MyFitnessGenes®

HEARTGENETICS
GENETICS & BIOTECHNOLOGY

HEALTHY • LAB®

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Genetic Evaluation of Athletic Potential

CASE INDEX	
Name:	**N.A.**
Gender:	**N.A.**
Date of birth:	**N.A.**
Age:	**N.A.**
Ethnicity:	**N.A.**
Referral number:	**N.A.**
Reason:	**Training plan adequacy**
Purpose:	**Genetics of athletic performance**
Specimen type:	**N.A.**

CUSTOMER INSTITUTION	
Referring physician:	**N.A.**
Reference:	**N.A.**
Place of harvest:	**N.A.**
Referring facility:	**N.A.**
Requisition date:	**N.A.**
Fulfillment date:	**N.A.**

1. WHAT IS ANALYSED IN THIS GENETIC TEST?

This genetic test analyses DNA in order to evaluate 43 genetic variants from 34 genes. This test is 99% accurate and only needs to be performed once in a lifetime.

This test identifies the athletic genetic profile aiming to inform about athletic potential as well as preventive measures and needs.

The recommendations provided in this report can be used to guide you and your personal trainer to optimise your training plan.

2. IMPORTANT DISCLAIMER

Athletic performance is a concept used by athletes and sports amateurs that determines the ability to reach maximum athletic potential. The information on genetic predisposition should be integrated with information on physical characteristics (e.g. age, gender, muscle mass index, VO_2 max) and behaviour (e.g. eating habits, physical activity) in order to establish the best personalised training plan.

There is no evidence that genetic data can be used to determine sport talents. Existent research studies inform about what type of training works best to enable the established goals. HeartGenetics uses up-to-date information, and takes the latest research into consideration for genetic data interpretation. However, there is still much to be known about genetic profiles and sport talents.

The results of this genetic test do not depend on the physical or clinical condition or on the therapeutic management of the individual tested. The information supplied does not confirm nor replace any medical condition diagnosis or status, and cannot be used for disease prevention or clinical condition identification. In case of any questions regarding this report's information, or any concerns about the personal health or medical conditions, it is advised to contact a qualified healthcare professional.

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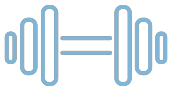
3. AREAS UNDER ANALYSIS



Power | power ability

Discover your genetic potential to exert substantial force in a short period of time and improve your power training performance.

Strength and sprint, fibre type, energy generation, metabolic efficiency, blood pressure regulation, cardiac output, muscle hypertrophy

Endurance | endurance capacity

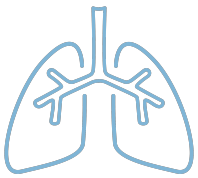
Discover if you are naturally suited to repeat an activity for an extended period of time without experiencing fatigue.

Cardiopulmonary capacity, blood pressure regulation, metabolic efficiency, fibre type, oxygen supply to muscles, fatigue tolerance, angiogenesis, muscular performance, running economy

Power-Endurance | muscular performance and power exercise ability

Discover if your genetic predisposition favours your performance in mixed aerobic-anaerobic sports, which rely on repeated sub-maximal muscle contraction.

Energy generation, oxygen supply to muscles, glucose homeostasis, lipid metabolism, blood pressure regulation, angiogenesis



VO_2 max | aerobic capacity

Understand your ability to perform dynamic and moderate- to high-intensity exercise that has an impact in your cardiorespiratory fitness.

VO_2 max, oxygen supply to muscles, fatigue tolerance

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Muscle Building | muscle growth capacity

Discover how easy it is for you to gain muscle strength following power training.

Muscle damage and regeneration, muscle hypertrophy, strength and power, muscle mass

Injury | injury proneness

Be aware if you have a predisposition to an increased rate of tendon and ligament injuries.

Soft tissue damage, tendinopathies and ligaments rupture

Recovery Needs | muscle regeneration capacity

Know how long it takes for your muscles to repair after exercising.

Muscle repair, collagen formation, inflammation, insulin signalling

Energy Refuel Needs | nutritional needs

Know about your nutritional needs and about the balance between training and the adequate intake of antioxidants or omega-3 fatty acids.

Antioxidant needs, PUFA needs

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4. YOUR GENETIC ATHLETIC PROFILE

This section presents your genetic predisposition associated with your athletic performance potential with two different views: 1) your "Athletic Potential"; 2) your "Preventive Measures and Needs". This genetic test identified 23 genetic variants (out of 43 analysed) with a significant impact in the definition of your athlete profile. Your genetic athletic profile leads to a clear set of actions that should be considered when defining personalised training recommendations, depending on your current level of physical activity, desired exercise intensity, and fitness goals. Consult your Fitness/Personal Trainer on how to leverage this capacity to improve your fitness routines.

Athletic Potential

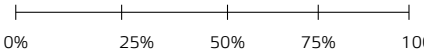
Power

Endurance

Power-Endurance

VO_2 max

Muscle Building

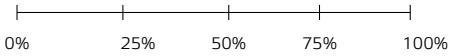


Preventive Measures and Needs

Injury

Recovery Needs

Energy Refuel Needs



If you find this symbol next to a bar, it means you have an exceptional profile in the area under evaluation.

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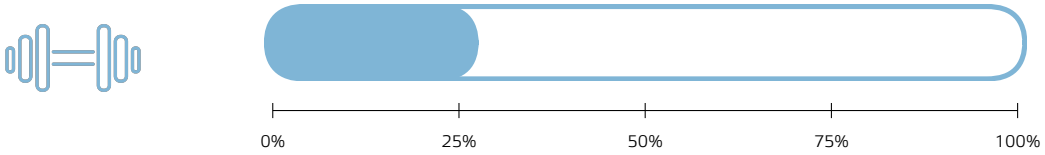
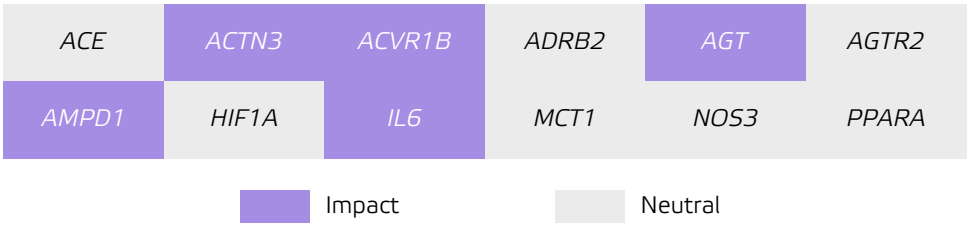
5. POWER



Power-oriented sports are those that require the production of maximal force over a short period of time. The powerful bursts of movements activate fast-twitch fibres, which contract rapidly and fatigue fast. Weightlifting, sprinting and short distance swimming are examples of power sports.

- Your genetic results indicate that you have a decreased potential towards power. If you wish to work further on this capacity you should include strength exercises in your workout routine, gradually increasing the intensity.
- Your genotype for the *ACTN3* gene is associated with a higher proportion of fast-twitch fibres, which are critical for the athletic performance in power-oriented sports.
- The recruitment of fast-twitch muscle fibres increases with exercise intensity. This recruitment promotes fibre conversion, favouring the fast-twitch ones. Therefore, you should focus on high-intensity training (closer to maximum aerobic capacity) if you want to maximize the development of fast-twitch fibres. By way of example, in a weightlifting workout you can do 2- 3 sets with 8-12 repetitions, choosing a weight that corresponds to a difficulty of 8 (on a scale of 1 to 10, 10 being the hardest effort you can give). The last repetition should be difficult to complete. You should consult your trainer in order to define a customised exercise plan.

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



Recommendation to training plan according to guidelines:

Advanced, intermediate or beginner level - Your genetic data shows a decreased affiliation with power-type activities. Power-type activities include many sports like sprinting, weight-lifting, powerlifting, etc. Your genes do not dictate that these sports should be avoided, but it is highly probable that you would have a much tougher time reaching the same performance as someone genetically predisposed to power activities. There are sports that involve power where you could excel at, for example mixed-type sports. While you may not have a genetic advantage for power, you can and should still include strength exercises in your daily routine, including body-weight exercises and strength/resistance exercises, among others. You should start with a full-body workout that gradually and safely allows you to build up to a more specific strength routine. Later, you can separate your workout by muscle groups. In order to prevent injuries, ensure to first focus on volume and then on intensity.

Recommendations according to the American College of Sports Medicine [1].

