NUTRIGENOMICS FOR SPORT AND EXERCISE PERFORMANCE

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INTRODUCTION

The goal of personalized nutrition in sport is to optimize health, body composition and exercise performance by targeting dietary recommendations to an athlete's goals, personal health status, food preferences and genetic profile. This necessitates a more modern view of sports nutrition that is shifting away from a universal, one-size-fits-all "team" approach toward multidimensional and dynamic nutrition strategies that focus on the individual.

Nutrigenomics uses genomic technologies and genetic information to address issues important to nutrition and health, body composition and performance indicators and other outcomes[1,2]. Genetics play an influential role in determining how an athlete responds to foods and nutrients, and the surge in research into gene-diet interactions over the past decade has provided a scientific basis for the expansion of this research as seen in the growing number of published studies on this topic[1]. It is now widely recognized that genetic variants affect the way we absorb, metabolize, utilize and transport nutrients, and gene-diet interactions can modify metabolic pathways that are relevant to athlete health and performance[3]. These more nuanced approaches encompass overall dietary patterns, appropriate macronutrient ratios, micronutrient requirements, eating behaviors (e.g., nutrient timing) and the prudent use of ergogenic aids. Personal genetic testing can provide information that will guide recommendations for dietary strategies that are more effective at the individual level than current dietary advice, which has been set by public health and various sport agencies[4–6]. Disclosure of genetic information has also been shown to enhance motivation, strengthen behavioral changes and improve adherence to the dietary recommendations provided[7–13].

The demand for genetic testing for personalized sport is growing, and there is an increased need for dietitian-nutritionists, coaches and other sports medicine practitioners to understand the current evidence in this developing field[14–17]. This review will provide some examples of genetic markers that pertain to athletes as well as some practical tips and updates in the field.

NUTRIGENOMICS: AN EXAMPLE

Although the term nutrigenomics is relatively new, the concept has been around for some time. Lactose intolerance is one example of how clinicians have long been incorporating nutrigenomics into their practice and how different versions of a gene

Image: Novak Djokovic eating dates in between matches. 2020 French Open at Roland Garros (illustration).

can lead to different responses to dietary components and different recommended dietary guidelines. Individuals who are not lactose-intolerant possess a version of a gene that produces sufficient amounts of lactase, the enzyme responsible for breaking down lactose, and can enjoy dairy products without side effects. However, individuals who are lactose-intolerant possess a version of the gene that does not produce functional lactase and they are likely to experience acute gastrointestinal discomfort if they consume lactose. Nutritionists and other healthcare workers counsel these clients and help them to identify alternatives to lactose-containing foods, while ensuring that their nutritional needs are met.

GENES ASSOCIATED WITH NUTRIENT METABOLISM

Iron

Iron is an essential mineral required for the production of red blood cells (RBCs)[18]. Due to iron's role in the production of RBCs and oxygen delivery, low iron status may result in impaired athletic performance[19,20]. The prevalence of low iron storage and anemia is greater in elite athletes compared to the general population[19–22]. Iron requirements rise due to an increase in erythropoiesis as a result of heavy training loads. Low energy intakes especially in female athletes may result in iron deficiency[23,24]. Recreational and elite athletes are advised to regularly monitor their iron levels for optimal health and performance. Variation in the TMPRSS6, TF and TFR2 genes have also been shown to influences an individual's susceptibility to low iron status[20].

TMPRSS6, TF and TFR2 genes

Three SNPs, TMPRSS6 (rs4820268), TF (rs3811647) and TFR2 (rs7385804) have been associated with low iron status[20] through their regulation of hepcidin, which inhibits iron transport[25–27]. Low iron anemia reduces the oxygen carrying capacity of hemoglobin and myoglobin and which can impair performance[28,29]. Low iron status can be predicted by certain combinations of genotypes, using an algorithm, within SNPs of the TMPRSS6, TF and TRF2 genes[30,31]. If an athlete is at risk for low iron, modifications can be made through diet or supplementation to offset such risks. Despite being at an increased risk for low iron status, athletes should monitor their supplemental iron intake and serum ferritin to ensure they are not consuming excessive amounts of iron. Indeed, variation in the HFE gene has been shown to influences one's susceptibility to iron overload (hereditary hemochromatosis)[32,33].

