Genome-wide association study identifies a novel association between a cardiovascular gene polymorphism and superior athletic performance

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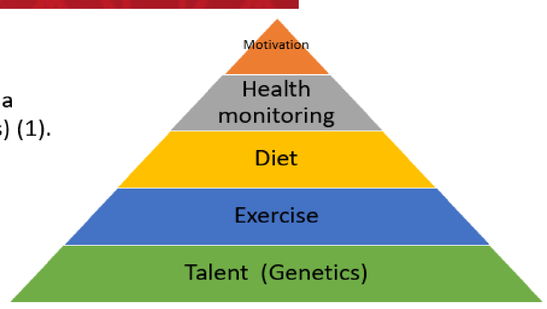
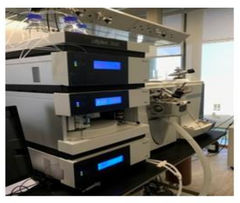
INTRODUCTION

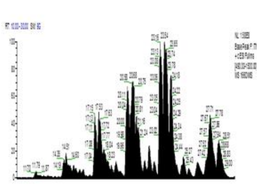
Introduction

- The superior physical performance of elite athletes is a multifactorial trait (environmental and genetic factors) (1).
- There is ample evidence of genetic influence of multiple genetic variants with small effect size over several phenotypic traits (2). However, not reproducible!

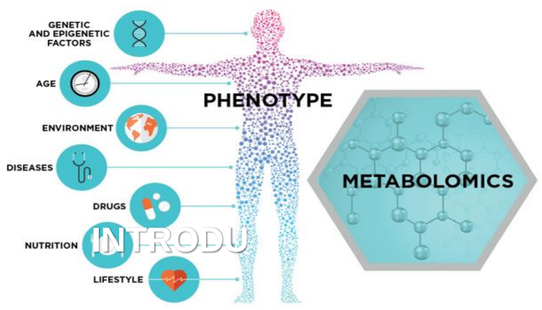


- GWAS in athletes versus non-athletes have uncovered new loci, none of which has reached GWAS significance (3,4).
- Thus, there is no concrete evidence of genetic predisposition of athletic performance due to small sample size, small effect size and complex phenotype (5).
- The advancement of metabolomics tools including mass spectrometry technologies has offered a unique opportunity to complement genomics data with intermediate phenotypes.





- Identified metabolites show direct functional association with genetic variants with a greater effect size (6).
- The integration of genomics and metabolomics technologies has also allowed a better chance to reveal genetic predisposition of complex metabolic pathways (7,8).



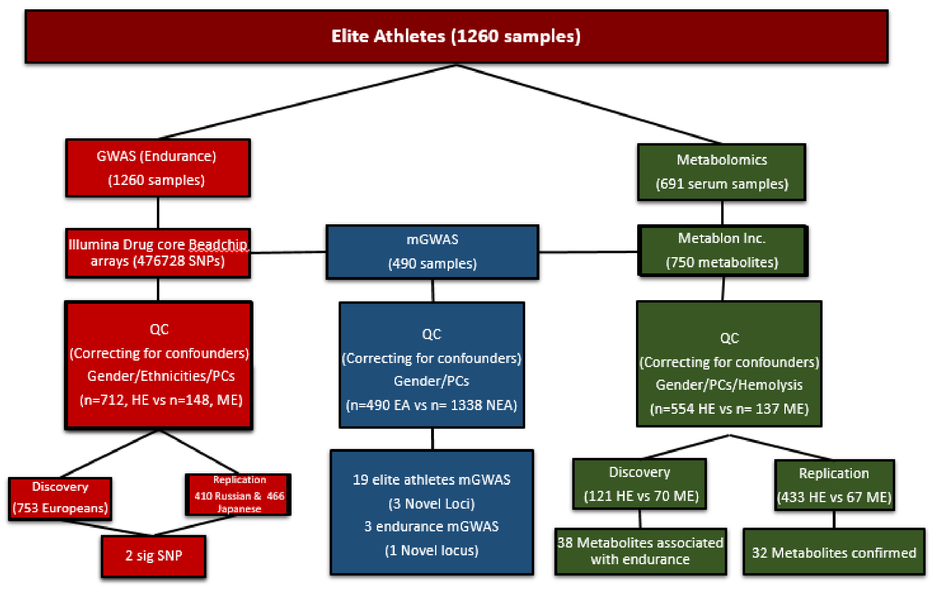
AIMS

1. To carry out the largest metabolomics study in elite athletes to identify metabolic signatures of endurance sports .
2. To carry out the largest GWAS in elite athletes to identify genetic predisposition to high endurance sports.
3. To discover novel genetic loci affecting metabolites in elite athletes compared to previously published loci in non-elite athletes.
4. To discover novel genetic loci associated with endurance metabolites.