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The following table lists all variants whose identified result is relevant for this parameter:

Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
ACTN3	rs1815739	c.1729C>T	–	TC
ACVR1B	rs2854464	c.*997A>G	–	A
AGT	rs699	c.803T>C	p.Met268Thr	C
AMPD1	rs17602729	c.133C>T	p.Gln45Ter	C
IL6	rs1800795	c.-237C>G	–	G

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (http://www.ensembl.org).

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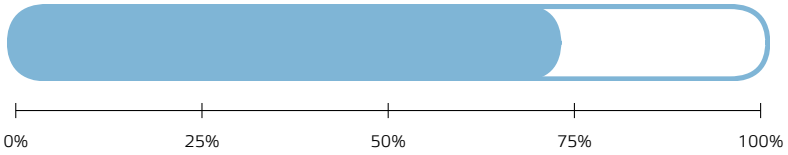
6. ENDURANCE



Endurance-oriented sports require low-force movements over extended periods of time. These movements activate slow-twitch muscle fibres, which rely on aerobic metabolism as a steady source of energy. Cycling and long-distance running or swimming are examples of endurance sports.

- Your genetic results indicate that you have an increased potential towards endurance. Your profile shares genetic variants with professional endurance athletes. You may excel at aerobic exercises such as distance running, road cyclism, thriathlon, etc.
- It was identified in your genome a variant of the *AGTR2* gene that is associated with a higher proportion of slow-twitch muscle fibres.
- Your genotype for the *PPARGC1A* gene is associated with a better response to endurance training, namely to the increase of slow-twitch muscle fibres.
- Individuals carrying the same *ACE* gene variant that was indentified in your genome show, on average, a higher proportion of slow-twitch muscle fibres.
- Your results show the presence of a *PPARA* gene variant associated with a higher mean percentage of slow-twitch muscle fibres.
- The recruitment of slow-twitch muscle fibres is maximised by low-intensity exercises, under 40% of maximal aerobic capacity This recruitment promotes fibre conversion, favouring the slow-twitch ones. A good way to promote muscle adaptation is to include in your routine, as a complement to training, brisk walking or light jogging, cycling or moderate swimming. During training, aerobic exercise should be adapted to maximize continuous exercise time. You should consult your trainer in order to define a customised exercise plan.

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

ACE	*ACTN3*	*ADRB2*	*AGTR2*	*BDKRB2*	*EDN1*
HIF1A	*MCT1*	*NRF1*	*PPARA*	*PPARGC1A*	*UCP2*
UCP3	*VEGFA*				

Impact Neutral

Recommendation to training plan according to guidelines:

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Advanced level - If you are involved in an endurance sport, be aware that your strengths most likely lie in the longer distance exercises. Within your current training programme, ensure that you stimulate your aerobic energy systems 4-6 days per week (depending on training background and fitness goals) turning it into the foundation of your training. To excel in your training, it is also important to include specific strength and conditioning, core stability and speed training.

Intermediate level - If you are involved in a training programme, be aware that your strengths may lie in longer distances, but you should increase the volume or intensity of your training gradually. Ensure that you stimulate your aerobic energy systems 3-5 days per week (depending on your training background and fitness goals) turning it into the foundation of your training. For a well-balanced training programme, it is also important to include specific strength and conditioning, core stability and agility training.

Beginner level - If you are new to physical exercise and although you have an increased genetic potential towards endurance, make sure you start a training programme that gradually and safely allows you to build up to about an hour of steady aerobic exercise. Within your future training regime, you can stimulate your aerobic energy system 2-4 days per week, turning it into the foundation of your training (if it converges with your fitness goals). For a well-designed training programme, make sure you include strength and conditioning exercises, core stability, balance and flexibility.

Recommendations according to the American College of Sports Medicine [1].

The following table lists all variants whose identified result is relevant for this parameter:

Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
ACE	rs4646994	c.2306-109_2306-108ins(289BP ALU)	–	DEL.INS
ADRB2	rs1042714	c.79C>G	p.Gln27Glu	C
AGTR2	rs11091046	c.*501A>C	–	C
BDKRB2	rs1799722	c.-192C>T	–	T
HIF1A	rs11549465	c.1744C>T	p.Pro582Ser	C
MCT1	rs1049434	c.1470T>A	p.Asp490Glu	A
NRF1	rs6949152	g.129286436A>G	–	A
NRF1	rs2402970	c.1348+12596C>T	–	C
PPARA	rs4253778	c.1160-396G>C	–	G
PPARGC1A	rs8192678	c.1459G>A	p.Gly487Ser	G

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (http://www.ensembl.org).

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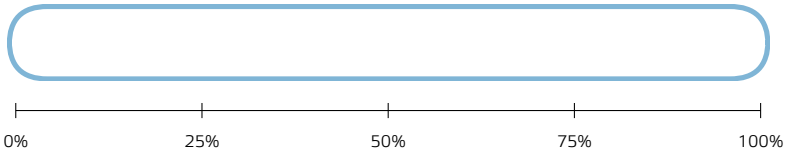
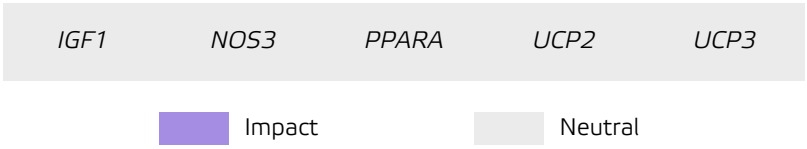
7. POWER-ENDURANCE



Power-endurance sports require sub-maximal muscle contraction over relatively long periods of time. Climbing and tennis are two examples of such type of sports. The biological mechanisms that impact on the performance of power and endurance sports are also relevant for power-endurance. As such, the results of sections **5. Power** and **6. Endurance** should be considered for an integrated analysis. The genetic variants studied in this section are considered to be more directly associated with power-endurance performance since they are described in the literature either in power-endurance athletes or favouring simultaneously power and endurance performance.

- Your genetic results indicate that you have a decreased potential towards power-endurance. In order to make the most of your genetic predisposition, you should perform cross-training by consistently including both endurance and power activities in your training program.

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



Recommendation to training plan according to guidelines:

Advanced, intermediate or beginner levels - Genetic data show a decreased predisposition for power-endurance-type activities, for example tennis, mixed martial arts or combat sports. Your genetic profile does not dictate that these sports should be avoided, but it is highly probable that you would have a much tougher time reaching the same performance as someone genetically predisposed to power-endurance activities. Consider mixed-type sports involving power-endurance, where you could have the possibility to excel. While you may not have a genetic advantage for power-endurance, make sure you practice specific strength exercises in your daily routine, including body-weight exercises and strength/resistance exercises that stimulate your local endurance ability. You should start with a full-body programme that gradually and safely allows you to build up to a more specific power-endurance routine. Later, you can alternate your fitness routine between interval and power training workouts.

Recommendations according to the American College of Sports Medicine [1].

No genetic variants with significant impact.

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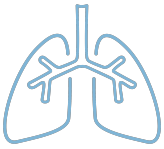
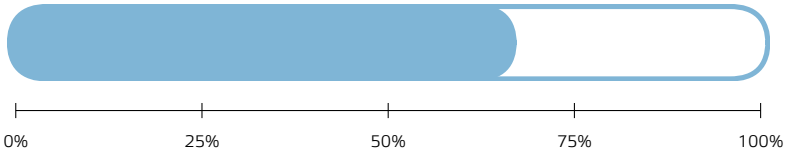
8. VO_2 MAX





- Your genetic results indicate that you have a typical potential towards maximal oxygen uptake response as a result of aerobic training. However, you can improve your oxygen uptake efficiency by engaging in consistent and moderate aerobic conditioning.

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:

Recommendation to training plan according to guidelines:

Advanced level - If you are a high performance athlete or have been under the supervision of a fitness or personal trainer for a long time, in order to make the most of your natural aerobic capacity, you should cross-train by consistently including both endurance and power activities in your training programme. The resting intervals between exercises should be longer at first and shortened gradually. Make sure to work out at around 70-85% of your target heart rate. In order to calculate your target heart rate, you must first determine your maximum heart rate which is: 208 - (0.7 x Age) [2]. To excel at this capacity, it is important to include specific strength and conditioning, core stability and speed training.

Intermediate level - If you are an athlete or under the supervision of a fitness or personal trainer for quite some time, you can include both endurance and power activities in your training programme to improve your intermediate VO_2 max. The resting intervals between exercises should be longer at first and shortened gradually. Make sure to work out at around 65-80% of your target heart rate. In order to calculate your target heart rate, you must first determine your maximum heart rate which is: 208 - (0.7 x Age) [2]. For a well-balanced training programme, it is also important to include specific strength and conditioning, core stability and agility training.