HFE gene

Athletes choosing to take iron supplements in order to prevent or treat low iron may be at risk of excessive intakes[33]. This may also negatively impact performance due to the tissue-damaging effects of excess iron[32] through the increased production of free radicals[34]. The gene associated with hemochromatosis is HFE, and there are 2 SNPs in this gene (rs1800562 and rs1799945) that can be used to predict the risk of hemochromatosis[23,24]. Those with the AA (rs1800562) and GG (rs1799945) genotypes of HFE, possess the greatest risk for hemochromatosis[31,35,36]. Those with the GA (rs1800562) and GC (rs1799945) genotypes are at a medium risk and those with the GG (rs1800562) and CC (rs1799945) genotypes are at a low risk for hemochromatosis. Athletes who are genetically at risk for iron overload and higher iron levels, appear to have a genetic advantage to excel in certain sports because of a greater

oxygen-carrying capacity, and elite athletes tend to possess the risk variant more-so than the general population[3,36]. Indeed, in recent work from our lab, we report that individuals possessing the medium/high risk HFE genotypes (rs1800562 & rs1799945) outperformed those with the low risk genotypes in a 10km cycling time trial – Thakkar et al[37,38]. Furthermore, individuals in the medium/high risk group possessed a greater $VO2_{peak}$ compared to those with a low risk for hemochromatosis. Recently, Delgado et al[39] also showed that medium-risk or heterozygosity in the two HFE polymorphisms might confer an intermediate phenotype in terms of iron absorption that might favour endurance performance.

These results highlight the importance of monitoring and optimizing an athletes' iron status, since the benefit of higher iron absorption could also be a detriment if excessive iron levels persist and cause oxidative tissue damage[31,35,36]. Athletes that possess an elevated risk of hemochromatosis should be cautioned on the consumption of iron supplements to avoid iron overload[37].

VITAMIN B12

Individuals who are deficient in vitamin B12 may experience megaloblastic anemia and increased homocysteine levels[38,39]. Megaloblastic anemia results in enlarged RBCs, thereby decreasing the oxygen carrying capacity of the two proteins myoglobin and hemoglobin in the blood. Variation in the FUT2 gene has been shown to influence one's susceptibility to vitamin B12 deficiency[40,41].

FUT2 gene

Vitamin B12 is absorbed and transported between cells by the fucosyltransferase 2 (FUT2) enzyme, which is encoded by the FUT2 gene[40,41]. Individuals who possess the risk variant of FUT2 may be at risk for B12 deficiency if intakes are low. This is due to a SNP in FUT2 (rs601338), which can alter vitamin B12 absorption[39]. The deficiency is observed more in vegetarian and vegan compared to omnivore athletes[39,40]. Individuals possess an elevated risk for B12 deficiency if they are a FUT2 G-allele carrier compared to those with the AA genotype[40]. Highly bioavailable sources of vitamin B12 such as meat and fish products can be consumed to ensure adequate vitamin B12 levels. It is recommended that vegan and vegetarian athletes choose vitamin B12 fortified plant milks and plant-based meat alternatives and/or supplement with vitamin B12 tablets to ensure adequate levels.

VITAMIN A

Vitamin A is a fat-soluble vitamin/antioxidant necessary to optimize immunity and vision[42-44]. Low vitamin A intake is associated with immune dysfunction[44]. As an antioxidant, vitamin A reduces the risk of ocular diseases and may improve vision[43]. The majority of sports require optimal vision and hand-eye coordination to excel[45]. In sports such as ice hockey and baseball, the objects of interest, the puck and ball, respectively, rapidly move during play[45,46]. Athletes may be at a greater risk for a sport-related injury if they possess slow visuomotor reaction time (VMRT)[47].

Low vitamin A intake may result in an individual being more susceptible to infection due to immune dysfunction[43,44]. Low energy intake, in addition to physical/psychological stress, poor food choices, jet lag as well as exposure to foreign food, water and pathogens is common amongst athletes and has the potential to increase the likelihood of an infection[24,48]. Vitamin A is formed by the BCMO1 enzyme expressed in enterocytes of the intestinal mucosa, which converts dietary carotenoids, such as β-Carotene, into vitamin A[49]. However, β-Carotene must then be converted to retinal or retinoic acid for vitamin A to exert its actions in the body. Variation in the BCMO1 gene has been shown to influence the conversion of carotenoids into the bioavailable form of vitamin A[50].

