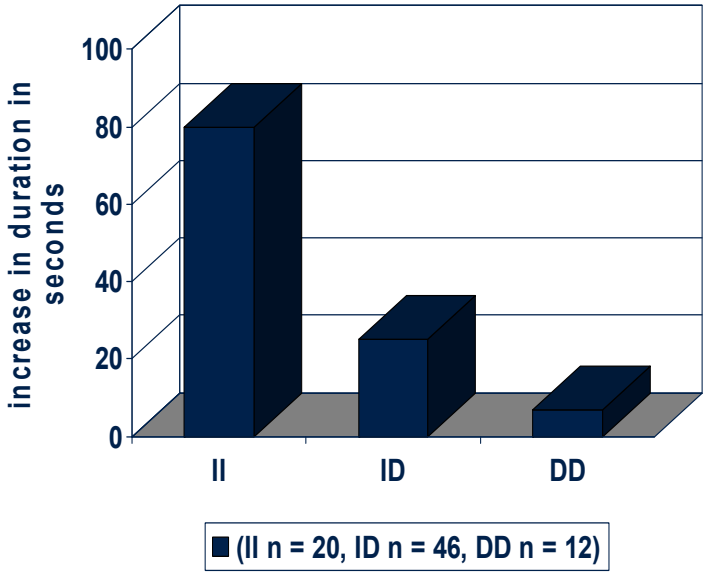
A gene for physical performance !?

• 78 unrelated Caucasian males after a 10 week general physical training program

• repetitive elbow flexion with 15kg barbell and increasing cycle frequency (maximum duration in seconds)

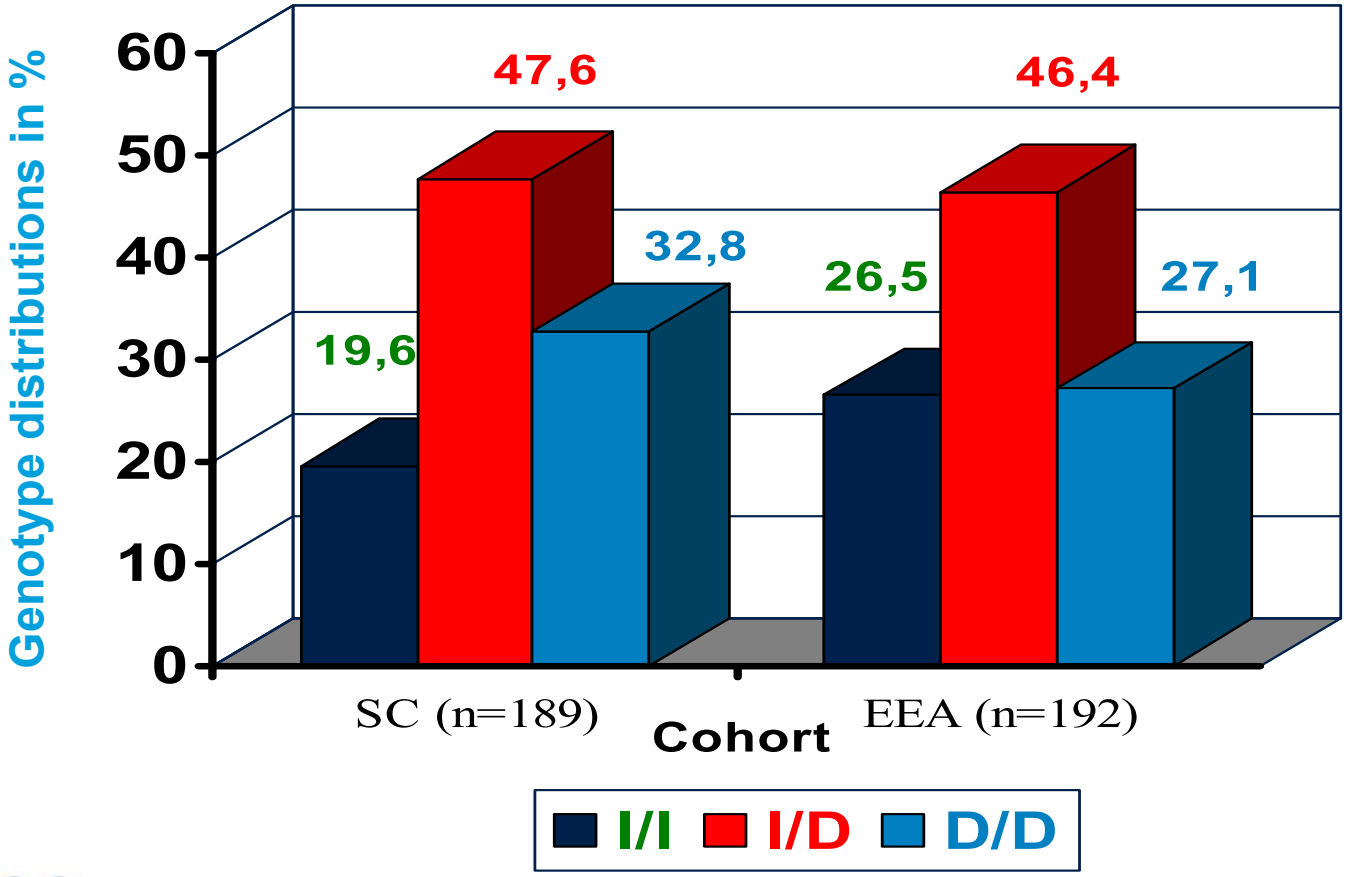
• no difference in ACE genotype at baseline