Beginner level - If you are new to physical exercise and if you have a typical genetic potential towards VO_2max, make sure to start a training programme that gradually and safely allows you to build up to half an hour of consistent aerobic exercise. Since you are new to exercise, ensure to work out at around 60% of your target heart rate. In order to calculate your target heart rate, you must first determine your maximum heart rate which is: 208 - (0.7 x Age) [2]. For a well-balanced training programme, it is also important to include specific strength and conditioning, core stability and agility training.

Recommendations according to the American College of Sports Medicine [1].

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The following table lists all variants whose identified result is relevant for this parameter:

Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
AGTR2	rs11091046	c.*501A>C	–	C
HIF1A	rs11549465	c.1744C>T	p.Pro582Ser	C
PPARGC1A	rs8192678	c.1459G>A	p.Gly487Ser	G
VEGFA	rs2010963	c.-94C>G	–	CG

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (`http://www.ensembl.org`).

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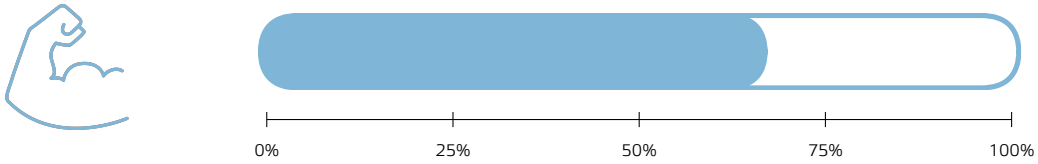
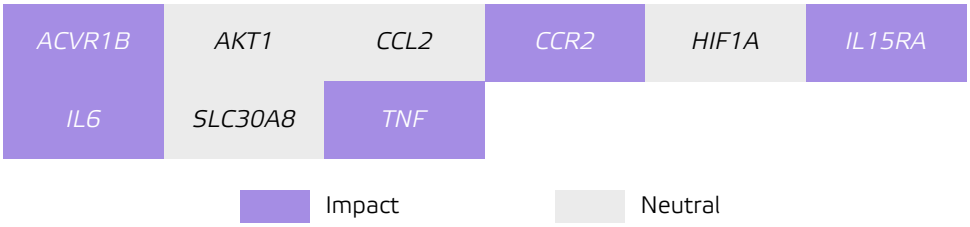
9. MUSCLE BUILDING



- Your genetic results indicate you have a typical potential towards muscle building. You should have the capacity to undertake a moderate training load.

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



Recommendation to training plan according to guidelines:

Advanced level - If you are already practicing a specific workout routine where the focus is on muscle hypertrophy, consider working out 4-5 times a week depending on how you organise your workout programme. Remember that the process of muscle growth occurs while you rest. Ensure giving your muscle groups at least 48 hours rest so they can recover and reconstruct properly. It is important to get an adequate amount of protein and aminoacid intake after you exercise to rebuild your muscles.

Intermediate level - If you have been practicing a specific workout routine for just a while, consider working out 3-4 times a week, depending on how you organise your workout programme and what your fitness goals are. Remember that the process of muscle growth occurs while you rest. Ensure giving your muscle groups at least 72 hours rest so they can recover and reconstruct properly. It is important to get an adequate amount of protein and aminoacid intake after you exercise to rebuild your muscles.

Beginner level - If you are new to physical exercise, consider starting your fitness programme with a general focus on both strength and endurance exercises 1-3 times a week. If you start to work out towards specific hypertrophy training, you may get injured because your body is not fully prepared to undertake that kind of training intensity yet. It is important consider an adequate recovery time and an adequate nutritional plan.

Recommendations according to the American College of Sports Medicine [1].

The following table lists all variants whose identified result is relevant for this parameter:

Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
ACVR1B	rs2854464	c.*997A>G	–	A
CCR2	rs3918358	g.46394419C>A	–	A

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CCR2	rs768539	–	–	C
IL15RA	rs2296135	g.5994694A>C	–	CA
IL6	rs1800795	c.-237C>G	–	G
TNF	rs1800629	c.-488G>A	–	G

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (http://www.ensembl.org).

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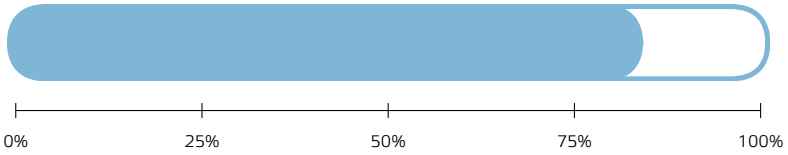
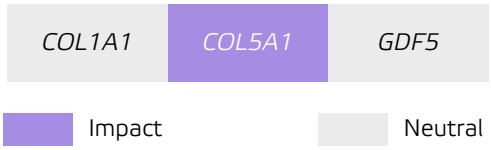
10. INJURY



- Your genetic results indicate that you have a predisposition for an overall increased risk of exercise related soft tissue injury. Therefore, this should be taken into consideration when planning your training. Strength and resistance exercises are important for strengthening bones, muscles and connective tissue, reducing injury risk. In addition, you could include flexibility workout in order to prevent joint or tendon injuries and improve your maximal Range of Motion (ROM). According to the American College of Sports Medicine, flexibility exercises improve ROM not only acutely but also chronically.
- The analysis of your genetic predisposition for lesions should be complemented with your results from section **11. Recovery**, which inform about the tendency to a marked inflammatory process after a strenuous workout. This inflammatory process results in a temporary reduction of muscle force and consequent decrease in physical performance, which increases the risk of muscle injury when training the same muscle group without ensuring enough time for proper muscle regeneration [3].

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



Recommendation to training plan according to guidelines:

Genetic susceptibility to injury does not automatically mean poorer athletic potential, but it does mean that a more balanced training programme is required. Strong emphasis should be given to recovery strategies and conditioning exercises.

Advanced level - If you are an elite athlete, consider following a sport-specific conditioning exercise routine 3-4 times/week.

Intermediate level - If you practice sports or exercise regularly, make sure to workout 2-3 times per week for general conditioning.

Beginner level - If you are new to physical exercise, make sure you have a well-designed exercise routine that includes strength training, mobility and joint flexibility. Take care not to over-exercise or exceed your body's limits. You are recommended to give your body time to adjust to new exercises and make sure you learn the techniques properly.

Never skip the warm-up and you should increase warm-up volume and intensity in colder environmental conditions. Increase speed, strength and power gradually during the warm-up. Consider doing flexibility exercises after a complete warm-up. If you are doing both aerobic and weight training, practice aerobic exercises first. Avoid increasing the volume and intensity of your workouts at the same time. Be sure to recover fully before starting a high intensity training. It has also been suggested that optimal hydration before and after exercise may prevent ligament injury. Consult a sports physician or a personal trainer on how to best strengthen your joints, tendons, ligaments and muscles. Use massage or ice packs to reduce inflammation (on the advice of a qualified professional). Always warm up, stretch, strengthen your muscles, and work on agility, change of direction and speed.

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Recommendations according to the American College of Sports Medicine [1].

The following table lists all variants whose identified result is relevant for this parameter:

Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
COL5A1	rs12722	c.*267C>T	–	T

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (http://www.ensembl.org).

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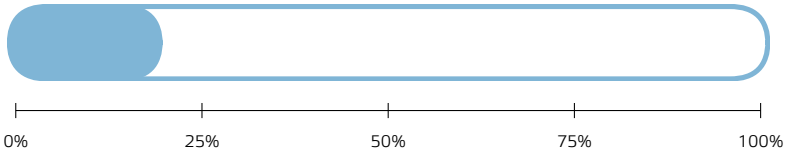
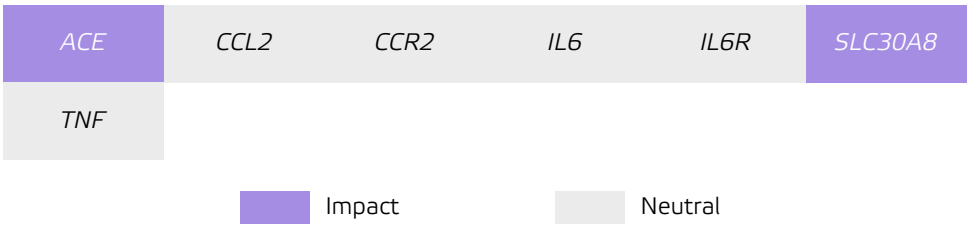
11. RECOVERY NEEDS



- Your genetic results indicate you have a decreased recovery needs, which means that you have a predisposition to recover at a faster rate from exercise. You should have the capacity to undertake a higher training load, with higher inputs of exercise. Although, it is important to provide sufficient recovery time before the next training session. It is important to be noted that training performance depends from genetic factors and training capacity over the course of years.