METHODS

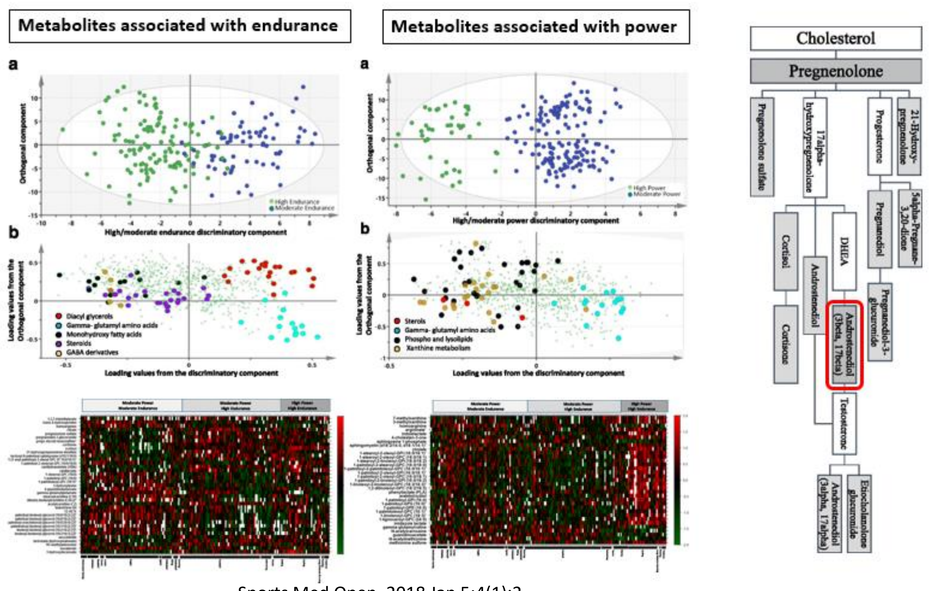
Study design

Elite athletes are competing athletes at national and international sport events who have their samples sent for doping tests at ADLQ and FMSI



METHODS

A pilot study comparing the metabolic profiles of elite-level athletes from different sporting disciplines



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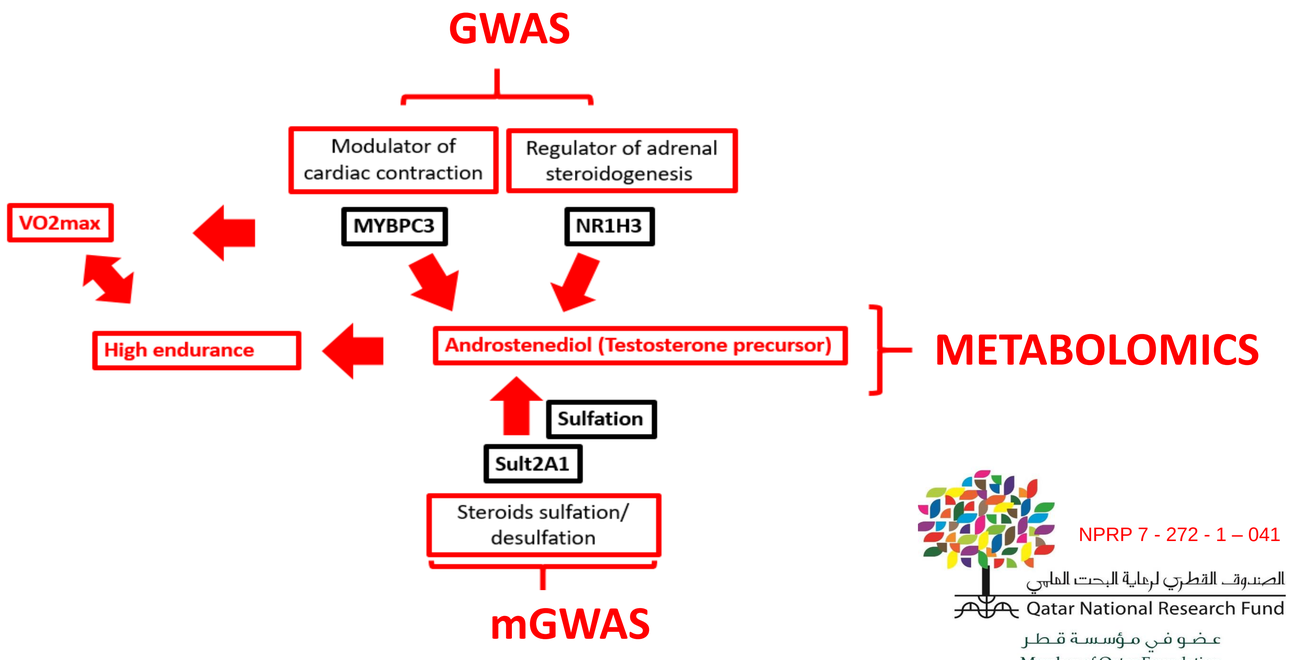
CONCLUSIONS