BCMO1 gene

The BCMO1 gene encodes the β-carotene mono-oxygenase 1 (BCMO1) enzyme, which converts carotenoids into vitamin A's biologically active form[50]. A SNP in BCMO1 (rs11645428) can modify the conversion of carotenoids into vitamin A's biologically active form increasing one's risk for low vitamin A levels. Those who possess the GG genotype of BCMO1 (rs11645428) have a greater risk for vitamin A deficiency due to the poor conversion of carotenoids to the biologically active form of vitamin A[51]. Those with the GG genotype may want to consume pre-formed vitamin A (found in animal products) in their diet to bypass the inefficient conversion of carotenoids into vitamin A[49-51]. Alternatively, those who prefer to consume more of the plant-sourced Vit A precursor, β-carotene, can increase their consumption of spinach and other vegetables and fruits that are orange-red in colour. This will ensure that vision and immune health are optimal for an athlete to perform in game and to ensure long term viability without infection.

ERGOGENIC AIDS

Caffeine

Caffeine is widely used in the sporting world and has dominated the sport supplements research domain over the past several decades[52-54]. Numerous studies have investigated the effect of supplemental caffeine on exercise performance, but there is considerable inter-individual variability in the magnitude of these effects[52,54,55], or in the lack of an effect[56,57] when compared to placebo. These inter-individual differences, along with other "health" responses to caffeine, appear to be partly due to genetic variation[58].

Caffeine and Anxiety

In elite athletes, 50% face mental health issues sometime during their career[59]. Sport psychologists often work with athletes to help them overcome performance-associated anxiety during competitions. Anxiety before or during athletic competitions can interfere not only in performance, but also increased injury risk[60]. Stress related disorders (burnout), poor quality sleep patterns and possibly the response to caffeine may contribute to anxiety in athletes[61]. Caffeine is widely consumed across most sports both socially in the diet and as an ergogenic aid[54,62].

Caffeine blocks adenosine receptors, resulting in the stimulating effects of caffeine[58]. A common variation in the ADORA2A (adenosine A2A receptor) gene contributes to the differences in subjective feelings of anxiety after caffeine ingestion[63,64], especially in those who are habitually low caffeine consumers[65]. This may be particularly relevant to athletes who possess the TT variant of rs5751876 in the ADORA2A gene. These individuals are likely to be more sensitive to the stimulating effects of caffeine and experience greater increases in feelings of anxiety after caffeine intake than do individuals with either the CT or CC variant[63-65]. Athletes who are more prone to performance anxiety

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may exacerbate their risk for feelings of anxiety depending on their caffeine use and which variant of the ADORA2A gene they possess. Monitoring the actions of caffeine in those individuals who are susceptible, may alleviate some of the related feeling of anxiety with caffeine use.

Caffeine and Performance - Inter-individual Responses

Most studies on caffeine and performance do not explore the basis for the inter-individual variation in response, which has been well-documented in several studies[55,57,66–68].

The largest caffeine and exercise study to date[69] examined the effects of caffeine and CYP1A2 genotype on 10-km cycling time in competitive male athletes and found a 3% improvement in time trial cycling time in the moderate dose in all subjects, which is consistent with previous studies using similar doses[54,70]. However, improvements in performance were only seen in those with the AA genotype who are 'fast metabolizers' of caffeine. In that group, the 6.8% improvement in cycling time was observed at 4 mg/kg, which is greater than the 2% to 4% mean improvement seen in several other cycling time trial studies, using similar doses[54,67,70-74]. Among those with the CC genotype, "slow metabolizers", 4 mg/kg caffeine impaired performance by 13.7%, and in those with the AC (heterozygous) genotype there was no effect of either dose[69]. The findings are consistent with a previous study[75], which observed a caffeine-gene interaction and improved time trial cycling performance with caffeine only in those with the AA genotype. However, they are in contrast to two recent studies in adolescents[76] and adults[77] where caffeine supplementation improved exercise performance outcomes independent of their CYP1A2 genotype.

The effects of genotype on performance are most prominent during training or competition of longer duration or an accumulation of fatigue, i.e. muscular endurance, where caffeine appears to provide its greatest benefits, and where the adverse effects to slow metabolizers are more likely to manifest[78,79]. In two separate studies of professional handball[79] and elite basketball players[80], caffeine supplementation improved ball throwing and repeated jumps (muscular endurance), respectively, but only in those with the CYP1A2 AA genotype compared to C-allele carriers. However, no genotype differences were detected on other performance tests[79,80]. Similarly, in a cross-over design of 30 resistance-trained men, caffeine ingestion resulted in a greater volume of work compared to placebo conditions, but only in those with the CYP1A2 AA genotype[81]. There appears to be growing support for the role of CYP1A2 in modifying the effects of caffeine ingestion on aerobic or muscular endurance-type exercise, but more research is needed before strong conclusions can be made.

