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Sports Nutrigenomics – Caffeine: A Review

Monika and Ashok Kumar

Abstract

Aim: The aim of this article is to review the research studies related to sports nutrigenomics-caffeine. **Conclusion:** The research in the field of genetics and sports nutrition (i.e. gene-diet interaction) is linking genetic variation to nutritional or supplemental needs of athletes with a focus on sport performance.

Monika
Assistant Professor
Department of Biotechnology
Mata Gujri College, Fatehgarh Sahib (Punjab), India
E-mail:monika187@rediffmail.com
Ashok Kumar
Professor
Department of Sports Science
Punjabi University Patiala (Punjab), India

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Nutrigenomics is also known as nutritional genomics. Nutrigenomics is well-defined as the association among nutrients, diet, and gene expression (Chadwick 2004). The mapping of human DNA sequencing after the success of Human Genome Project in the 1990s, starting the field of nutrigenomics that we see today (Mathers 2017). In addition to the effect of genes on the phenotype (i.e. the physical expression of genetic traits), genes can also respond to environmental influences (stimuli) – of which nutrition is one such influence. The general dietary patterns such as diets with a high Glycemic Index (GI) load have also been associated with gene expression, for example the association between a high GI diet and exaggerated polymorphism of the Adiponectin gene, contributing to insulin resistance and diabetes type II. Nutrigenomics as a research field very much depends on the modern development of cutting-edge technologies that allow to process a large amount of data relating to gene variants. These so-called '-omic' technologies like proteomic, metabolomics, genomic, and transcriptomic, allow to identify and measure several different types

of molecules instantaneously. This is significant that most chronic diseases are not caused by monogenic mutations (as in the case of leptin deficiency), or single genetic effects affected by a single dietary exposure (such as phenylalanine and PKU), but by complex interactions among a very large number of different gene variants (Mead 2007). The intricate biology of human beings makes a mechanistic understanding of exactly how dietary bio-actives react in our bodies difficult to elicit. How to define the optimal intake of individual nutrients for the maintenance of human cells in a 'genomically stable' way remains largely unknown. Diverse genetic backgrounds further confuse the forecast of phenotypes, with some more vulnerable to certain conditions than others. For example, the APOE (apolipoprotein E) gene has three different phenotypes, each with a different probability of CVD (cardiovascular diseases) risk, and all responding differently to diet and lifestyle factors. Nutrigenomics and nutrigenetics uses genomic information and genetic testing technologies to study the role of individual genetic differences in altering an athlete's response to nutrients and other food constituents. Now the field of nutrigenomics is fast moving, with the potential to lay the foundations of 'personalised nutrition' methods custom-made to persons (Ordovas et al., 2018). It also poses both ethical and regulatory challenges. The establishment of pan-national organisations such as the European Nutrigenomics Organisation (NUGO) and the International Society for Nutrigenomics & Nutrigenetics have further served to increase the infrastructure and international collaboration around nutrigenomics research. Given the increasing global burden of nutrition-related noncommunicable diseases (WHO 2014), nutrigenomics could help to develop more sustainable approaches to encouraging dietary change at a population-level, although a lack of human experimental trials remains a barrier for translating research into policy and practice (Lampe et al., 2013).