• 11 fold greater improvement in subjects carrying II than DD genotype (between II and DD p=0,007)



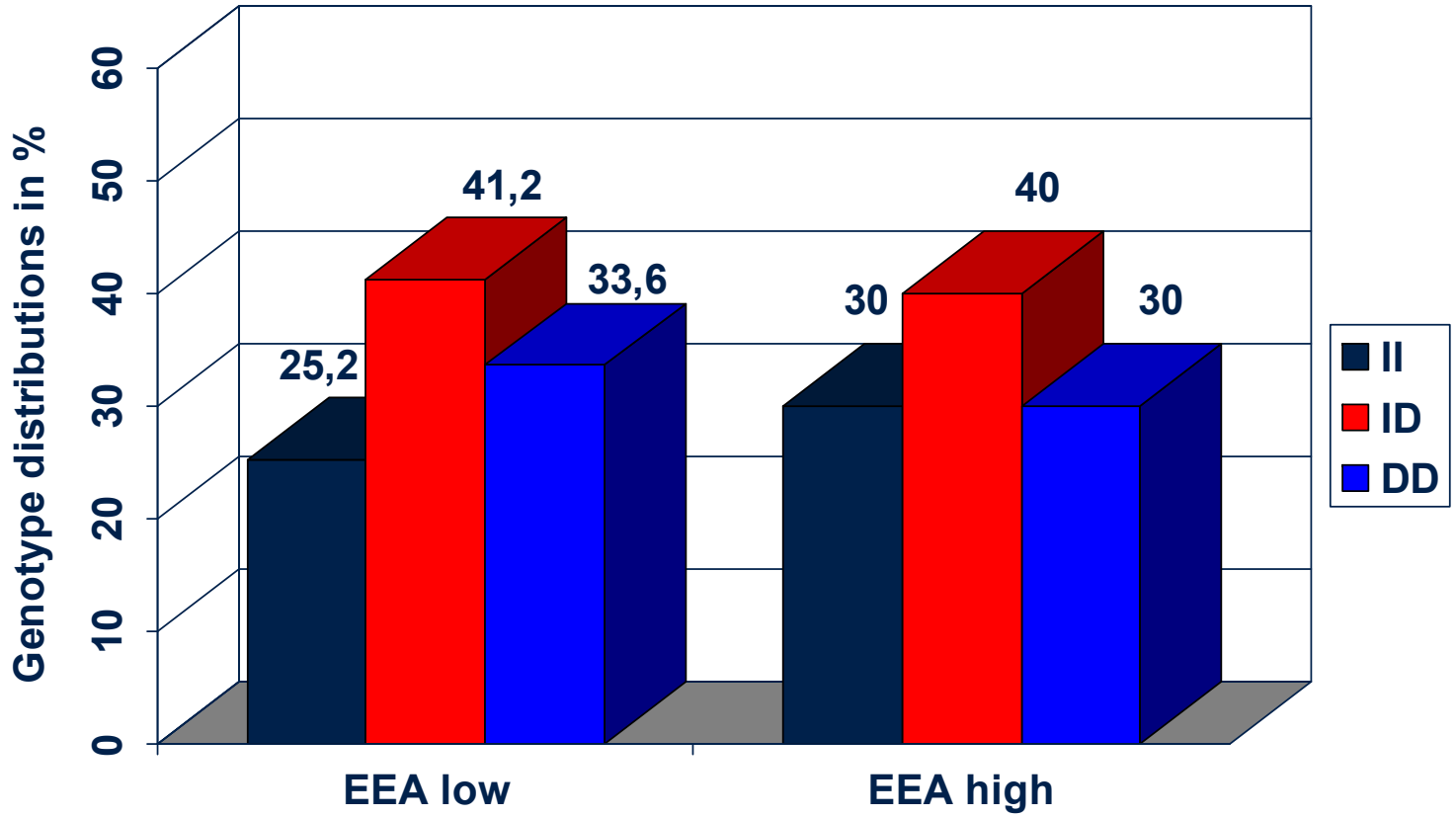
from Montgomery H.E. et al, Nature, 393: 221 (21 May 1998)

