Predictive Genomics DNA Profiling for Athletic Performance

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Abstract

Genes control biological processes such as muscle, cartilage and bone formation, muscle energy production and metabolism (mitochondriogenesis, lactic acid removal), blood and tissue oxygenation (erythropoiesis, angiogenesis, vasodilatation), all essential in sport and athletic performance. DNA sequence variations in such genes confer genetic advantages that can be exploited, and/or genetic 'barriers' that could be overcome to achieve optimal athletic performance.

Predictive Genomic DNA Profiling for athletic performance reveals genetic variations that may be associated with better suitability for endurance or strength and speed, vulnerability to sports-related injuries and individualized nutritional requirements. Knowledge of genetic 'suitability'

in respect to endurance capacity or strength and speed would lead to appropriate sport and athletic activity selection. Knowledge of genetic advantages and barriers would 'direct' an individualized training program, nutritional plan and nutritional supplementation to achieving optimal performance, overcoming 'pain barriers' that results from intense exercise and pressure under competition with minimum waste of time and energy and avoidance of health risks (hypertension, cardiovascular disease, inflammation and injuries to tendons and bones) related to exercise, training and competition.

Predictive Genomics DNA profiling for Athletics and Sports performance is developing into an essential tool for proper Athletic activity and Sport selection as well as for the formulation of individualized and personalized training and nutritional programs for optimizing health and performance for the athlete.

Introduction

Human athletic performance is a highly complex phenotype that could be considered a Multi-factorial, Polygenic trait. Multi-factorial due to the multitude of involved and contributing factors that influence physical fitness, including environment, physiological and psychological traits. Polygenic due the multitude of genes involved that influence biological processes that contribute to the physical fitness and performance phenotype. DNA sequence variations in relevant genes have been associated with specific phenotypes involved in athletic performance: endurance capacity, muscle performance, susceptibility to injuries, body mass composition, and psychological aptitude. Information derived from DNA profiling of relevant genes, can indicate both advantages as well as genetic barriers that reflect on the athletic performance phenotype. Personalized and individualized performance improvement strategies to enhance and exploit the genetic advantages or overcome genetic barriers can be implemented to optimize the physical fitness and sports performance phenotype and safeguard the optimal health of an athlete.

The recent breakthroughs in Genomic association studies have paved the way for predictive, preventive and personalized medicine. Multiple genomic variants –most functional variants in exonic regions of relevant genes- have been associated with common, multi-factorial and often

serious diseases, such as cardiovascular diseases, diabetes, cancer etc. These confer increased risk, relative to the general population, which can be counter-acted by corrective actions and the necessary individualized preventive measures. Modifying the non-genetic factors (nutrition, smoking, lifestyle, clinical surveillance, etc.) results in the reduction risk, avoidance or delay of the onset of disease and in increased quality of life. As with all multi-factorial conditions, genetic makeup plays a major role in determining the complex phenotype of athletic performance and knowledge of genetic advantages and barriers conferred by the presence of such genomic variations can be of utmost importance and benefit to athletes guidance.[1,2,3]

Sports DNA Profiling in Practice

Predictive genomics DNA profiling can not detect or determine superior athletes, but can predict abilities and weaknesses associated with sports performance. The general concept of predictive genomics allows to detect low penetrance sequence variation [not every person carrying the genomic variant will develop the respective traits], not proven to be causative, but which function in a cumulative fashion, contributing to the phenotypic manifestation of the relevant trait.

The nature of predictive genomics testing is qualitative rather than quantitative in nature. The predisposition for certain physiological traits when carrying specific genomic variations and the overall predisposition for a certain profile are not estimated in percentages, as this is scientifically unorthodox at least for the time being. The conclusions drawn on the presence of genomic sequence variations (genetic profile) - based on documented association studies in the scientific literature – will indicate whether a predisposing genomic variant is present and whether the overall genetic profile for the genes tested indicates certain abilities or weaknesses relevant and related to the sports performance phenotype.

We have grouped genetic variants based on their effects on different aspects of athletic performance and selected each of them to fulfill the following criteria:

Relevant with direct influence over the biological system of interest and the association to the respective traits clearly documented in the medical and scientific literature.

Prevalent: The genomic variant is relatively common in the general population. Every attempt has been made to exclude genomic variants with less than 1% population frequency although it has not been possible in some instances.

Modifiable: The effect of the genomic variant can - to a marked degree - be modifiable by application of appropriate measures and corrective actions.

Measurable: The impact of the corrective actions that can modify the effects of the genomic variants should be measurable –given the proper time for corrective actions to take effect- by laboratory or physiological assays when possible.

This review presents the major genetic variants –as selected by the authors- associated with specific aspects of sports performance and how information from DNA profiling can be used to individualize and personalize training programs, nutrition and nutritional supplementation, to achieve optimal athletic performance and health of an athlete.

Endurance ability

Performance of individuals in endurance and mixed aerobic-anaerobic sports depends on aerobic power. Aerobic power is defined as the maximum amount of oxygen the body can utilize usually during intense exercise. Aerobic power is a physiological trait with strong genetic basis, and contributes significantly to the performance of an individual in sports requiring endurance.

Genetic predisposition regarding aerobic fitness is estimated by testing for a panel of genomic variants associated mainly with oxygen supply to tissues (cardiorespiratory fitness) and energy metabolism in muscles (Table 1.)