Genes and Athletes - Over the years, sports performance has been related with several factors that modify the athlete's capacity to acclimatize to the effort required to perform their sports specific activities. Recent research studies showed that these factors correspond not only to the sports training routines that the athletes follow, but also to their genetic characteristics that contribute to a improved response of the individuals through changes that comprised processes like protein synthesis to rise in the metabolic rate or the manufacture of the components of contractile machinery. Furthermore, the genetic characters found in the athletes allow avoiding injuries or conditions that could danger their life by recognizing typical markers of these pathologies. There are numerous physical traits that determine the athletic capacity, generally the strength of the skeletal muscle and the predominant kind of fibres on it. Additional traits include aerobic capacity that is the maximum capacity of the body to deliver oxygen to the tissues, muscle mass, height, flexibility, coordination, intellectual capacity and personality. On average, 66% of the variation in athlete status can be clarified by genetic factors. The remaining variation is due to environmental factors, such as deliberate practice, food and ergogenic aid (Semenova et al., 2023). Some of the genetic factors for example ACTN3 gene, located in the chromosome 11 and responsible for encoding the α-actinin-3 protein (αA3) in the Z-line of the skeletal muscle sarcomere of the fast-twitch fibres (Pickering 2017). The mutations in ACTN3 gene can occur in the R and X alleles, which allow synthesising the αA3 protein. The combination of these alleles produces the RX, RR and XX genotypes. RR and RX genotypes provide a greater stability to the contractile structure in the muscle fibre, leading to a greater strength production. There is a significant association between the RR genotype and athletic performance of speed/power, however, its effectivity manifests in the strong anaerobic contractions, besides, this genotype increases the area in the transversal section of the type IIa and Ix fibres to favour the short efforts with intensity of 95% or even more. The RR plus RX genotypes is associated to the athletic status of both speed/power and to the long-distance runners. About the XX genotype, it is very probably its contribution to the aerobic resistance performance by giving a physiological advantage to the bearers of this gene in the competences

when the aerobic resistance and muscle efficiency are much more important than the speed and power, and also contributes to modifying the muscle structure to increase the adaptation to exercise and reduce the risk of suffering injuries (Peña et al., 2022; Pickering et al., 2017).

Nutrigenomics and Athletes - There are many environmental factors that can influence the athletes' development according to their individual genetic characteristics, among which includes the nutrition. Generally, diets are planned without bearing in mind genetic characteristics that can affect the way in which the nutrients are used by the individual, or its ability to absorb them. It is at this point where nutrigenomics takes a very significant role by establishing a relation between these variables and the sportsperson's heredities, with the purpose of taking full benefit of the individual genetic characteristics through nutrition. However generally diets are planned in a personalised mode, it is not sufficient only to consider the energetic requirements of the individual, particularly in the case of the high-performance athletes, for which there have been implemented techniques like the genetic tests that cover aspects such as the athlete's reaction to the feeding and the way in which the metabolic pathways process the nutrients supplied. The typical examples of these genetic variances are the lactose intolerance and phenylketonuria, which makes it difficult to develop nutrition plans adaptable to a wide range of the people and, besides, it establishes the significance of individualising the nutrients supply. In the case of phenylketonuria, there are individuals that cannot metabolise other molecules, which results in a risk for their health that can produce serious consequences (Guest et al., 2019). Nutrigenomics has seen its advancement improved by the great genetic variety expressed in changes like the Single nucleotide polymorphisms (SNPs), capable of inciting an extensive range of metabolic responses. The effects of the physical exercise on the metabolism changes and muscle adaptations are owing to chromatin changes in different levels, such as DNA and histones hypomethylation, which promotes the transcription and protein synthesis (Światowy et al., 2021; Guest et al., 2019).

Caffeine and Genes - Caffeine, found naturally in numerous plant species including coffee, cocoa, tea and guarana, is extensively used in sport as an ergogenic aid or performance enhancer frequently in the form of caffeinated chews or gels and tablets. In the arena of nutrigenomics, caffeine is the most extensively researched compound with numerous randomized controlled trials examining the changing effects of genetic difference on sports performance (Guest et al., 2018; Womack et al., 2012; Pataky et al., 2016). Several research studies have explored the result of supplemental caffeine on physical workout performance, but there is significant inter-individual variability in the magnitude of these effects (Higgins et al., 2016; Ganio et al., 2009; Graham & Spriet 1991), or in the lack of an effect (Roelands et al., 2011; Hunter et al., 2002) when compared to placebo. These inter-individual differences seem to be partially due to variation in genes for example CYP1A2 and possibly ADORA2, which are related with caffeine metabolism, sensitivity and response (Yang et al.,2010). More than 95% of caffeine is metabolized by the CYP1A2 enzyme, which is encoded by the CYP1A2 gene (Begas et al.,2007). The−163A>C (rs762551) single nucleotide polymorphism (SNP) has been shown to alter CYP1A2 enzyme activity (Koonrungsesomboon et al., 2017; Djordjevic et al., 2008; Ghotbi et al., 2007) and has been used to recognize individuals as "fast" or "slow" metabolizers of caffeine. Persons who are considered slow metabolizers, that is with the AC or CC genotype, have an elevated risk of myocardial infarction (Cornelis et al.,2006), hypertension and elevated blood pressure (Soares et al., 2018; Palatini et al.,2009) and pre-diabetes (Palatini et al.,2015) with increasing caffeinated coffee drinking, whereas those with the AA genotype (fast metabolizers) do not seem to carry these risks. The largest caffeine and physical exercise study (Guest et al., 2018), examined the effects of caffeine and CYP1A2 genotype, on 10-km cycling time performance in competitive male athletes after ingestion of caffeine at 0mg, 2mg (low dose) or 4mg (moderate dose) per kg body mass. There was a 3% improvement in cycling time performance in the moderate dose in athletes, which is consistent with