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



Recommendation to training plan according to guidelines:

Advanced, intermediate or beginner level - You have a low genetic predisposition towards muscle soreness and enhanced muscle repair and/or recovery. You can increase the intensity or volume of your workouts more quickly than most. Consider practicing high intensity training and concentrating your workouts on strength/force/speed training. You need shorter periods of recovery between your workout routines (24 hours or less, depending on how strenuous your workout was or in what phase of your athletic preparation you are, 24-48 hours if your goal is to increase your muscle size). "Recovery" does not necessarily mean not doing exercise either. When recovering, practice yoga, pilates, light jogging or swimming, depending on your level of fitness.

Recommendations according to the American College of Sports Medicine [1].

The following table lists all variants whose identified result is relevant for this parameter:

Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
ACE	rs4646994	c.2306-109_2306-108ins(289BP ALU)	–	DEL.INS
SLC30A8	rs13266634	c.826C>T	p.Arg276Trp	C

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (http://www.ensembl.org).

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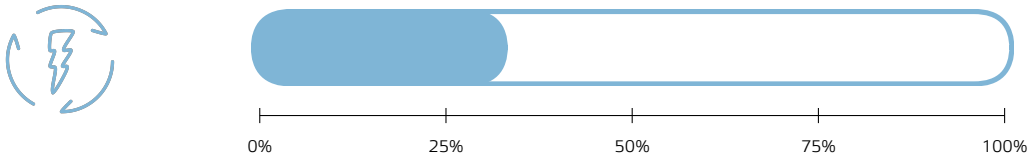
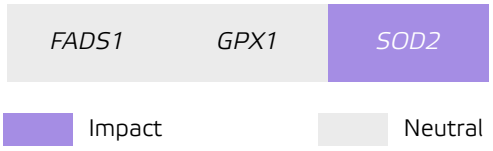
12. ENERGY REFUEL NEEDS



- Your genetic results indicate that you have a predisposition for a typical requirement of energy refuel. It is important to repair your muscles through an adequate nutritional support before the next training session.

The following diagram shows the genes that contribute to this parameter, i.e. those with impact, among all evaluated:



FADS1: Omega-3 needs
Your genetic profile predisposes for a normal requirement of dietary intake of long chain omega-3 fatty acids.

GPX1: Antioxidants needs
Your genotype for this gene predisposes for a normal requirement of dietary antioxidant intake.

SOD2: Antioxidants needs
According to your genetic predisposition, you are likely to benefit from an increased dietary intake of selenium and antioxidants, including vitamin C and polyphenols. This way you can delay muscle fatigue, prevent exercise-induced oxidative damage and promote recovery at the same time. Current evidences indicate that reactive oxygen species (ROS) are one of the primary sources of exercise-induced damage related to the muscle redox balance, as they promote oxidative injury and muscle fatigue. Several studies have showed that antioxidant-rich supplements attenuate the inflammatory effects of exercise by promoting muscle recovery and diminishing fatigue. However, a topic of discussion in sports nutrition is whether the use of supplements may compromise the natural recovery processes. It is known that dietary supplements can augment natural antioxidant capacities in the case of very intense demands associated with endurance training. As there is a cooperative interaction between endogenous antioxidants and dietary antioxidants, the last may improve the muscle fibre's ability to scavenge ROS and protect the exercising muscle against exercise-induced oxidative damage and fatigue. In turn, some studies showed that antioxidant supplementation may interfere with the cell-signalling function of ROS, and therefore prevent the adaptations that are necessary for performance improvements. Further studies are needed to resolve this controversy.

The following table lists all variants whose identified result is relevant for this parameter:

Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Result
SOD2	rs4880	c.47T>C	p.Val16Ala	T

[1] The identification associated with each genetic variant is indexed to a reference sequence from the Ensembl database (http://www.ensembl.org).

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13. TECHNICAL INFORMATION

13.1. METHODOLOGY

1. The DNA extraction was done in the automatic extraction equipment MagNA Pure Compact (ROCHE) through the use of the MagNA Pure Compact Nucleic Acid Isolation Kit I kit (ROCHE). The concentration and quality evaluation was done through the use of the Spectrophotometer MultiskanGo (Thermo Scientific).
2. Genotyping was made via the study of 43 genetic variants in 34 genes, described as associated with athletic potential.
3. Genotyping was achieved using a high-throughput DNA Microchip platform, the iPLEX® MassARRAY® system (Agena Bioscience, Inc.). This array platform allows an optimal genetic analysis by combining the benefits of accurate primer extension chemistry with MALDI-TOF mass spectrometry. The different masses of each generated PCR product are then converted into genotype information.
4. In accordance with Agena Bioscience's iPLEX® chemistry flyer, the MassARRAY® system performs SNP genotyping with a high level of accuracy and reproducibility (>99% accuracy on validated assays).

13.2. GENETIC PANEL

ACE	**angiotensin I converting enzyme** | NM_000789
ACSL1	**acyl-CoA synthetase long-chain family member 1** | NC_000004
ACTN3	**actinin alpha 3 (gene pseudogene)** | NM_001104
ACVR1B	**activin A receptor type 1B** | NM_004302
ADRB2	**Adrenoceptor Beta 2** | ENSG00000169252
AGT	**angiotensinogen** | NM_000029
AGTR2	**angiotensin II receptor type 2** | NM_000686
AKT1	**AKT serine threonine kinase 1** | NM_005163
AMPD1	**adenosine monophosphate deaminase 1** | NM_000036
BDKRB2	**bradykinin receptor B2** | NM_000623
CCL2	**C-C motif chemokine ligand 2** | NC_000017
CCR2	**C-C motif chemokine receptor 2** | NC_000003
COL1A1	**collagen type I alpha 1 chain** | NM_000088
COL5A1	**collagen type V alpha 1 chain** | NM_000093
EDN1	**endothelin 1** | NM_001955
FADS1	**Fatty Acid Desaturase 1** | NM_013402.4
GDF5	**growth differentiation factor 5** | NM_000557.3
GPX1	**glutathione peroxidase 1** | NM_000581.3
HIF1A	**hypoxia inducible factor 1 alpha subunit** | NM_001530
IGF1	**insulin like growth factor 1** | NM_000618
IL15RA	**interleukin 15 receptor subunit alpha** | NC_000010
IL6	**interleukin 6** | NM_000600.3
IL6R	**interleukin 6 receptor** | NM_000565
MCT1	**solute carrier family 16 member 1 (SLC16A1)** | NM_001166496
NOS3	**nitric oxide synthase 3** | NM_000603
NRF1	**nuclear respiratory factor 1** | NC_000007
PPARA	**peroxisome proliferator activated receptor alpha** | NM_001001928
PPARGC1A	**peroxisome proliferator-activated receptor gamma, coactivator 1 alpha** | NM_001330751
SLC30A8	**Solute Carrier Family 30 Member 8** | NM_001172811.1
SOD2	**Superoxide Dismutase 2, Mitochondrial** | NM_000636.2
TNF	**tumor necrosis factor** | NM_000594
UCP2	**uncoupling protein 2** | NM_003355
UCP3	**uncoupling protein 3** | NM_003356
VEGFA	**vascular endothelial growth factor A** | NM_001025366

13.3. RISKS AND LIMITATIONS

HeartGenetics, Genetics and Biotechnology SA applies a rigorous quality control which may not exclude the possibility of error that might influence the test results. The reliability of the results is always guaranteed as HeartGenetics, Genetics and Biotechnology SA standard quality recommendations have been followed for the execution of this genetic test. The results presented in this report are limited to the available scientific knowledge at the time this test was developed. The company guarantees the accuracy of the scientific knowledge presented in the report. It has been assumed as truthful all the above declarations about the individual and healthcare professional identity, the purpose of the study, index case and nature of analysed biological products.

13.4. QUALITY ASSURANCE

HeartGenetics, Genetics and Biotechnology SA is an ISO 9001 and ISO 13485 certified company for Quality Management System and applies an External Quality Assessment program from UK NEQAS. The laboratory that performs this genetic test complies, at all times, with all the applicable certifications and Law in its territory.

13.5. TERMS AND CONDITIONS

HeartGenetics, Genetics and Biotechnology SA will not be liable whether in contract, tort, warranty, or under any statute, or any other basis of special, incidental, indirect punitive, multiple, or consequential damages in connection with in arising from this document, or improper use of the product described herein or any use of such product outside the scope of the express written licenses or permissions granted by HeartGenetics, Genetics and Biotechnology SA, to the extent allowed by law.
The results presented in Section 13.6, Genetic Information, are the responsibility of the laboratory that performed the genetic test.