Genotype distributions
ACE I/D polymorphism



Rankinen, Wolfarth et al., JAP 2000

Genotype distributions for EEA groups



EEA low: EEA < 81,9 ml/kg/min-1 (n=119, mean 77,6, SD 2,06)
EEA high: EEA > 82,0 ml/kg/min-1 (n=40, mean 84,5, SD 2,29)

Rankinen, Wolfarth et al., JAP 2000

Recent / modern approaches

Claude Bouchard, Tuomo Rankinen, Mark Sarzynski,
Bernd Wolfarth

Predicting an Elite Endurance Athlete Status: a Genome-Wide Exploration

Recipient of the 2012 Prince Faisal Bin Fahad International Prize for Elite Sport Development Research

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Genome-wide Search of DNA Sequence Variants Associated with Elite Endurance Athlete Status

Wolfarth et al., MSSE 2013

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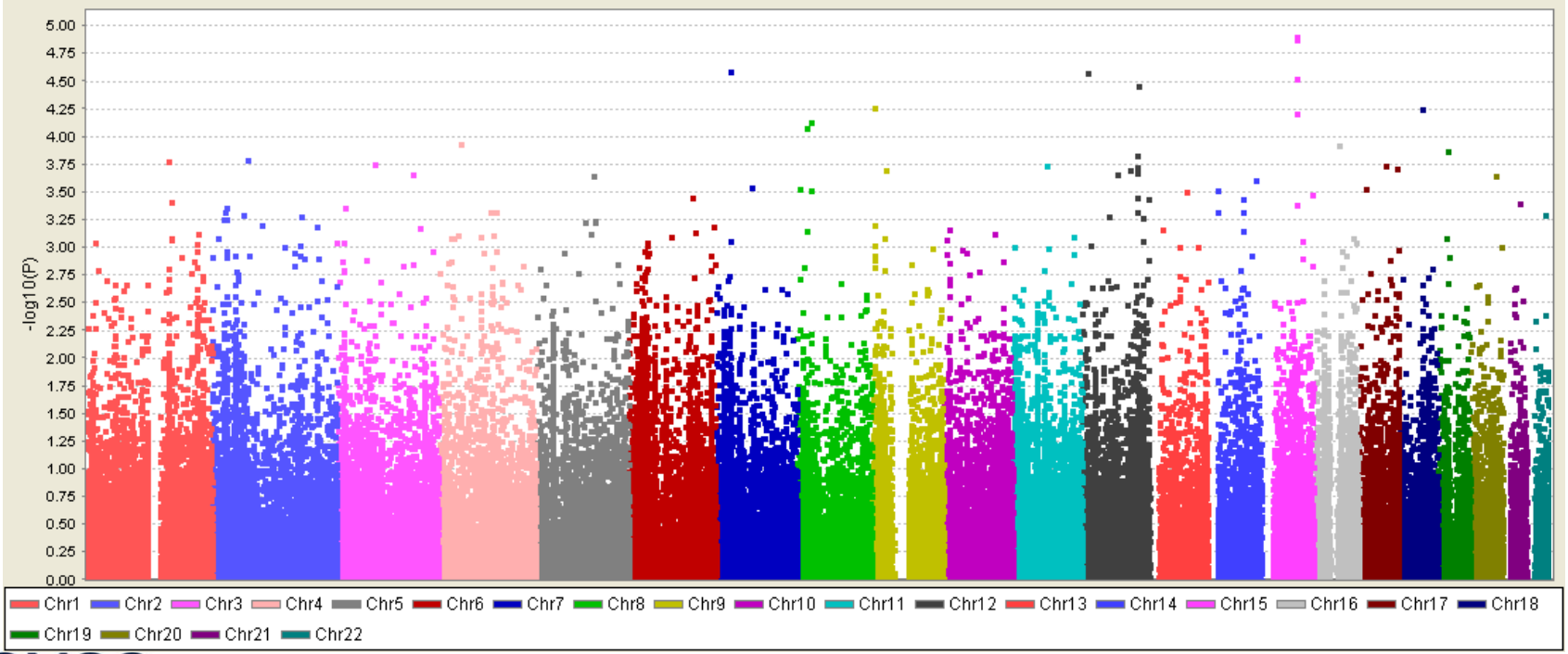
Association between CardioMetabochip SNPs and EEA status