In particular variants in genes involved in angiogenesis and vasodilation have been extensively studied for their effects to aerobic capacity and endurance performance. Elite athletes of endurance sports often share genomic variants that affect maximal oxygen consumption and energy supply of aerobic metabolism. Certain variants in genes such as *ACE,*[4,5] *BDKRB2,*[6,7] *NOS3,*[8] *HIF1,*[9] and *VEGF*[10,11] enhance oxygen supplies to muscle tissues, and favor increased endurance. Moreover polymorphisms in genes involved in red blood cells production and function, such as *EPOR* [12, 13, 14] and *HBB,*[15] have been associated with increased oxygen

supplies to muscles. Cardiorespiratory fitness depends also on heart rate recovery ability, and is genetically affected by *CHRM2* genomic variants[16] among others. Strong evidence support that increased endurance ability is based on increased mitochondrial function. A group of genes crucial for regulation of energy metabolism is *PPAR*s (Peroxisome Proliferator Activated Receptors) which determine mitochondrial activity and are involved in muscle fiber type composition[17,18]. Energy consumption in muscle cells is also influenced by the gene encoding for *CK-MM* (Creatine Kinase-Muscle Type) variant of this gene has been associated with energy savings during endurance training.[19,20]

Another extensively studied gene for its effects on athletic performance is *ACTN3*. The nonsense polymorphism R577X has been associated with a significant effect to the function of skeletal muscle fibers. The null genotype XX results in complete deficiency of protein *ACTN3*, leading to higher activity of slow fiber metabolism and enhancing endurance performance.[21,22]

Table 1: Genetic variants associated with endurance ability

GENE	BIOLOGICAL FUNCTION	VARIANT	RS NUMBER
Endurance Capacity			
ACE	Blood Pressure regulation Muscle performance Lipids & Glucose levels	INS/DEL	N/A ACE InDel
BDKRB2	Skeletal Muscle Metabolic Efficiency	-9/+9 bp	N/A BDKRB2
NOS3	Vasodilation O2 Supply to Tissues	$G_{894} \rightarrow T$	Rs 1799983
HIF-1α	Angiogenesis & Erythropoiesis O2 Supply to Tissues Basisal Metabolic Rate Rate of Recovery	C→ T ($P_{582} \rightarrow S$)	Rs 11549465
VEGF Angiogenesis	O2 Supply to Tissues	$A_{-2578} \rightarrow C$	Rs 699947
		$G_{-1154} \rightarrow A$	Rs 1570360
		$G_{-634} \rightarrow C$	Rs 2010963

EPOR	Erythroblast Proliferation & Differentiation O2 Supply to Tissues	G_{6002}→ A (Try_{439}→ Stop)	N/A EPOR
HBB	Cardio-Respiratory Adaptation to Training	C_{16} → G	Rs 12788013
		C_{551}→ T	Rs 11036351
CHRM2	Heart Rate Recovery	A_{616}→ G	Rs 324640
PPARγ-C1	Energy Generation	G → A (G_{482}→ S)	Rs 8192678
PPARD	Lipid & Carbohydrate Metabolism	A_{294} → G	Rs 2016520
CK-MM	Energy consumption in muscles	*NcoI* restriction A_{214}→ G	Rs 1803285
ACTN3	Rapid Muscle Contraction	C → T (R_{577} → X)	Rs 1815739

Muscle Performance

Muscle strength and general muscle performance are major factors for athletes involved in power, sprint and semi-endurance sports.

Several genetic variants contribute to the ability of muscles to perform during intense exercise (Table 2). Variants in genes affecting oxygen supply to muscles and energy consumption affect muscle strength phenotypes, as well as endurance capacity, either with similar genotype effects (*NOS3*[2,8] and *HIF-1,*[2,23] enhancing oxygen transfer to muscles) or different genotype (*ACE,*[4,5] *ACTN3*[21,22]) effects. The *ACTN3* wild type allele "R" for example is overrepresented in sprint and power athletes, favoring fast muscle fibers contraction, in contrast to the "X" null allele that favors endurance athletes. [21,22]

Muscle function is strongly associated with genes affecting muscle energy metabolism during intense exercise, such as *AMPD1*. A nonsense genomic variant in the gene is associated with

acute exercise intolerance, creating a genetic barrier for intense muscle performance. Sedentary individuals who are deficient for the enzyme develop symptoms such as cramps, easy fatigability, and myalgia after exercise.[24,25] A major factor for muscle fatigue after intense power exercise is the rates of lactic acid removal. A variant in the MCT-1 gene affects lactate transport capability and thus intensity of performance.[26] On the other hand, a gene variant in *DIO1* affects positively anaerobic exercise phenotypes, enhancing muscular strength.[24,27]

Table 2: Genetic variants associated with muscular performance and power exercise phenotypes.

GENE	BIOLOGICAAL FUNCTION	VARIANT	RS NUMBER
Muscle Performance			
HIF-1α	Angiogenesis & Erythropoiesis O2 Supply to Tissues Basal Metabolic Rate Rate of Recovery	C→T (P_{582} → S)	Rs 11549465
NOS3	Vasodilation O2 Supply to Tissues	G_{894} → T	Rs 1799983
ACE	Blood Pressure regulation Muscle performance Lipids & Glucose levels	INS/DEL	N/A ACE InDel
ACTN3	Rapid Muscle Contraction	C → T (R_{577} → X)	Rs 1815739
AMPD1	Muscle Performance	G_{34} → A	Rs 17602729
DIO1	Thyroid Hormone Regulation Muscle Strength	C_{785} → T	Rs 11206244
MCT-1	Lactic Acid Clearance Muscle Fatigue	A_{1470} → T	Rs 1049434

Utility and Guidelines for Improve Performance

Predictive genomics DNA profiling results from the panels of endurance capacity and muscle performance (Tables 1 and 2) provide information that can be utilized in two major areas:

a) **Choice of Sport or Athletic Activity.**

Choosing a suitable sport or athletic activity is a complex process and usually takes into account several factors, including anthropological and biochemical measurements, technical skills, and first and foremost social and economic factors. Along with these factors, information derived from predictive genomics DNA profiling should also contribute to the decision.