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13.6. GENETIC INFORMATION

The table below presents the genetic variants that have been identified as relevant for the design of a personalised training plan. The results are described according to the HGVS nomenclature (http://www.hgvs.org), accessed on February 2019.

No other molecular markers from the genetic panel were identified with impact on athletic potential, than those shown in the table.

Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Impact allele
ACE	rs4646994	c.2306-109_2306-108ins(289BP ALU)	–	DEL.INS
ACTN3	rs1815739	c.1729C>T	–	TC
ACVR1B	rs2854464	c.*997A>G	–	A
ADRB2	rs1042714	c.79C>G	p.Gln27Glu	C
AGT	rs699	c.803T>C	p.Met268Thr	C
AGTR2	rs11091046	c.*501A>C	–	C
AMPD1	rs17602729	c.133C>T	p.Gln45Ter	C
BDKRB2	rs1799722	c.-192C>T	–	T
CCR2	rs3918358	g.46394419C>A	–	A
CCR2	rs768539	–	–	C
COL5A1	rs12722	c.*267C>T	–	T
HIF1A	rs11549465	c.1744C>T	p.Pro582Ser	C
IL15RA	rs2296135	g.5994694A>C	–	CA
IL6	rs1800795	c.-237C>G	–	G
MCT1	rs1049434	c.1470T>A	p.Asp490Glu	A
NRF1	rs2402970	c.1348+12596C>T	–	C
NRF1	rs6949152	g.129286436A>G	–	A
PPARA	rs4253778	c.1160-396G>C	–	G
PPARGC1A	rs8192678	c.1459G>A	p.Gly487Ser	G
SLC30A8	rs13266634	c.826C>T	p.Arg276Trp	C
SOD2	rs4880	c.47T>C	p.Val16Ala	T
TNF	rs1800629	c.-488G>A	–	G
VEGFA	rs2010963	c.-94C>G	–	CG

[1] The numeric identification associated with each variant is indexed to a reference sequence obtained from Ensembl database (http://www.ensembl.org/index.html).

The table below presents the genetic variants that have no impact on the definition of your training plan.

Gene	Ensembl	Nucleotidic change [1]	Aminoacidic change	Impact allele
ACSL1	rs6552828	g.184804262A>G	–	GA
ADRB2	rs1042713	c.46A>G	p.Arg16Gly	AG
AKT1	rs1130214	c.-350G>T	–	G
CCL2	rs13900	c.*65C>T	–	C
CCL2	rs1860189	–	–	T
CCL2	rs3917878	g.32578855C>T	–	C
COL1A1	rs1800012	c.104-441G>T	–	G
EDN1	rs5370	c.594G>T	–	G
FADS1	rs174546	g.61802358C>T	–	C
GDF5	rs143383	c.-275C>T	–	CT
GPX1	rs1050450	c.599C>T	p.Pro200Leu	C
IGF1	rs35767	c.-1410T>C	–	C
IL6R	rs2228145	c.1073A>C	p.Asp358Ala	A
NOS3	rs1799983	c.894T>G	p.Asp298Glu	GT
NOS3	rs2070744	c.-51-762C>T	–	CT
PPARGC1A	rs6821591	c.*445G>A	–	GA
TNF	rs1799964	c.-1211T>C	–	T
TNF	rs1800630	c.-1043C>A	–	C
UCP2	rs660339	c.164C>T	p.Ala55Val	C
UCP3	rs1800849	c.-238C>T	–	C

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[1] The numeric identification associated with each variant is indexed to a reference sequence obtained from Ensembl database (`http://www.ensembl.org/index.html`).

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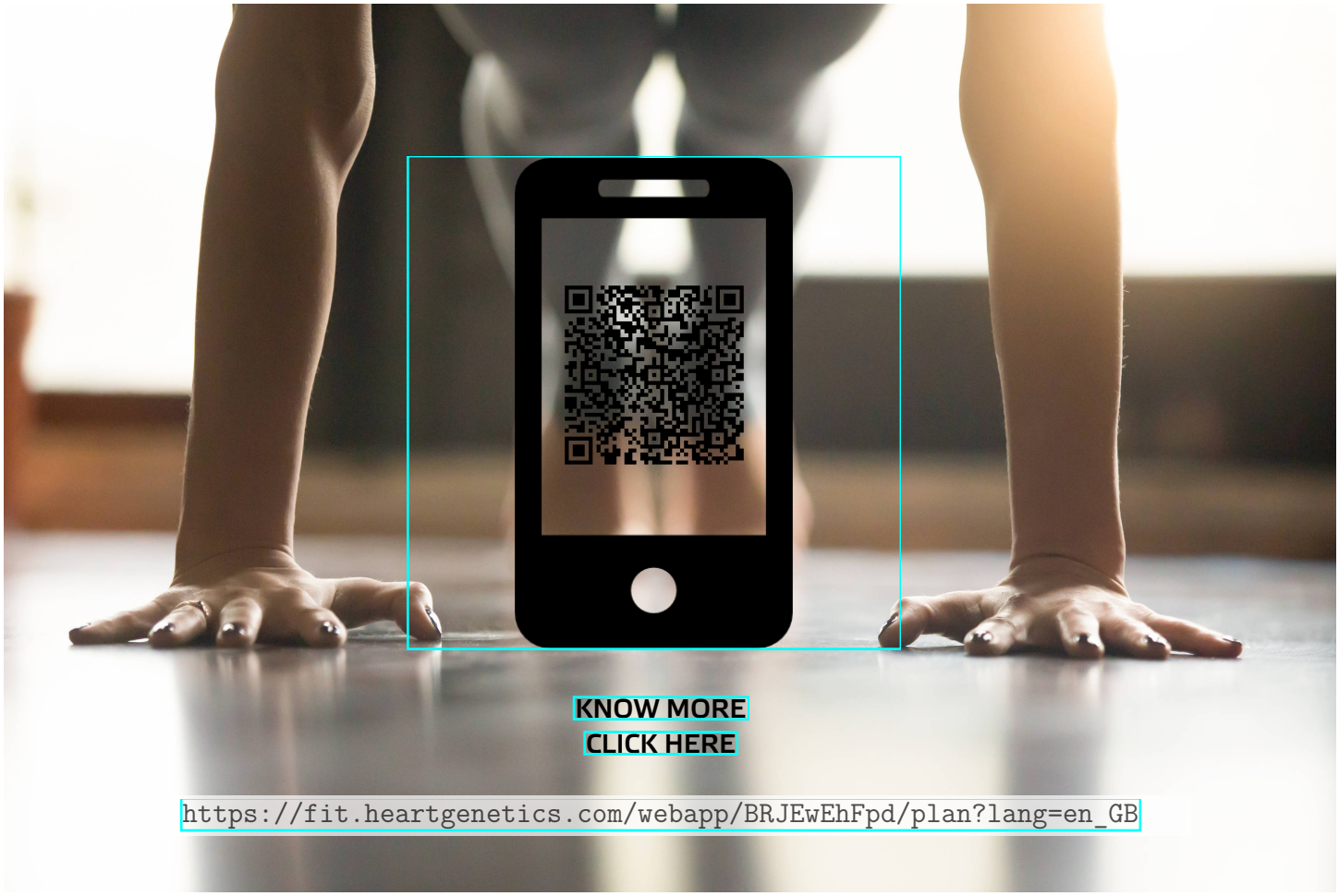

14. APPENDIX

14.1. EVIDENCES FOR MOLECULAR MARKERS

This appendix includes a detailed interpretation of the genetic study. All evidences are supported through scientific articles indexed in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) accessed in February 2019.