Illumina CardioMetaboChip: app. 145,000 SNPs GWAS with cardiovascular and metabolic phenotypes



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Wolfarth et al., MSSE 2013

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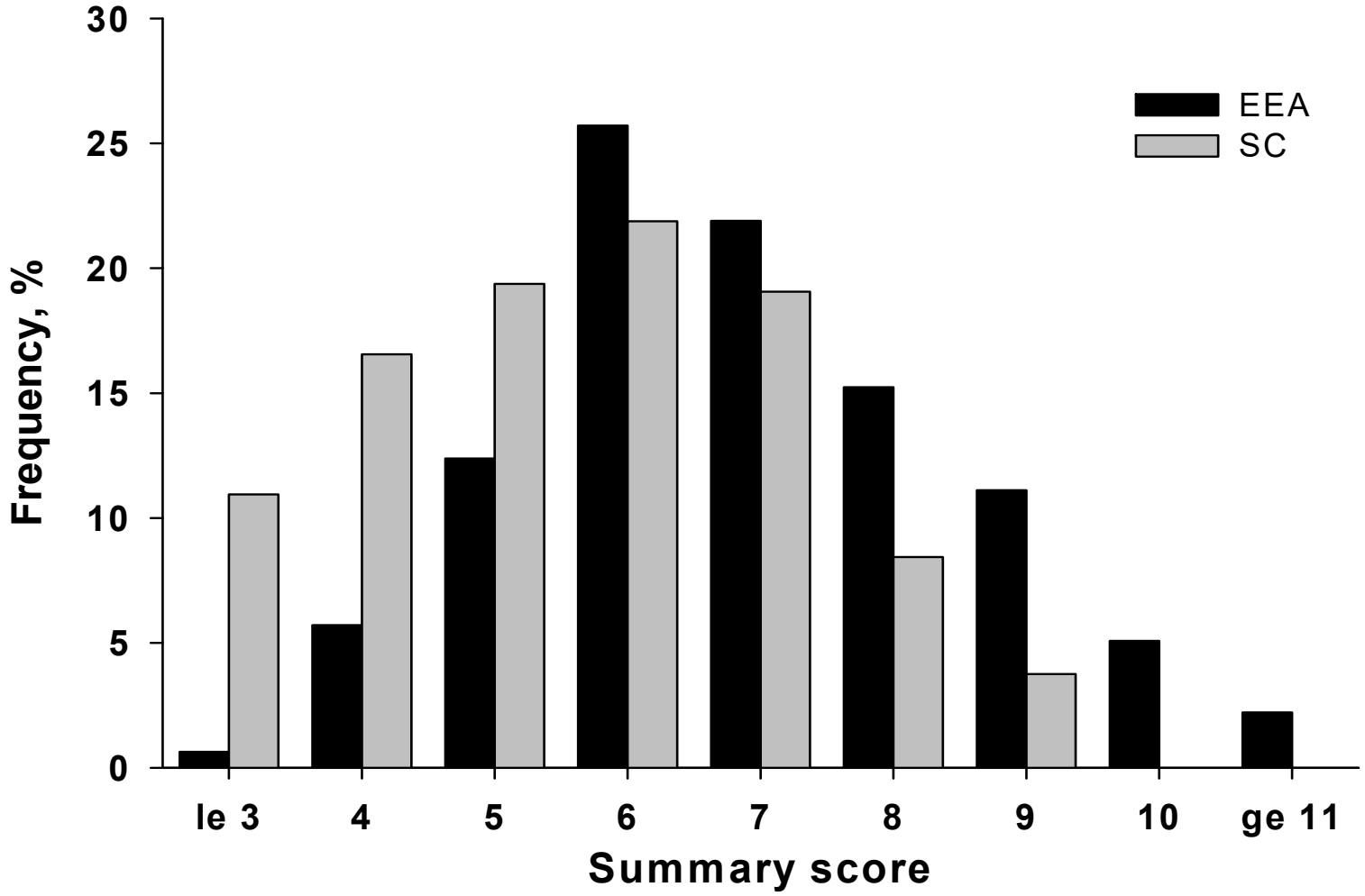
Significant associations between CardioMetabochip SNPs and EEA status