GENES ASSOCIATED WITH PERFORMANCE OR INJURY

Vitamin D, Calcium and Bone Health

Vitamin D is essential to calcium metabolism, increasing calcium absorption for optimal bone health, which is relevant to all athletes, but particularly those participating in sports with a high risk of stress fracture such as running[82–86]. Two genes that have been shown to impact vitamin D status are the GC gene and the CYP2R1 gene[85,86].

GC and CYP2R1 genes

Vitamin D 25-hydroxylase is the key enzyme that activates vitamin D from its pre-formed type, which is obtained through sun exposure and the diet[82,83]. This enzyme is encoded by the CYP2R1 gene and a variant of this gene has been associated with low circulating levels of vitamin D[85,86]. The GC gene encodes the vitamin D-binding protein, which binds vitamin D and transports it to tissues. A variant in this gene has also been associated with an increased risk of low circulating levels of vitamin D. In one study, individuals with GG or GA genotype of CYP2R1 were nearly four times more likely to have insufficient vitamin D levels compared to those with the AA genotype after vitamin D supplementation[86]. Those with the GG genotype of the GC gene were significantly more likely to have low vitamin D levels compared to those with the TT genotype. These results were consistent with the Study of Underlying Genetic Determinants of Vitamin D and Highly Related Traits (SUNLIGHT) which studied three genetic variants, including CYP2R1 (rs10741657) and GC (rs2282679) in over 30,000 subjects and their vitamin D status[85,86]. Those with the risk variants may not efficiently absorb calcium, increasing their risk for stress and other bone fractures[87]. Athletes who engage in higher risk sports such as long distance

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running, should monitor their vitamin D and calcium intake to decrease their risk of stress fractures and other bone fractures[88-90].

Muscle Damage

Delayed onset muscle soreness (DOMS) is commonly experienced in the days following unaccustomed or strenuous training, and it is characterized by tender, inflamed muscles which can also cause a temporary reduction in strength and range of motion[91]. Exercise-induced muscle damage at low levels is a necessary positive stimulus for muscle hypertrophy and strength gains[92]. However, excessive damage coupled with inadequate recovery may cause persistent and unnecessary soreness which can impede strength and aerobic gains and increase the risk of developing over-use injuries[93]. DOMS is caused by oxidative stress, inflammation, and muscle protein degradation[95]. There is considerable variability in an individual's response to muscle-damaging exercise, due to factors such as age, training and sport history and genetics[95]. Research shows that variation in the ACTN3 gene influences one's susceptibility to muscle damage after strenuous or unaccustomed exercise[96].

ACTN3 gene

The ACTN3 (rs1815739) gene encodes the alpha-actin 3 protein, which plays a key role in the contraction of fast-twitch or power-type muscle fibers during short bursts of intense activities, such as sprinting[97]. Genetic variation in ACTN3 affects the expression of the resulting protein in fast-twitch fibers, and individuals who carry at least one copy of the T variant produce a lower functioning ACTN3 protein that has been linked to increased risk of muscle damage[98]. For example experienced endurance athletes with the T variant had higher levels of markers of muscle damage after a competitive marathon[96] compared to individuals with the CC variant, and a similar trend was observed in a study where healthy young men performed knee extension exercises to failure to induce DOMS[95].

Athletes who are T-allele carriers for the ACTN3 (rs1815739) gene, have an increased susceptibility to muscle damage after strenuous or unaccustomed exercise and may be at greater risk of developing over-use injuries if not adequately recovered from the previous training sessions[99]. Athletes who frequently experience more severe cases of DOMS should prioritize rest and recovery and also ensure an adequate total protein intake as well as frequency of intake throughout the day for muscle repair[93]. The consumption of plenty of antioxidant-rich plant foods such as fruits, vegetables, nuts and seeds may help to reduce inflammation[100] and mitigate the negative effects of oxidative stress caused by muscle damage[101].

SUMMARY

The ultimate goal of personalized sport nutrition is to offer tailored dietary recommendations that directly (performance) and indirectly (health, body composition) improve athletic performance. Personalized nutrition strategies for athletes will continue to develop as research identifies new genetic markers that enable these valuable targeted interventions. Genetic testing for personalized sport nutrition is an effective and widely available non-invasive tool that can be implemented into the practice of sport clinicians, nutritionists and coaches to guide nutritional strategies and meal planning with the aim of optimizing athletic performance.

Disclosure

NSG is on the Science Advisory Board of Nutrigenomix Inc.

References

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