ACE / rs4646994

ENDURANCE: Increased Endurance Performance, Fibre Type (Type I)

The *ACE* gene codes for angiotensin-I converting enzyme, a key enzyme of the renin-angiotensin system responsible for controlling blood pressure [4]. The ACE enzyme gene converts inactive angiotensin I into active angiotensin II in the liver and degrades bradykinin and other vasodilator peptides. It modulates vasoconstriction, salt and water balance, red blood cell production (erythropoiesis), inflammation, tissue oxygenation, and muscle efficiency [5]. The rs4646994 polymorphism refers to the absence (deletion, D allele) or the presence (insertion, I allele) of a 287-base-pair fragment in the *ACE* gene [6, 7]. The I-allele (genotype ID or II) is associated with lower ACE serum levels and lower ACE activity in tissues [6, 8]. The ACE II or ID genotypes are consistently associated with endurance performance and higher exercise efficiency and with greater strength gains in response to training [9, 10]. These genotypes are associated with greater improvements in medium duration aerobic performance [11], as well as with an increase in effectiveness of muscles and an increase in the proportion of free fibres (type I muscle fibres) [12]. It must be noted that, in overall performance, other genetic polymorphisms related to the ACE genotype, such as polymorphisms in the bradykinin 2 gene, also influence skeletal muscle strength [13]. Moreover, it was observed that after eccentric exercise, the II or ID genotype carriers have the higher CK response after strenuous exercise, suggesting that I-allele is associated with a greater susceptibility to muscle damage. It is important to remember that CK level is only one of several indirect biomarkers for exercise-induced muscle damage [14, 15]. Angiotensin-II is known to be involved in inflammatory processes following muscle damage [16] mediating skeletal muscle damage by influencing angiogenesis in response to exercise. It is well known that, in a damaged muscle in the days following eccentric exercise, resting capillary blood flow is elevated and vasodilatation occurs. The capillary density of skeletal muscle is lower in untrained carriers of the ACE I-allele compared to DD carriers. Lower capillary density might impair the migration of neutrophils and macrophages as well as the removal of cellular debris, which could negatively affect the extent of muscle damage and possibly

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muscle remodelling [17].

ACTN3 / rs1815739

POWER: Increased Power Performance, Strength

ACTN3 encodes for a key protein of the sarcomeric Z-line in skeletal muscle. It is considered the world's most famous "gene for speed". Expression of α-actinin-3 is limited to type II muscle fibres (i.e. fast-twitch, mostly glycolytic) which can generate more force at high velocity [10, 18]. The rs1815739 polymorphism is a C to T substitution that results in the conversion of the codon for arginine (R) at position 577 to a premature stop codon (X) (R577X) [19]. The R-allele codes for a functional α-actinin-3 protein whereas the X allele results in α-actinin-3 deficiency [19]. Studies have demonstrated that the frequency of the RR genotype is higher in power and sprint athletes than in controls and endurance athletes [18]. The R-allele (genotypes RR or RX) has been consistently associated with greater muscle strength, explosive power, and elite power and sprint performance [8, 18, 20, 21, 22, 23, 24, 25]. α-actinin-3 was also suggested to play a role in the determination of muscle fibre type, with the R-allele being associated with an increased proportion of fast-twitch fibres [18, 26] that probably justifies the more dynamic muscle power (power output) demonstrated by athletes with the RR genotype and their advantage in power performance [25].

ACVR1B / rs2854464

POWER: Increased Power Performance, Strength, Sprint

MUSCLE BUILDING: Muscle Strength

The activin receptor type-1B, encoded by the *ACVR1B* gene, has a key a role in regulating the signaling of myostatin, which is in turn a potent regulator of skeletal muscle mass [27, 28]. It is therefore considered a muscle strength gene and a potential regulator of the adaptation to resistance exercise. Genetic studies demonstrated that genetic variations in *ACVR1B* gene influence human muscle strength [29, 30]. The A-allele (genotype AA or GA) was found to be differently associated with sprint and power performance in a large cohort of Caucasian and Brazilian athletes. The A allele is overrepresented in Caucasian (Italian, Polish, and Russian) sprint and power athletes, and this association is even more pronounced when only elite-level athletes are considered [30]. This association was, however, found likely to be ethnicity-dependent due to an observed trend towards an underrepresentation of the A allele in sprint and power Brazilian athletes [30]. In addition, carriers of AA genotype, from the Leuven Genes for Muscular Strength study (LGfMS) cohort, demonstrated higher knee strength compared with G-allele carriers [29]. Enhanced strength with regard to dynamic knee extensor strength was also observed for the AA genotype in follow-up replication analyses in an independent but size-limited study [29].

ADRB2 / rs1042714

ENDURANCE: Increased Endurance Performance, Vasodilatation

Beta-2 adrenergic receptor (ADRB2) is a member of the G protein-coupled receptor superfamily and plays a functional role in the regulation of the cardiac and pulmonary responses as well as the appropriate substrate metabolism required for athletic ability. ADRB2 is a major lipolytic receptor in adipocytes, regulating energy expenditure from adipose tissue upon catecholamine binding [31]. Catecholamine levels increase markedly during physical exercise [32]. Genetic polymorphisms that affect ADRB2 function are therefore likely to interact with exercise, i.e. to modulate the response to training interventions. In particular, the CC genotype of the *ADRB2* rs1042714 SNP was shown to be more frequent among elite endurance athletes and associated with higher VO_2max consumption [33]. Carriers of this genotype are therefore more likely to excel in endurance-oriented activities rather than in power sports.

AGT / rs699

POWER: Increased Power Performance, Strength, Sprint, Blood Pressure Regulation

Angiotensinogen is an essential component of the renin-angiotensin system that regulates vascular resistance and sodium homeostasis, thus contributing to blood pressure responses to exercise and being denoted associations with skeletal and cardiac muscle growth. The C-allele (genotype CC or CT) is associated with power related phenotypes favouring power and strength sports performance. These individuals have a greater response to specific strength and power training exercises compared to endurance sports. Studies have shown that their training is better suited around low repetition work, or an increased load. This could be attributed to the higher activity of angiotensin II, a skeletal muscle growth factor [34, 34, 35, 36, 37, 38, 39, 40]. Data also show that the C-allele carriers have a greater ratio strength:muscular size [39, 40]. In addition, studies also demonstrate that carriers of the C-allele benefit from training to reduce submaximal exercise diastolic blood pressure in greater levels compared to TT.

AGTR2 / rs11091046

ENDURANCE: Increased Endurance Performance, Fibre Type

VO_2 MAX: Relative Maximal Oxygen Uptake

The *AGTR2* gene encodes for an integral membrane protein that functions as a receptor for angiotensin II. The accumulated evidence suggests that the role of this type-2 receptor opposes that of the type-1, thereby being involved in vasodilation and vasoprotection, and associated with anti-proliferative, anti-hypertrophic, anti-oxidative and anti-fibrotic processes [41, 42, 43, 44]. This gene is located on chromosome X, which means that females carry two alleles for this polymorphism (CC, CA or AA genotypes), whereas males are hemizygotes, i.e. only harbour one allele (C or A). The CC genotype and the C allele are significantly more frequent in female and male endurance athletes, respectively, compared with power athletes and control subjects, being therefore associated with better aerobic performance (higher VO_2max) and increased proportion of slow-twitch muscle fibres [45].

AMPD1 / rs17602729

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POWER: Increased Power Performance, Sprint
AMPD1 encodes for a skeletal muscle-specific isoform of adenosine monophosphate deaminase. This enzyme, known as a muscle energy metabolism regulator during exercise, plays a key role in anaerobic capacity. The *AMPD1* rs17602729 polymorphism is a C to T transition that causes a premature stop codon, resulting in an abnormally short (truncated) protein and therefore in AMPD deficiency [46]. C-allele (genotype TC or CC) carriers are therefore able to produce functional AMPD and have a better response to exercise, as demonstrated by a slower power decrease in a 30s Wingate cycling test compared with those with TT genotype [47]. In addition, the C allele is more frequent among sprint- and power-oriented athletes compared with those mixed and endurance-oriented, and therefore may predispose athletes to attain elite status in sprint- and power-oriented sports [48, 49]. This polymorphism is more common in Caucasian populations.

BDKRB2 / rs1799722

ENDURANCE: Increased Endurance Performance, Blood Pressure Regulation
The *BDKRB2* gene encodes a receptor for bradykinin, a pro-inflammatory vasodilator polypeptide that acts locally to modulate peripheral vascular resistance and tissue blood flow. The activation of this gene is also thought to increase glucose uptake by skeletal muscle during exercise [50, 51]. The T-allele (genotype TT or TC) promotes an increase of the transcription rate of *BDKRB2* [52]. The TT or TC genotypes were found to be overrepresented in a cohort of endurance athletes, and hence associated with an increased predisposition to excel at endurance-oriented activities [53].