Identification of genetic advantages in either endurance or power/speed or both can be used in selection of individuals who may have better or even elite performance in certain types of sports. In the case of an individual with the favorable variants shown in Table 1 with positive effects on endurance, the athlete may show an extra potential in sports requiring high aerobic power. On the other hand, if an individual's genetic profile (for variants in shown in Table 2) favors muscle power and anaerobic metabolism, this individual would exhibit extra advantage in sports requiring increased speed and strength performance. In case the genetic makeup is advantageous for both endurance and muscle power, mixed aerobic-anaerobic sports may be the activities of choice.

b) **Tailoring of training programs.**

Based on specific genomic variants that an athlete carries, sports professionals (coaches, strength, conditioning trainers and sports scientists) can take measures to maximize the athlete's potential. This is extremely beneficial in cases of individuals who already have chosen a sport without taking into consideration their genetic predisposition and desire to improve their endurance and muscle performance, respectively, based on indicative DNA profiling.

Depending on the biological effect of certain polymorphisms, individualized training strategies can be followed either to enhance genetic advantages or overcome genetic barriers. In Table 3, we provide sample recommendations to improve endurance and power performance, respectively based on indicative DNA profile. The aforementioned genetic variants have been chosen to affect the most important systems affecting endurance and muscle power. Moreover, certain nutritional adjustments based on NutriGenetic / NutriGenomic DNA variants can impact markedly sports performance.

Individual with genotypes conferring significantly reduced muscle power (*ACTN3* "XX" null genotype) or muscles overload (*CKMM* A_{214}→ G), may benefit from an increase in protein intake. Increase in lactic acid clearance to prevent muscle fatigue after intense exercise can be achieved with a high alkaline diet. Increased risk for hypertension requires special caution in sodium intake for individuals homozygotes for the ACE "DD" genotype as well as special medical surveillance including blood pressure monitoring before, during and after training and cardiovascular examination, including echocardiograms.

Table 3. Training recommendations based on DNA profiling for genetic variants associated with Athletic Performance

Variant	**Genotype**	**Effect on Sports Performance**	**Training Recommendations**
ACE: In/Del	**DD**	Reduced endurance capacity / increased muscle performance	Training to increase anaerobic (a-lactic) performance. Increase progressively but fast the number of training sessions on weekly schedule. If required, emphasis on training to increase endurance. Perform training for strength in high frequency with sub-maximum loads.
		Increased Cardio-Respiratory Adaptation to endurance training Faster adaptation to long distance or	Reevaluate substrate and energy use at the race pace or at three different intensities (at aerobic threshold, 5% below lactate

HBB C_{551}→ T	**CC**	endurance training with improved running economy. Lower energy needs and glycogen sparing during long distance training or events.	threshold and 5% above lactate threshold) and recalculate individual energy and substrate (carbohydrates, protein, fat) needs for the specific race distance.
EPOR G_{6002}→ A (Try_{439}→ Stop)	**AA**	Increased red blood cells production- advantageous for endurance Suitability for endurance and mixed aerobic-anaerobic sports or for speed sports with duration over 40sec.	
ACTN3 **(R_{577}→ X)**	**XX**	Increased slow muscle fiber metabolism- reduced muscle power	Long term physical preparation to achieve technical perfection. Perform many routes of the competition distance / repetitive routes of similar overall distance. Advantage in rapid muscle contraction confers increased risk of muscle injury when performing exercises with maximum intensity. Perform exercises in sub

			maximum intensity or increase progressively the intensity of the exercise.
CK-MM *NcoI* restriction A_{214}→ G	**GG**	Muscles overload after intensive training	For increased endurance train for a longer period of time to reach the desirable level of performance and increase breaks during training.
MCT-1	**TT**	Reduced lactic acid clearance	Increase lactic acid removal by increasing training intensity to moderate or high levels at least twice every week. Perform active recovery using aerobic exercises at intensities that are optimal for faster lactic acid removal (50-60% HRR). Take longer intervals during intensive training depending on the genotype. After injury, prolong time to full rehabilitation. Measure lactate removal rate on a regular basis

Susceptibility to injuries

Individuals involved in amateur athletic activities or professional sports may suffer from sports related injuries. Genetic predisposition and increased risk for tendinopathies and tendon sports related injuries is conferred by the genetic variants listed in Table 4.

Table 4: Genetic variants associated with tendinopathies risk.

GENE	BIOLOGICAL FUNCTION	VARIANT	RS NUMBER
Susceptibility to Injury			
Tendons			
COL1A1	Collagen formation in cartilage, bone, skin & connective tissue	$G_{2046} \rightarrow T$	Rs 1800012
COL5A1	Collagen formation in cartilage, bone, skin & connective tissue	$C_{401} \rightarrow T$	Rs 12722
MMP3	Collagen –Connective tissue degradation Wound repair	$A_{301} \rightarrow G$	Rs 679620

Genomic variants in genes encoding various collagen types (*COL1A1,*[28,29] *COL5A1*[30,31]) confer increased risk for tendinopathies since collagen is the main structural component of tendons and ligaments. Moreover the specific variant in the *MMP3* gene encoding a matrix metalloproteinase interacts with *COL5A1,*[32] and confers increased risk for Achilles tendinopathy. The risk is further increased for individuals who have unfavorable variants in both *COL5A1* and *MMP3* genes.