				Athletes		Controls			
SNP	Chr	Gene	Allele	N	freq	N	freq	OR	p-value
rs17055965	8	ADRA1A	G	168	0.125	320	0.041	3.37	8.69×10^{-7}
rs9543114	13	DIS3	C	168	0.098	320	0.030	3.56	5.92×10^{-6}
rs4808571	19	MYO9B	A	168	0.268	320	0.155	2.00	2.13×10^{-5}
rs9301108	13	DAOA | EFNB2	C	168	0.095	320	0.033	3.10	4.33×10^{-5}
rs11856981	15	LOC145837 | TLE3	T	168	0.557	320	0.422	1.72	6.17×10^{-5}
rs12573965	11	KCNQ1	C	168	0.170	320	0.084	2.22	6.70×10^{-5}
rs17054974	9	SEMA4D | GADD45G	C	168	0.098	320	0.036	2.92	7.04×10^{-5}
rs10499127	6	NKAIN2	G	168	0.146	320	0.069	2.31	9.74×10^{-5}
rs4776471	15	LOC145837 | TLE3	T	168	0.464	320	0.338	1.70	1.07×10^{-4}
rs2118908	2	ACOXL	G	168	0.164	320	0.083	2.17	1.30×10^{-4}
rs1654546	19	LOC390956	G	168	0.033	320	0.102	0.30	1.38×10^{-4}
rs4777184	15	LOC145837 | TLE3	T	168	0.470	320	0.345	1.68	1.42×10^{-4}

“Genomic Summary Score”

distribution in the GENATHLETE cohort



The GENATHLETE Study

Summary and outview

- GENATHLETE CardioMetabochip results showed first evidence for associations between human performance phenotypes and DNA sequence variations in SNPs related to cardiovascular function, insulin metabolism and apoptosis
- Replication studies are urgently needed

“Meta-study”

Study	Number of Athletes	Number of Controls
GENATHLETE (Germany, Finland, Canada, USA)	315	320
Spain	184	290
Japan	203	814
Kenya and Ethiopia	353	283
North’s Athletes (Australia, Poland, Italy, Greece)	418	395
TOTAL	1473	2102

Rankinen T, Fuku N, Wolfarth B, et al. (2016), PLoS ONE 11(1): e0147330

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Future research

- **Data pooling with other major studies to increase statistical power**

- **Animal models will be established by cross-breeding techniques to undertake genome scans for QTLs.**

- **Other techniques will provide new possibilities to detect molecular differences between individuals (e.g. RDA, Transcriptomics, Metabochip).**

MSSE Jahresreport

BASIC SCIENCES

Advances in Exercise, Fitness, and Performance Genomics in 2015

MARK A. SARZYNSKI[1], RUTH J. F. LOOS[2], ALEJANDRO LUCIA[3], LOUIS PÉRUSSE[4], STEPHEN M. ROTH[5], BERND WOLFARTH[6], TUOMO RANKINEN[7], and CLAUDE BOUCHARD[7]

[1]Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC; [2]The Genetics of Obesity and Related Metabolic Traits Program, The Charles Bronfman Institute for Personalized Medicine, The Mindich Child Health and Development Institute, The Icahn School of Medicine at Mount Sinai, New York, NY; [3]Universidad Europea and Research Institute, Hospital 12 de Octubre (i+12), Madrid, SPAIN; [4]Faculty of Medicine, Department of Kinesiology, Laval University, Ste-Foy, Québec, CANADA; [5]Department of Kinesiology, School of Public Health, University of Maryland, College Park, MD; [6]Department of Sport Medicine, Humboldt University and Charité University School of Medicine, Berlin, GERMANY; and [7]Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA

J Appl Physiol 110: 46–59, 2011.
First published October 7, 2010; doi:10.1152/japplphysiol.00634.2010.