CCR2 / rs3918358

RECOVERY: Inflammatory Response
MUSCLE BUILDING: Muscle Hypertrophy, Muscle Size, Exercise Induced Muscle Damage, Muscle Strength - Benefit
CCR2, chemokine (C-C motif) receptor 2, also known as Monocyte Chemoattractant Protein 1 Receptor (MCP1-R), binds CCL2 (chemokine (C-C motif) ligand 2) and can be classified as an exercise factor, as it mediates systemic changes induced by exercise training [54]. It is considered a potential inflammatory mediator of muscle growth as a significant upregulation of CCR2 is found after muscle injury and during muscle regeneration [55, 56, 57, 58]. *CCR2* polymorphisms are interesting to evaluate with respect to muscle size and strength gain in response to resistance exercise, given that satellite cell activation by macrophages is a critical step in muscle repair and subsequent growth [59]. CCR2 is mainly expressed within the interstitial space between myofibres following muscle damaging exercise, a strong interaction being noticed between CCL2/CCR2 and the immune response after muscle damage [60, 61]. In individuals with the AA genotype, the response of 1-RM strength to the 12-wk training programme was greater [62].

CCR2 / rs768539

RECOVERY: Inflammatory Response
MUSCLE BUILDING: Muscle Hypertrophy, Muscle Size, Exercise Induced Muscle Damage, Muscle Strength
CCR2, chemokine (C-C motif) receptor 2, also known as Monocyte Chemoattractant Protein 1 Receptor (MCP1-R), binds CCL2 (chemokine (C-C motif) ligand 2) and can be classified as an exercise factor, as it mediates systemic changes induced by exercise training [54]. It is considered a potential inflammatory mediator of muscle growth as a significant upregulation of CCR2 is found after muscle injury and during muscle regeneration [55, 56, 57, 58]. *CCR2* polymorphisms are interesting to evaluate with respect to muscle size and strength gain in response to resistance exercise, given that satellite cell activation by macrophages is a critical step in muscle repair and subsequent growth [59]. CCR2 is mainly expressed within the interstitial space between myofibres following muscle damaging exercise, a strong interaction being noticed between CCL2/CCR2 and the immune response after muscle damage [60, 61]. Novel eccentric (lengthening contraction) exercise typically results in muscle damage, which manifests as prolonged muscle dysfunction, delayed onset muscle soreness, and leakage of muscle proteins into circulation [60, 63, 64]. *CCR2* polymorphisms are associated with exercise-induced skeletal muscle damage markers. The CC genotype is associated with higher values for pretraining muscle quality in men and with higher 1-RM strength in women [62].

COL5A1 / rs12722

INJURY: Tendinopathies And Ligament Ruptures - Injury Risk
Type V collagen is a minor component of tissues containing type I collagen, such as skin, tendons, ligaments, bone, and blood vessels [65]. Range of motion (ROM) is considered to be one of the factors associated with musculoskeletal performance, and musculoskeletal flexibility is defined as the ability to move a joint through its complete ROM [1, 66]. *COL5A1* polymorphims are associated with running performance, Achilles tendon injuries and ROM [67]. TT genotype is associated with collagen fibres containing smaller and more densely packed fibrils and hence a reduced joint ROM and increased risk of specific musculoskeletal soft tissue injuries. The causes of "increased risk" phenotype may be the result of increased musculotendinous stiffness and decreased ROM [68]. Individuals with a TT genotype would have less extensible tendon structures, resulting in a lower range of motion (ROM) compared to individuals with at least one copy of the C allele [67].

HIF1A / rs11549465

ENDURANCE: Increased Endurance Performance
VO_2 MAX: Maximal Oxygen Uptake
Hypoxia-inducible factor 1 alpha (HIF-1-α) is a transcription factor that regulates gene expression in response to hypoxia, meaning an inadequate oxygen supply to the cells and tissues of the body [69, 70]. *HIF1A* rs11549465 polymorphism is associated with athletic performance, and might be related to a greater responsiveness to endurance training [70, 71, 72]. In the Genathlete cohort, an association was found between elite endurance athletes and CC genotype [72]. An intervention study showed that the C-allele (genotype CC or CT) is associated with VO_2 max before and after 24 weeks of aerobic exercise training in elderly people. Carriers of CC genotype aged 60 and over exhibited significantly greater changes in VO_2 max after training than those carrying the TT genotype [71]. Moreover, sprint performance was found to be positively influenced by an interaction effect

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between the CC genotype of both *HIF1a* rs11549465 and *ACTN3* R577X polymorphisms [72].

IL15RA / rs2296135

MUSCLE BUILDING: Muscle Hypertrophy, Muscle Strength

Interleukin-15 (IL-15) is one of the most abundant cytokines in skeletal muscle with anabolic properties. It is a growth factor that stimulates the proliferation of T-lymphocytes; and it is involved in the regulation of the immune response. Increased levels of IL-15 are associated with muscle growth and are increased immediately after exercise [73]. Scientific evidence demonstrated associations between IL-15 and IL-15 α-receptor (*IL15RA*) gene polymorphisms with muscle and strength phenotypes. For instance, the polymorphism rs2296135 is strongly associated with muscle hypertrophy, although those subjects with the greatest hypertrophy had lower muscle strength and muscle quality increases. The C-allele (genotype CA or CC) is associated with training induced strength gains in women and with lean body mass in men and women after resistance training [74, 75, 76, 77]. This polymorphism is therefore gender-specific, since C-allele is associated with greater improvements in post-training isometric strength in females.

IL6 / rs1800795

POWER: Increased Power Performance, Exercise-Induced Muscle Hypertrophy

RECOVERY: Inflammatory Response, Muscle Regeneration

MUSCLE BUILDING: Muscle Hypertrophy

IL-6 is a multi-functional pro-inflammatory and immunomodulatory cytokine that is relevant to health and exercise-related phenotypes [78]. IL-6 is expressed in adipose, skeletal muscle and hypothalamus, and is important for the regulation of body energy [79]. IL-6 stimulates an immune response to strenuous exercise acting as pro- and anti- inflammatory factor [80, 81]. It is also thought to be involved into nutrient mobilisation and delivery, making it important for performance and recovery [82]. IL-6 plays a pivotal role in muscle hypertrophy and repair following exercise-related muscle damage [83]. Exercise can promote increases in muscle derived *IL-6* mRNA and subsequent elevations in circulating IL-6 [84, 85]. In turn, an increase of circulating IL-6 concentration following exercise is related to exercise intensity and duration, the mass of recruited muscles and endurance capacity [85]. The genetic polymorphism rs1800795 functionally affects IL-6 levels [86]. The GG genotype is associated with higher plasma IL-6 levels [87] and, in turn, IL-6 plasma concentration is affected by exercise duration and intensity, and the amount of muscle mass involved, particularly during weight-bearing exercise [88]. The GG genotype is associated with increased power performance [89] as it is overrepresented in elite power athletes compared to endurance athletes and to non-athlete subjects [89]. In power-oriented sports the GG genotype might have benefits for faster recovery and elevated satellite cell proliferation in the long term. This genotype is also associated with lower levels of inflammation after hard training sessions, leading to quicker recovery times [89].

MCT1 / rs1049434

ENDURANCE: Increased Endurance Performance, Fatigue Tolerance/Blood Lactate

The *MCT1* gene, also known as *SLC16A1*, encodes for a plasma membrane protein that catalyses the transport of short chain monocarboxylates, including, among others, lactate, pyruvate, and certain ketone bodies. Central metabolic pathways and insulin secretion are influenced by cellular levels of lactate and pyruvate, with the skeletal muscle being the major producer of lactate in the body. MCT1 catalyses the transport of lactate into myocytes for oxidation and the rs1049434 polymorphism is demonstrated to be associated with lactate transport rates in skeletal muscles. Among a group of athletes, the AA genotype is associated with lower blood lactate concentrations compared to T-allele carriers [90]. The A-allele (genotype AA or AT) is more frequent among endurance-oriented athletes [90]. As such, carriers of the A allele, especially those with AA, have an increased predisposition to excel at endurance-oriented activities. Among a group of athletes, the AA genotype is associated with lower blood lactate concentrations compared to T-allele carriers [90].

NRF1 / rs2402970

ENDURANCE: Increased Endurance Performance, Metabolic Efficiency

The *NRF1* gene encodes for a transcriptional factor that activates the expression of key metabolic genes regulating cellular growth and nuclear genes required for respiration, heme biosynthesis, and mitochondrial DNA transcription and replication, therefore modulating energy generation in response to physiological signals, including those derived from physical exercise [91]. The rs2402970 polymorphism influences aerobic capacity, with CC genotype carriers presenting greater submaximal aerobic capacity (ventilatory threshold) both at baseline (pre-training state) and after completing an endurance training programme, and also improved running economy post-programme (vs CT genotype) [91]. Better running economy has been associated with a higher proportion of slow twitch fibres, and therefore those harbouring the CC genotype are more likely to have better training adaptation/response to endurance sports [91, 92].