Tendinopathies require lengthy management and recovery. Also, patients often respond poorly to treatment. Preventive measures and corrective action for individuals at increased soft tissue injury risk include, among others, the following:

Avoid increasing body weight
Correct misalignment with appropriate customized insoles
Avoid wearing brand new shoes in hard surface
Look for reduced flexibility or reduced range of motion upon waking up in the morning
Avoid very hard or very soft surfaces or training in artificial grass
Use grass trail instead of a sidewalk
Soft beach sand running not recommended
If involved in both aerobic training & weight lifting, perform aerobic workout first

Avoid training uphill or excessive plyometric training or excessive speed training

Excessive stiffness of the posterior leg muscles (i.e. hamstrings or calf muscles) can increase the load on the tendons

Increase warm up volume & intensity in cold environmental conditions

Increase speed or jump height gradually during warm up

The day after a game or high intensity training or hard surface training reduce load on tendons using non-weight bearing activities (i.e. swimming, biking}

Be aware of minor muscle, joint or bone injuries.

Assure complete recovery before assuming high intensity training

Encourage team medical staff to check tendons for any unusual finding, soreness, swelling, cracking or pain.

Massage calf muscles & Achilles tendons after training

Studies demonstrating association of genomic variants to susceptibility, predisposition and increased risk for bone injury are rather limited. However, multiple association studies [mostly in menopausal women] link Bone Mineral / Mass Density, a significant indicator of bone health in general to functional genomic variants in the Vitamin D receptor gene (*VDR* which mediates calcium absorption) - [33,34,35] [Table 5].

Table 5: Genomic variants associated with reduced bones mass density.

GENE	BIOLOGICAL FUNCTION	VARIANT	RS NUMBER
Susceptibility to Injuries			
Bones			
VDR	Regulation of collagen formation Bone formation and replacement Connective tissue degradation	$T_{Taq1} \rightarrow C$	Rs 731236
		$A_{BSM1} \rightarrow G$	Rs 1544410
		$C_{FOK1} \rightarrow T$	Rs 2228570

Increased risk for sports related bone injury could be reduced by frequent clinical surveillance and monitoring. Recommendations include pelmatography with correction (customized insoles are considered beneficial for decreasing strains imposed on the skeleton of the lower limb), bone density measurements, biochemical evaluations for Vitamin D, Calcium and Phosphorus blood

concentration. Calcium and Vitamin D dietary supplements coupled to increased exposure to sunlight (at least 15 minutes daily) contribute to improved overall bone health that results in the reduction of frequency or even avoidance of sports related bone injuries

Body Composition

Body mass composition [fat vs muscle mass as reflected by the Body Mass Index (BMI)] is one of the major factors affecting sports performance. Variants Adrenergic Receptor genes (*ADRA2A, ADRB1, ADRB1*) affect biological processes such as Energy Expenditure, Lipolysis and thermogenesis conferring compromised lipolysis regulation and increased fat accumulation [36, 37, 38, 39, 40] [Table 6].

Table 6: Genomic variants associated with defects in lipolysis and BMI regulation.

GENE	BIOLOGICAL FUNCTION	VARIANT	RS NUMBER
Body Mass Index (BMI)			
ADRB2	Lipolysis Regulation Thermogenesis Drug Response	A → G (Arg_{16}→Gly)	Rs 1042713
		C→G (Gln_{27} →Glu)	Rs 1042714
ADRA2A	Lipolysis Inhibition	C_{-1291}→ G	Rs 1800544
ADRB1	Energy Expenditure Lipolysis Regulation Blood Pressure Regulation	A →G (Ser_{49}→Gly)	Rs 1801252
		C → G (Arg_{389} →Gly)	Rs 1801253

Physical activity is beneficial not only for athletes but also for the population at large in terms of body weight management and BMI reduction. Depending on the DNA profile for genes involved in body mass composition, physical activity alone might not be sufficient to achieve lean fat mass, maintain a good BMI and improve sports performance. Proper nutrition and

nutritional supplementation are essential for individuals with at-risk DNA profiles. Physicians, trainers and nutritionists can tailor nutritional recommendations [Table 7] according to sport or athletic activity of choice as well as anthropometric and biochemical measurements.

Table 7: Guidelines for preventing fat accumulation and muscle mass increase.

Lifestyle recommendations	Nutritional recommendations
Maintain normal body weight or BMI < 25. Quit Smoking *Increase aerobic activity o30-60min, 3-6 days/week), using large muscle activities, at 50-80% of HRmax or 40-70% of HR reserve or 40-70% of VO2max, 700kcal/week as an initial goal (ACSM Exercise Management for Persons with Chronic Disease and Disabilities)]. Emphasize duration rather than intensity	Fat intake should not account for more than 20-25% of total calories. Prefer ω-3 fatty acids (salmon, sardines etc) – and consume fish at least twice every week. Reduce saturated fat (animal fat). Intake must be limited to a maximum of 5-7% of total calories. Limit cholesterol intake to 150mg / day or less Use olive oil. Reduce consumption of sugars Consume seeds, nuts, garlic Limit alcohol to no more than 1 oz/day of ethanol, 10oz of wine, 20oz of beer or 2oz of whiskey for men

Psychological aptitude

Determination is very important for athletes especially for those performing at high level. Along with many socio-psychological factors and relationships, motivation to exercise has a strong genetic basis. The gene *BDNF* is involved in the development and survival of nervous system, both central (in brain) and peripheral. The polymorphism $G_{196} \rightarrow A$ (rs6265) affects the psychological response to stress and also motivation to exercise. In particular, it has significant effects on the individual's positive/ negative thinking during intense exercise and competition[41, 42, 43]. Thus, an athlete can be guided more appropriately and efficiently for better emotions and stress management to achieve optimal performance.