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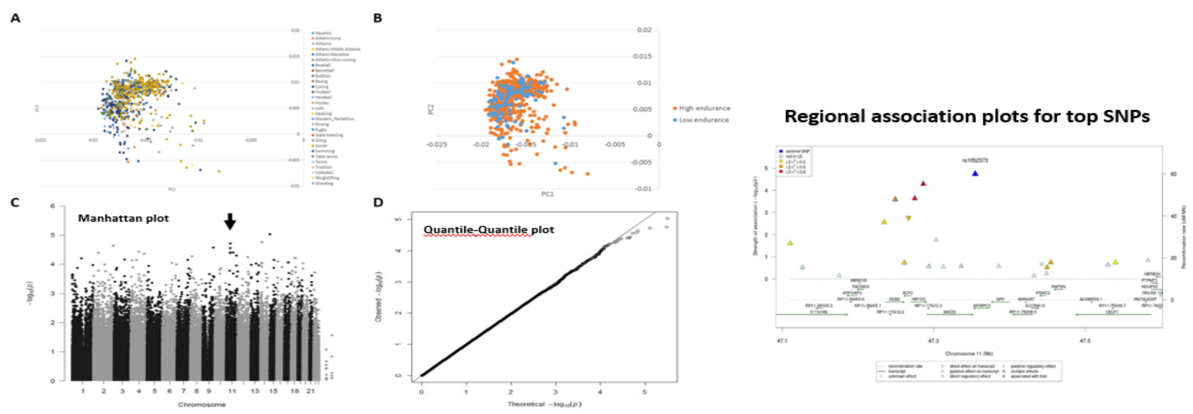
GWAS: Top SNPs associated with endurance



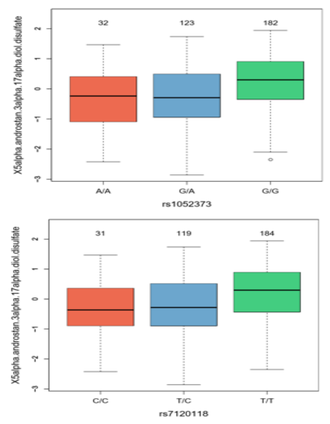
			European (712 HE & 148 ME)		Russian (242 HE & 168 LE)		Japanese (60 HE & 406 Ct)		Combined			
Chr	SNP	RG	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	I^2	P_{het}
11	rs1052373	GG	5.48×10^{-6}	2.61 (1.72-3.94)	0.012	1.67 (1.12-2.49)	0.002	2.92 (1.41-6.05)	1.43×10^{-8}	2.17 (1.67-2.84)	35	0.2
11	rs7120118	TT	1.26×10^{-5}	2.49 (1.65-3.75)	0.016	1.64 (1.10-2.45)	0.035	2.48 (1.10-5.56)	1.66×10^{-7}	2.07 (1.59-2.70)	12	0.3

List of genes in eQTL with rs1052373 in the blood including their function and associated diseases

SNP	Minor Allele	Gene name	P-value	Gene Function	Associated diseases
rs1052373	A	Spi-1 (Spi-1 Proto-Oncogene)	3.3251×10^{-69}	An ETS-domain transcription factor that activates gene expression during myeloid and B-lymphoid cell development	Inflammatory Diarrhea and Primary Mediastinal B-Cell Lymphoma
		Myosin Binding Protein C, Cardiac (MYBPC3)		A myosin-associated protein found in the cross-bridge-bearing zone (C region) of A bands in striated muscle. Its phosphorylation modulates cardiac contraction	Hypertrophic cardiomyopathy
		MAP Kinase Activating Death Domain (MADD)	1.2009×10^{-59}	A death domain-containing adaptor protein that interacts with the death domain of TNF-alpha receptor 1 to activate mitogen-activated protein kinase (MAPK) and propagate the apoptotic signal.	Diastolic Heart Failure & cardiac hypertrophy
		ACP2 (Acid Phosphatase 2, Lysosomal)	2.1617×10^{-53}	A histidine acid phosphatase that hydrolyzes orthophosphoric monoesters to alcohol and phosphate.	Bone structure alterations, lysosomal storage defects, and an increased tendency towards seizures
		NR1H3 (Nuclear Receptor Subfamily 1 Group H Member 3)	4.56×10^{-53}	A nuclear receptor that works as a key regulator of macrophage function, controlling transcriptional programs involved in lipid homeostasis and inflammation. Plays an important role in the regulation of cholesterol homeostasis. Liver X receptors regulate adrenal steroidogenesis (Testosterone production is significantly lower in KO mice)	Multiple Sclerosis and Cerebrotendinous Xanthomatosis. Among its related pathways are Lipoprotein metabolism and Nuclear Receptors in Lipid Metabolism and Toxicity