NRF1 / rs6949152

ENDURANCE: Increased Endurance Performance

The *NRF1* gene encodes for a transcriptional factor that activates the expression of key metabolic genes regulating cellular growth and nuclear genes required for respiration, heme biosynthesis, and mitochondrial DNA transcription and replication, therefore modulating energy generation in response to physiological signals, including those derived from physical exercise [91]. A significant interaction was found between the rs6949152 polymorphism genotype and endurance training, with carriers of the AA genotype (vs AG) showing a greater trainability expressed as ventilatory threshold [91, 92].

PPARA / rs4253778

ENDURANCE: Increased Endurance Performance, Fibre Type

Peroxisome proliferator-activated receptor-α (PPARα) is a transcription factor that regulates lipid, glucose and energy homeostasis. It is involved

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in enhancing skeletal muscle oxidative capacity in endurance training. The rs4253778 polymorphism is associated with both endurance and power ability. Scientific evidences revealed a higher proportion of the GG genotype in elite endurance athletes. The GG genotype is associated with a greater mean percentage of type I muscle fibre [39] and with high values of oxygen pulse in rowers [93].

PPARGC1A / rs8192678

ENDURANCE: Increased Endurance Performance, Angiogenesis, Fibre Type
VO_2 MAX: Maximal Oxygen Uptake
The peroxisome proliferator-activated receptor gamma coactivator-1-alpha (PGC-1α, encoded by the *PPARGC1A* gene) is a transcriptional coactivator of the PPAR family and a key component of mitochondrial biogenesis, fatty acid oxidation, glucose metabolism, thermogenesis, angiogenesis, and remodelling of skeletal muscle fibre composition toward slow-twitch fibres, therefore being of relevance in training-induced muscle adaptation [94, 95, 96]. Variants of the *PPARGC1A* gene have been associated with endurance performance. In particular, the A allele (AA and GA genotypes) of the rs8192678 polymorphism was found to be underrepresented in several cohorts of endurance athletes [94, 97, 98] and associated with a lower response to endurance training [99]. In turn, the GG genotype is associated with greater aerobic capacity and with elite endurance athletic status [94, 96, 100, 101, 102, 103]. Carriers of the this genotype might thus have an increased predisposition to excel at endurance-oriented activities.

SLC30A8 / rs13266634

RECOVERY: Muscle Regeneration, Exercise-Induced Muscle Damage, Soreness, Strength Loss
The *SLC30A8* gene encodes for a zinc efflux transporter (ZnT-8) that is mainly expressed in pancreatic islet beta cells. ZnT-8 transports zinc from the cytoplasm into intracellular vesicles, where it co-crystallises with insulin to form secretory granules, therefore also contributing to insulin storage efficiency [104, 105, 106]. The TC and CC genotypes are associated, in men, with more soreness and strength loss, and higher plasma CK levels after training intervention (vs TT genotype) [107]. The C-allele (TC or CC genotypes) is also associated with decreased fasting insulin levels [108] and reduced insulin secretion in response to glucose intake [109]. The C-allele is thus likely to affect muscle anabolism, which is promoted by insulin signalling during rest [110]. Carriers of TC or CC genotypes are therefore more likely to need longer recovery times when compared with those with TT genotype [59].

SOD2 / rs4880

ENERGY REFUEL: Oxidative Stress, Inflammatory Response
The reactive oxygen anion superoxide is formed as a by-product of the mitochondrial electron transport chain, therefore increasing along with aerobic metabolism, and is toxic, causing oxidative cell damage. The *SOD2* gene encodes for a mitochondrial superoxide dismutase, which catalyses the conversion of the superoxide into hydrogen peroxide and diatomic oxygen. SOD2 is one of the main endogenous enzymes with antioxidant function thus being vital to protect cells against the oxidative stress caused by free radicals. Some variations in the *SOD2* gene affect the activity of the encoded enzyme, thereby influencing endogenous protection against oxidative damage. The TT genotype of the rs1799725 polymorphism is associated with a less efficient production and mitochondrial trafficking of SOD2, and consequently with decreased capacity of superoxide metabolization [111]. Increased levels of superoxide promote lipid peroxidation by reacting with nitric oxide, therefore damaging biomembranes [112]. Acute exercise is a pro-inflammatory condition that induces oxidative stress. The TT genotype is associated with increased production of proinflammatory cytokines [113]and might be unfavorable for high-intensity athletic events, being significantly less frequent in high-intensity groups compared with controls and low intensity exercise groups [114, 115]. The T-allele (TC or TT genotypes) is also significantly associated with increased markers of muscle damage, namely creatine kinase (CK) activity in females and creatinine levels in both males and females [115]. Carriers of the TT genotype are likely to benefit from an increased dietary intake of manganese, the co-factor of SOD2, and antioxidants, including the lipid-soluble vitamin E (α-tocopherol) and carotenoids, which are radical-scavenging antioxidants effective against lipid peroxidation [116, 117, 118]. These vitamins can be found in eggs, liver, vegetable oils, nuts and seeds and also, in less quantities, in colourful (yellow and orange) vegetables.

TNF / rs1800629

MUSCLE BUILDING: Muscle Remodelling
Tumour necrosis factor alpha (TNFα) is a pro-inflammatory cytokine, denoted for its ability to induce skeletal muscle atrophy and to stimulate the acute phase of inflammation [119]. The TNFα level increases after intensive exercise. When muscle cells are exposed to increasing concentrations of TNFα there is a concurrent decrease in the amount of myosin heavy chain (major myofibrillar protein), highlighting its role in controlling muscle mass. It is released from muscle fibres, fibroblasts, neutrophils and macrophages, being the level of expression determined by intensity and duration of exercise [120, 121, 122, 123]. The invading neutrophils and macrophages express TNF at the early phase of inflammatory response [121]. At the cellular level, exercise also promotes an increased oxidative metabolism within the mitochondria, leading to an increased level of reactive oxygen species (ROS) and hence to elevated oxidative stress [124]. This process promotes a greater lipid peroxidation and consequently tissue damage. Mechanical load also increases muscle damage by promoting an inflammatory response partially driven by TNF and interleukin-6 (IL-6) [59, 86]. TNFα has been shown to inhibit the expression and activity of proteins such as growth hormone and IGF-I that are important contributors to skeletal muscle growth. Carriers of the *TNF*α rs1800629 A-allele (GA or AA genotypes) might have a higher susceptibility to muscle atrophy and sarcopenia due to the impaired ability of muscle remodelling. Because you do not harbour a copy of the A-allele, you are not predisposed to muscle catabolism and, therefore, are likely to gain muscle mass more easily.

VEGFA / rs2010963

ENDURANCE: Increased Endurance Performance, Angiogenesis
VO_2 MAX: Maximal Oxygen Uptake
Vascular endothelial growth factor A (VEGFA) is an important signal molecule that transmits extracellular signals inside the cell and is involved in the

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growth of blood vessels. It is considered one of the most important capillary growth factors in skeletal muscle, being essential to basal capillarisation in the tissue and increased capillary growth in response to exercise training [125, 126]. *VEGFA* promoter polymorphisms are related to VO_2max before and after aerobic exercise training [125, 126]. Studies have demonstrated that C-allele (genotype CC or CG) significantly more frequent among endurance athletes and is positively associated with aerobic performance, contributing to higher VO_2 levels [126]. Furthermore, a number of studies demonstrate a role for VEGFA in skeletal muscle tissue regeneration. VEGFA mediates angiogenesis that is a biologic process fundamental in the adaptation to aerobic exercise training. C-allele is associated with an increase in the efficiency of skeletal muscle repair by increasing angiogenesis and at the same time reducing the accumulation of fibrosis [125, 126].

14.2. KEYWORDS AND CONCEPTS

ARC training - Aerobic, Respiration and Capillarity: Training approach to develop aerobic endurance by encouraging muscle vascular development [127].
Ballistic training: Type of strength training that consist of maximum velocity and acceleration exercises over a short period of time, projecting the body or an object into space [128].
Cross-training: circuit training that combines exercises of other disciplines with the current training modality to build strength and flexibility in muscles that are not usually used [127].
DOMS - Delayed Onset Muscle Soreness: common exercise-related pain and stiffness stressed in the muscles tissue beyond what it is accustomed to, causing increased discomfort between 24 and 72 hours after exercise [129].
Hypertrophy training: method of strength training intended to induce the fastest muscle growth possible, without losing efficacy over an extended period of time [130].
Interval training / HIIT - High Intensity Interval Training: training technique with short bursts of high intensity exercise, followed by brief and low-intensity recovery periods [131, 132].
Overtraining: occurs when exercise volume and intensity exceeds the recovery capacity. It is common to experience progress cease, strength and fitness loss [133, 134, 135].

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