Substance abuse control

Doping control for testosterone abuse is based on detection of testosterone by-products in urine. Levels of testosterone metabolites vary widely among individuals, even if they have not involved in testosterone abuse. A genomic variant (deletion / insertion polymorphism) in the *UGT2B17* gene directly influences levels of testosterone by-products in urine. Individuals with the insertion allele show markedly increased levels of urine testosterone that might lead to false positive results in anti-doping biochemical testing. [44, 45] Currently, the World Anti-Doping Agency (WADA) does not take into account the DNA profiling of athletes in anti-doping monitoring. However this information is crucial since higher levels of testosterone and testosterone by-products in the urine do depend on an individual's genotype, and could produce false positive results at doping control.

DNA Profiling in Sports Nutrition

Nutritional genomics encompasses the fields of Nutri-Genomics (how dietary bioactive compounds affects function of genes and proteins) and Nutri-Genetics (how certain inheritable genetic variants interact with bioactive dietary compounds affecting health status). The ultimate purpose of nutritional genomics is to determine for each individual their personalized and individualized nutritional needs, which are essential and beneficial to promote optimal health and

well-being. Understanding the genetic nutritional needs of an athlete provides an additional valuable tool in strategies to optimize sports performance [46, 47, 48].

Several functional genomic variants affect basic aspects of human health. Vitamin B complex has a key role (folic acid, Vitamin B6, Vitamin B12) in cell metabolism and especially DNA synthesis and repair processes. Associations of variants in genes responsible for the metabolism of these vitamins (*MTHFR*, *MTR*, *MTRR*, etc.) [49, 50] dictate increased folic acid intake and appropriate supplementation. Similarly accumulation of variants in genes affecting anti-oxidation and detoxification (among other *GSTT1, GPX1, CAT*) [51, 52, 53, 54] confer compromised ability to defend against free radical damage and oxidative stress insults. Individualized nutritional guidance can significantly enhance anti-oxidation and detoxification abilities, promoting optimal health and consequently optimal sports performance. Athletes face increased risk of inflammation from intensive exercise, which is further intensified by functional genomic variants in genes such as *TNF-α*, *IL-6* and *CRP*).[55, 56, 57, 58] Thus it is crucial to enhance anti-inflammatory bioactive compounds in their diet.

Often nutrition professionals involved in guiding athletes regard increased iron intake and supplementation as a necessity, especially in athletes involved in endurance sports. However genetic profiles of individual athletes may be indicative of increased risk for Hemochromatosis, when specific variants in gene *HFE* are present.[59, 60] In these subjects, increased iron intake may lead to iron overload with serious toxic effects on tissues.

Nutritional programs for athlete are traditionally designed to accommodate the nutritional demands of the sport of choice on various biochemical markers that indicate specific nutritional needs. It is now possible to utilize DNA profiling to optimize the nutritional plan and supplementation of an athlete to enhance performance and avoid serious health risks.

In sports such as wrestling, rowing, weight lifting, tae kwon do, martial arts, boxing etc. athletes compete in specific weight classes. Failure to meet specific weight class requirements may be extremely disadvantageous for the athlete because he might be forced to compete with much heavier or powerful opponents. Thus, a well-structured dietary program, meeting the exact dietary and energy requirements for the particular athlete and competitive sport is crucial to success. A common practice in such sports is that few days before competition athletes are a

little heavier (1-3 Kg) compared to the weight class they compete. Then they tend to lose weight during the last 24 hours before competition following a calorie-restricted dietary plan. Since certain gene variants affect energy balance, DNA profiling may be taken into account when designing and implementing dietary programs for these sports.

Substrate utilization is crucial for optimum performance in long distance events such as marathon, ultra-marathon or triathlon. In sports with repetitive consecutive competition days (e.g. cycling) athletes need an individually tailored nutritional plan on a daily basis that meets the that day's energy needs. Maintaining optimal body weight is crucial since excess weight may affect running or cycling economy. Excess carbohydrate consumption may trigger excess insulin release and liposynthesis. Glucose sparing is crucial for success in these events and athletes often attempt not only to replenish glycogen stores after each event, but also to increase glucose uptake during the event by consuming foods or nutritional supplements (bars, gels, liquids etc.). Since certain genes are involved in glucose homeostasis and other genes may affect lipolysis, DNA profiling must be taken into account when designing competition meals for these athletes.

Nutritional programs for athletes are traditionally designed to accommodate the nutritional demands of the sport of choice and are based on various biochemical markers that indicate specific nutritional needs. It is now possible to utilize DNA profiling to optimize the nutritional plan and supplementation of the athlete to enhance performance and avoid serious health risks.

Conclusions and Considerations

Predictive Genomics DNA profiling for sports performance is a tool to be utilized along with other more commonly used tools (biological, biochemical and anthropometric measurements) by sports professionals to aid in sport selection and formulation of individualized and personalized training and nutrition programs to overcome performance barriers and achieve optimal performance for the specific individual athlete.

The benefits of sports DNA profiling are not limited to individuals involved in professional sports such as athletes competing at elite level, but to anyone that is physically active, involved in physical fitness and maintaining optimal health.