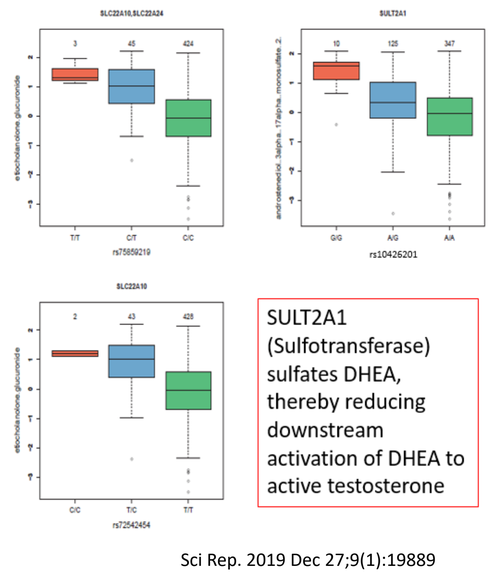
List of metabolites associated with top SNPs

SNP	Beta	SE.Beta	P	Metabolites	SUPER_PATHWAY	SUB_PATHWAY
rs1052373	-0.36	0.08	1.82×10^{-5}	5alpha-androstan-3alpha,17alpha-diol disulfate	Lipid	Androgenic Steroids
	-0.25	0.07	0.000248	2-hydroxy-3-methylvalerate	Amino Acid	Leucine, Isoleucine and Valine Metabolism
	-0.23	0.07	0.000879	alpha-hydroxyisovalerate	Amino Acid	Leucine, Isoleucine and Valine Metabolism
	0.31	0.09	0.000928	xylose	Carbohydrate	Pentose Metabolism
	-0.23	0.07	0.001226	N1-methylinosine	Nucleotide	Purine Metabolism, (Hypo)Xanthine/Inosine containing
	-0.23	0.07	0.001315	palmitoleoylcarnitine (C16:1)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)
	-0.23	0.07	0.001509	2-hydroxyadipate	Lipid	Fatty Acid, Dicarboxylate
	-0.22	0.07	0.001516	2-methylcitrate/homocitrate	Energy	TCA Cycle
	-0.21	0.07	0.001933	myristoleoylcarnitine (C14:1)*	Lipid	Fatty Acid Metabolism(Acyl Carnitine)
rs7120118	-0.33	0.08	5.17×10^{-5}	5alpha-androstan-3alpha,17alpha-diol disulfate	Lipid	Androgenic Steroids
	-0.27	0.07	0.000136	2-hydroxy-3-methylvalerate	Amino Acid	Leucine, Isoleucine and Valine Metabolism
	-0.24	0.07	0.000582	alpha-hydroxyisovalerate	Amino Acid	Leucine, Isoleucine and Valine Metabolism
	-0.24	0.07	0.000715	N1-methylinosine	Nucleotide	Purine Metabolism, (Hypo)Xanthine/Inosine containing
	0.31	0.09	0.001004	xylose	Carbohydrate	Pentose Metabolism
	-0.23	0.07	0.001527	2-hydroxyadipate	Lipid	Fatty Acid, Dicarboxylate
	0.28	0.09	0.001966	5-acetylamino-6-formylamino-3-methyluracil	Xenobiotics	Xanthine Metabolism
	-0.22	0.07	0.002116	alpha-hydroxyisocaproate	Amino Acid	Leucine, Isoleucine and Valine Metabolism
	-0.22	0.07	0.002216	2-methylcitrate/homocitrate	Energy	TCA Cycle
	-0.22	0.07	0.002266	glycerol	Lipid	Glycerolipid Metabolism



Novel mQTLs associated with endurance metabolites

Gene	rsID	Metabolites	P.Value	Beta	SE.Beta	SUB_PATHWAY	P.val (Long et al.)
SLC22A10, SLC22A24	rs75859219	Etiocholanolone glucuronide	5.04E-13	0.96	0.13	Androgenic Steroids	9.13×10-38
SULT2A1	rs10426201	Androstenediol (3alpha, 17alpha) monosulfate (2)	2.47E-10	0.52	0.08	Androgenic Steroids	1.30E-06
SLC22A10	rs72542454	Etiocholanolone glucuronide	1.90E-09	0.85	0.14	Androgenic Steroids	2.40×10-32



SULT2A1 (Sulfotransferase) sulfates DHEA, thereby reducing downstream activation of DHEA to active testosterone

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