A transcriptional map of the impact of endurance exercise training on skeletal muscle phenotype

Pernille Keller,[1,2] Niels B. J. Vollaard,[1] Thomas Gustafsson,[3] Iain J. Gallagher,[1] Carl Johan Sundberg,[4] Tuomo Rankinen,[5] Steven L. Britton,[6] Claude Bouchard,[5] Lauren G. Koch,[6] and James A. Timmons[7,8]

[1]Translational Biomedicine, Heriot-Watt University, Edinburgh, United Kingdom; [2]Department of Molecular and Integrative Physiology, University of Michigan Medical School, Ann Arbor, Michigan; [3]Department of Laboratory Medicine, Division of Clinical Physiology, Karolinska University Hospital, Stockholm, Sweden; [4]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; [5]Human Genomics Laboratory, Pennington Biomedical Research Center, Baton Rouge, Lousiana; [6]Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, Michigan; [7]Lifestyle Research Group, The Royal Veterinary College, University of London, Camden, United Kingdom; and [8]Centre for Healthy Ageing, Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

Submitted 9 June 2010; accepted in final form 5 October 2010

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Transcriptomics & Genomics

Keller et al. used a combination of transcriptomics and genomics to describe the impact of endurance training on skeletal muscle phenotypes.

In a prior publication, approximately 800 skeletal muscle gene transcripts were shown to be up- or down-regulated by 6 weeks of endurance training in sedentary subjects. These transcripts were identified as the training-responsive transcriptome (TRT) .

Keller P, Bouchard C et al. A transcriptional map of the impact of endurance exercise training on skeletal muscle phenotype. *J.Appl.Physiol*. 2011;110(1):46-59

Transcriptomics & Genomics

In the rat model, selected from 10 generations of high responders to aerobic training, there was evidence to the effect that in these animals the TRT and a subset of the human high-responder genes were regulated to a greater degree in the high-responder rodents.

These complex but internally consistent data were taken as evidence for a powerful gene expression program that characterizes successful adaptation to aerobic training. Interestingly, the transcripts involved belong mainly to development-, tumor biology-, and immunology-related pathways.

Keller P, Bouchard C et al. A transcriptional map of the impact of endurance exercise training on skeletal muscle phenotype. *J.Appl.Physiol*. 2011;110(1):46-59

Summary
+
future perspectives

Genetic markers and personalized exercise prescriptions

- Marker/SNP data are easily to access and to analyse using big scale and high throughput genotyping and sequenzing platforms
- The statistic methods are nowadays well established, robust and offering complex tools for sophisticated analysis. This complex statistical methods will gain more and more attention in future

Genetic markers and personalized exercise prescriptions

- Replication is missing / Validation is the key problem!!
- Clinical implementation without big scale confirmation studies is impossible
- Replication studies have to include different ethnical groups
- Replication should be performed comprising different activity modalities and –intensities
- Integration of other “omics” urgently needed/is essential

Screening for talent?!?

Genetic athletic selection

-

Fact or fiction

Genomics of elite sporting performance: what little we know and necessary advances

Yannis Pitsiladis,[1] Guan Wang,[1] Bernd Wolfarth,[2] Robert Scott,[3] Noriyuki Fuku,[4] Eri Mikami,[4] Zihong He,[5] Carmen Fiuza-Luces,[6] Nir Eynon,[7] Alejandro Lucia[6]

Pitsiladis, Wolfarth et al., BJSM 2013

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What are the new findings?

- Research has shifted from twin-based/family-based studies to the study of single nucleotide polymorphisms (SNPs) in populations.
- Over 200 SNPs associated with physical performance have been reported.
- Historically, genomics research has been hampered by small sample sizes.
- Candidate gene analysis is the most commonly used approach, and it is effective in detecting genetic variants with a small or modest influence.
- Genome-wide association approaches examine the association of genetic variation across a large number of SNPs simultaneously.
- The number of large genetic cohorts of world-class athletes is limited.
- With larger samples, genome-wide association would allow the detection of smaller gene effects and maximise the amount of variation captured

Current genetic testing has zero predicitve power on talent identification and should not be used by athletes, coaches or parents

Pitsiladis, Wolfarth et al., BJSM 2013

Summary
+ Outview

- Recently, much more quality in publications regarding genetics and physical activity/sports medicine
- Results from studies with small sample sizes or crude hypothesis are not publishable anymore
- Direction goes into clearly planned studies including exercise interventions and moreover towards case-control-studies with big sample-sizes and robust phenotypes
- Gene-gene- and gene-enviroment-interactions and in addition epigentic implications and the combination with other „omics“ will play an increasing role


STOP

„Walk the dog“

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Thank You !

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