DNA profiling for Athletic Performance should not be utilized for diagnostic purposes or for screening and selecting the next champion or Olympic games winner. It should not be used to detect athletes with elite potential or diagnose tendinopathies. It is indicative of genetic "trends" of individuals and a tool to guide athletes to the maximal utilization of their potential, possibly leading to improved performance in sports. DNA profiling is dynamic. Novel genomic discoveries should be taken into consideration when they are strongly and unequivocally associated with traits that contribute to the complex sports-performance phenotype. The more essential and meaningful genomic variants used and the more reliable the risk-assigning algorithms become, the greater the predictive value of the DNA profiling and sports performance improvement.

Predictive Genomics DNA Profiling for sport and athletic performance identifies genetic advantages to be exploited, genetic barriers to overcome, offers insights into sport and athletic activity selection (endurance, strength, mixed), determines increased risk for sports related injuries and uncovers sports performance hindrances (body mass, psychological attitude, substance abuse). Knowledge and utilization of DNA profiling leads to devise and implementation of protocols suited to sport and genotype via optimized, personalized and individualized training and nutritional programs for maximum performance and optimal health for the athlete.

References

1. Daniel G. MacArthur, Kathryn N. North: Genes and human elite athletic performance. *Hum Genet* 116: 331–339,2005.

2. Giuseppe Lippi, Umile Giuseppe Longo, and Nicola Maffulli: Genetics and sports. *Br Med Bull* 93 (1): 27-47,2010.

3. Brutsaert TD, Parra EJ. What makes a champion? Explaining variation in human athletic performance. *RespirPhysiolNeurobiol*151:109–123, 2006.

4. Myerson S, Hemingway H, Budget R.et al. Human angiotensin I-converting enzyme gene and endurance performance. *J ApplPhysiol*87(4):1313-6, 1999.

5. Woods DR, Humphries SE, Montgomery HE.The ACE I/D polymorphism and human physical performance.*Trends EndocrinolMetab*11(10):416-20, 2000.

6. Van Guilder GP, Pretorius M, Luther JM, Byrd JB, Hill K, Gainer JV, Brown NJ.Bradykinin type 2 receptor BE1 genotype influences bradykinin-dependent vasodilation during angiotensin-converting enzyme inhibition.*Hypertension*51(2):454-9, 2008.

7. Williams AG, Dhamrait SS, Wootton PT, Day SH, Hawe E, Payne JR, Myerson SG, World M, Budgett R, Humphries SE, Montgomery HE.Bradykinin receptor gene variant and human physical performance.*J ApplPhysiol*96(3):938-42, 2004.

8. Saunders CJ, Xenophontos SL, Cariolou MA, Anastassiades LC, Noakes TD, Collins M.The bradykinin beta 2 receptor (BDKRB2) and endothelial nitric oxide synthase 3 (NOS3) genes and endurance performance during Ironman Triathlons.*Hum Mol Genet*15(6):979-87, 2006.

9. Mason SD, Rundqvist H, Papandreou I, Duh R, McNulty WJ, Howlett RA, Olfert IM, Sundberg CJ, Denko NC, Poellinger L, Johnson RS.HIF-1alpha in endurance training: suppression of oxidative metabolism. Am *J PhysiolRegulIntegr Comp Physiol*293(5):R2059-69, 2007.

10. Kraus RM, Stallings HW 3rd, Yeager RC, Gavin TP. Circulating plasma VEGF response to exercise in sedentary and endurance-trained men.J ApplPhysiol 96(4):1445-50, 2004.

11. Prior SJ, Hagberg JM, Paton CM, Douglass LW, Brown MD, McLenithan JC, Roth SM.DNA sequence variation in the promoter region of the VEGF gene impacts VEGF gene expression and maximal oxygen consumption.Am J Physiol Heart Circ Physiol290(5):H1848-55, 2006.

12. Gregory D. Longmore.Erythropoietin receptor genomic varants and Olympic glory. *Nature Genetics* 4, 108 – 110, 1993.

13. Linda S. Pescatello, Steven M. Roth. Exercise Genomics. Springer 2011.

14. de la Chapelle A, Träskelin AL, Juvonen E. Truncated erythropoietin receptor causes dominantly inherited benign human erythrocytosis. *Proc NatlAcadSci U S A* 90(10): 4495-4499, 1993.

15. He Z, Hu Y, Feng L, Lu Y, Liu G, Xi Y, Wen L, Xu X, Xu K.Polymorphisms in the HBB gene relate to individual cardiorespiratoryadaptation in response to endurance training. *Br J Sports Med* 40: 998–1002, 2006.

16. Hautala AJ, Rankinen T, Kiviniemi AM, Mäkikallio TH, Huikuri HV, Bouchard C, Tulppo MP. Heart rate recovery after maximal exercise is associated with acetylcholine receptor M2 (CHRM2) gene polymorphism.*Am J Physiol Heart Circ Physiol*291(1):H459-66, 2006.

17. Lucia A, Gómez-Gallego F, Barroso I, Rabadán M, Bandrés F, San Juan AF, Chicharro JL, Ekelund U, Brage S, Earnest CP, Wareham NJ, Franks PW.PPARGC1A genotype (Gly482Ser) predicts exceptional endurance capacity in European men.*J ApplPhysiol*99(1):344-8, 2005.

18. Calvo JA, Daniels TG, Wang X, Paul A, Lin J, Spiegelman BM, Stevenson SC, Rangwala SM.Muscle-specific expression of PPARgamma coactivator-1alpha improves

exercise performance and increases peak oxygen uptake.*J ApplPhysiol*104(5):1304-12, 2008.

19. Echegaray M, Rivera MA.Role of creatine kinase isoenzymes on muscular and cardiorespiratory endurance: genetic and molecular evidence.*Sports Med* 31(13):919-34, 2001.

20. Zhou DQ, Hu Y, Liu G, Gong L, Xi Y, Wen L.Muscle-specific creatine kinase gene polymorphism and running economy responses to an 18-week 5000-m training programme.*Br J Sports Med* 40(12):988-91, 2006.

21. Niemi AK, Majamaa K.Mitochondrial DNA and ACTN3 genotypes in Finnish elite endurance and sprint athletes.*Eur J Hum Genet*13(8):965-9, 2005.

22. MacArthur DG, Seto JT, Chan S, Quinlan KG, Raftery JM, Turner N, Nicholson MD, Kee AJ, Hardeman EC, Gunning PW, Cooney GJ, Head SI, Yang N, North KN.An Actn3 knockout mouse provides mechanistic insights into the association between alpha-actinin-3 deficiency and human athletic performance. *Hum Mol Genet* 15;17(8):1076-86, 2008.

23. Eynon N, Alves AJ, Meckel Y, Yamin C, Ayalon M, Sagiv M, Sagiv M. Is the interaction between HIF1A P582S and ACTN3 R577X determinant for power/sprint performance?*Metabolism* 59(6):861-5, 2010.

24. Bray MS, Hagberg JM, Pérusse L, Rankinen T, Roth SM, Wolfarth B, Bouchard C.The human gene map for performance and health-related fitness phenotypes: the 2006-2007 update.*Med Sci Sports Exerc*41(1):35-73, 2009.

25. Rubio JC, Martín MA, Rabadán M, Gómez-Gallego F, San Juan AF, Alonso JM, Chicharro JL, Pérez M, Arenas J, Lucia A.Frequency of the C34T genomic varant of the AMPD1 gene in world-class endurance athletes: does this genomic varant impair performance?*J ApplPhysiol*98(6):2108-12, 2005.

26. Peeters RP, van den Beld AW, van Toor H, Uitterlinden AG, Janssen JA, Lamberts SW, Visser TJ.A polymorphism in type I deiodinase is associated with circulating free insulin-

like growth factor I levels and body composition in humans. *J ClinEndocrinolMetab*90(1):256-63, 2005.

27. Cupeiro R, Benito PJ, Maffulli N, Calderón FJ, González-Lamuño D.MCT1 genetic polymorphism influence in high intensity circuit training: a pilot study.*J Sci Med Sport*13(5):526-30, 2010.

28. Collins M, Posthumus M, Schwellnus MP. The COL1A1 gene and acute soft tissue ruptures.*Br J Sports Med* 44(14):1063-4, 2010.

29. Posthumus M, September AV, Keegan M, O'Cuinneagain D, Van der Merwe W, Schwellnus MP, Collins M. Genetic risk factors for anterior cruciate ligament ruptures: COL1A1 gene variant.*Br J Sports Med*43(5):352-6, 2009.

30. September AV, Cook J, Handley CJ, van der Merwe L, Schwellnus MP, Collins M.Variants within the COL5A1 gene are associated with Achilles tendinopathy in two populations.*Br J Sports Med*(5):357-65, 2009.

31. Mokone GG, Schwellnus MP, Noakes TD, Collins M. Scand.The COL5A1 gene and Achilles tendon pathology.*J Med Sci Sports*16(1):19-26, 2006.

32. Raleigh SM, van der Merwe L, Ribbans WJ, Smith RK, Schwellnus MP, Collins M.Variants within the MMP3 gene are associated with Achilles tendinopathy: possible interaction with the COL5A1 gene.*Br J Sports Med*43(7):514-20, 2009.

33. Nakamura O, Ishii T, Ando Y, Amagai H, Oto M, Imafuji T, Tokuyama K.Potential role of vitamin D receptor gene polymorphism in determining bone phenotype in young male athletes.*J ApplPhysiol*93(6):1973-9, 2002.

34. HeiniHartikka. Genetic Factors In BoneDisorders: OsteogenesisImperfecta, Juvenile Osteoporosis AndStress Fractures. University of Oulu, 2005.

35. Abrams SA, Griffin IJ, Hawthorne KM, Chen Z, Gunn SK, Wilde M, Darlington G, Shypailo RJ, Ellis KJ.Vitamin D receptor Fok1 polymorphisms affect calcium absorption, kinetics, and bone mineralization rates during puberty.*J Bone Miner Res*20(6):945-53, 2005.

36. Lima JJ, Feng H, Duckworth L, Wang J, Sylvester JE, Kissoon N, Garg H. Association analyses of adrenergic receptor polymorphisms with obesity and metabolic alterations.*Metabolism* 56(6):757-65, 2007.

37. Rosmond R, Bouchard C, Björntorp P. A C-1291G polymorphism in the alpha2A-adrenergic receptor gene (ADRA2A) promoter is associated with cortisol escape from dexamethasone and elevated glucose levels.*J Intern Med*251(3):252-7, 2002.

38. Masuo K, Katsuya T, Fu Y, Rakugi H, Ogihara T, Tuck ML. Beta2- and beta3-adrenergic receptor polymorphisms are related to the onset of weight gain and blood pressure elevation over 5 years. *Circulation*111(25):3429-34, 2005.

39. Park HS, Kim Y, Lee C. Single nucleotide variants in the beta2-adrenergic and beta3-adrenergic receptor genes explained 18.3% of adolescent obesity variation.*J Hum Genet*50(7):365-9, 2005.

40. Ellsworth DL, Coady SA, Chen W, Srinivasan SR, Boerwinkle E, Berenson GS.Interactive effects between polymorphisms in the beta-adrenergic receptors and longitudinal changes in obesity.*Obes Res*13(3):519-26, 2005.

41. Bryan A, Hutchison KE, Seals DR, Allen DL. A transdisciplinary model integrating genetic, physiological, and psychological correlates of voluntary exercise. *Health Psychol*26(1):30-9, 2007.

42. Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, Herrera DG, Toth M, Yang C, McEwen BS, Hempstead BL, Lee FS. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior.*Science* 314(5796):140-3, 2006.

43. Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, Herrera DG, Toth M, Yang C, McEwen BS, Hempstead BL, Lee FS.Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior.*Science*314(5796):140-3, 2006.

44. Jakobsson J, Ekström L, Inotsume N, Garle M, Lorentzon M, Ohlsson C, Roh HK, Carlström K, Rane A.Large differences in testosterone excretion in Korean and Swedish

men are strongly associated with a UDP-glucuronosyltransferase 2B17 polymorphism.*J ClinEndocrinolMetab*. 91(2):687-93, 2006.

45. Schulze JJ, Lundmark J, Garle M, Skilving I, Ekström L, Rane A.Doping test results dependent on genotype of uridinediphospho-glucuronosyltransferase 2B17, the major enzyme for testosterone glucuronidation. *J ClinEndocrinolMetab*93(7):2500-6, 2008.

46. Boehl T. Emerging science raises questions: what to tell your clients about nutritional genomics. *J Am Diet Assoc* 107(7):1094-6, 2007
47. Stover PJ, Caudill MA. Genetic and epigenetic contributions to human nutrition and health: managing genome-diet interactions. *J Am Diet Assoc* 108(9):1480-7, 2008.
48. DeBusk RM, Fogarty CP, Ordovas JM, Kornman KS.Nutritional genomics in practice: where do we begin? *J Am Diet Assoc* 105(4):589-98, 2005.
49. Ueland PM, Hustad S, Schneede J, Refsum H, Vollset SE. Biological and clinical implications of the MTHFR C677T polymorphism. *Trends Pharmacol Sci* 22(4):195-201, 2001.
50. Lu C, Xie H, Wang F, Shen H, Wang J.: Diet folate, DNA methylation and genetic polymorphisms of MTHFR C677T in association with the prognosis of esophageal squamous cell carcinoma. *BMC Cancer* 5(11):91, 2011.
51. Colin N. A. Palmer, Alex S. F. Doney, Simon P. Lee, Inez Murrie, Tahmina Ismail, Donald F. Macgregor and Somnath Mukhopadhyay: Glutathione S-Transferase M1 and P1 Genotype, Passive Smoking, and Peak Expiratory Flow in Asthma. *Pediatrics* 118:710-716, 2006.
52. Islam T, Berhane K, McConnell R, Gauderman W J, Avol E, Peters J M, Gilliland F D: Glutathione-S-transferase (GST) P1, GSTM1, exercise, ozone and asthma incidence in school children. *Thorax* 64(3):197-202, 2009.
53. Timothy R. Fennell, John P. MacNeela, Richard W. Morris, Mary Watson, Claudia L. Thompson, and Douglas A. Bell: Hemoglobin Adducts from Acrylonitrile and Ethylene Oxide in Cigarette Smokers: Effects of Glutathione S-Transferase T1-Null and M1-Null Genotypes. *Cancer Epidemiology, Biomarkers & Prevention* 9: 705–712, 2000.
54. Hans B. Ketelslegers, Ralph W.H. Gottschalk, Roger W.L. Godschalk, Ad M. Knaapen et al.: Inter-individual Variations in DNA Adduct Levels Assessed by Analysis of Multiple

Genetic Polymorphisms in Smokers. *Cancer Epidemiol Biomarkers Prev* 15(4):624–9, 2006.

55. Yamin C, Duarte JA, Oliveira JM, Amir O, Sagiv M, Eynon N, Sagiv M, Amir RE. IL6 (-174) and TNFA (-308) promoter polymorphisms are associated with systemic creatine kinase response to eccentric exercise. *Eur J Appl Physiol* 104(3):579-86, 2008.
56. Wang Q, Hunt SC, Xu Q, Chen YE, Province MA, Eckfeldt JH, Pankow JS, Song Q. Association study of CRP gene polymorphisms with serum CRP level and cardiovascular risk in the NHLBI Family Heart Study. *Am J Physiol Heart Circ Physiol* 291(6):H2752-7, 2006.
57. Almeida OP, Norman PE, Allcock R, van Bockxmeer F, Hankey GJ, Jamrozik K, Flicker L. Polymorphisms of the CRP gene inhibit inflammatory response and increase susceptibility to depression: the Health in Men Study. *Int J Epidemiol* 38(4):1049-59, 2009.
58. Cathy C. Lee, Nai-chieh Yuko You, Yiqing Song, Yi-Hsiang Hsu, JoAnn Manson, Lauren Nathan, Lesley Tinker, and Simin Liu. Relation of Genetic Variation in the Gene Coding for C-Reactive Protein with its Plasma Protein Concentrations: Findings from the Women's Health Initiative Observational Cohort. Clin Chem 55(2): 351–360, 2009.
59. Coppinn H, Bensaid M, Fruchon S, Borot N, Blanché H and Roth MP. Longevity and carrying the C282Y mutation for haemochromatosis on the HFE gene: case control study of 492 French centenarians. *BMJ* 327(7407): 132–133, 2003.
60. Chicharro J, Hoyos J, Gomez-Gallego F, Villa J, Bandres F, Celaya P, Jimenez F, Alonso J, Cordova A, and Lucia A. Mutations in the hereditary haemochromatosis gene HFE in professional endurance athletes. *Br J Sports Med* 38(4): 418–421, 2004.