earlier cycling time performance studies using similar doses of caffeine (Desbrow et al., 2012; Ganio et al., 2009). Though, there was an important caffeine-gene interaction where enhancements in performance were seen at both caffeine doses, but only in individuals with the AA genotype who are "fast metabolizers" of caffeine. In that group, a 6.8% improvement in cycling time performance was observed at 4 mg/kg, which is more than 2 to 4% mean enhancement seen in numerous other cycling time studies, using similar doses of caffeine (Graham-Paulson et al., 2016; Saunders et al., 2016; Bortolotti et al., 2014 ; Skinneret al., 2013; Desbrow et al., 2012; Ganio et al., 2009; Jenkins et al., 2008). Among individuals with the CC genotype, 4 mg/kg caffeine impaired performance by 13.7%, and in those with the AC genotype there was no effect of either caffeine dose (Guest et al., 2018). These research findings are consistent with an earlier study (Womack et al., 2012), which observed a caffeine-gene interaction and improved cycling performance time with caffeine only in those with the AA genotype. Some previous endurance-type research studies either did not observe any impact of the CYP1A2 gene on caffeine-exercise performances (Salinero et al., 2017; Algrain et al., 2016) or reported benefits only in slow metabolizers (Pataky et al., 2016). There are numerous reasons that may clarify discrepancies in study outcomes including smaller sample sizes (that cause very low numbers and/or no subjects with the CC genotype (Salinero et al., 2017; Pataky et al., 2016 ; Joy et al., 2014), and shorter distance or different type (power vs. endurance) of performance test (Pataky et al., 2016), compared to those that reported improved endurance after caffeine ingestion in those with the AA genotype of CYP1A2 (Guest et al., 2018 ; Womack et al., 2012). The effects of genotype on exercise performance seem to be most prominent during exercise of longer duration or a buildup of fatigue (aerobic or muscular endurance) (Shen et al., 2018; Dohertyet al., 2004). Fast metabolizers may rapidly metabolize caffeine and achieve the benefits of caffeine metabolites as exercise progresses, or override the short duration of negative influences (the initial stages of exercise), whereas the adverse effects of restricted blood flow and/or other impacts of adenosine blockage in slow metabolizers are probable to remain for a longer duration (Higginset al., 2013; Namdar et al., 2009). Indeed, in a study of basketball performance in elite players, caffeine improved repeated jumps (muscular endurance; an accumulation of fatigue), but only in those with the AA genotype, however, there was no genotype effect in the other two performance components of the basketball simulation (Puente et al., 2018). Similarly, a cross-over design of 30 resistance trained men found that caffeine ingestion resulted in a higher number of repetitions in repeated sets of three different exercises, and for total repetitions in all resistance exercises combined, which resulted in a greater volume of work compared to placebo conditions, but only in those with the CYP1A2AA genotype (Rahimi et al., 2018). Thus, the weight of the evidence of such research studies supports the role of CYP1A2 in modifying the effects of caffeine ingestion on aerobic or muscular endurance-type exercise. The ADORA2A gene is another potential genetic modifier of the effects of caffeine on exercise performance. The adenosine A2A receptor, encoded by the ADORA2A gene, has been shown to regulate myocardial oxygen demand and increase coronary circulation by vasodilation (Higginset al., 2013; Namdar et al., 2009). The A2A receptor is also expressed in the brain, where it regulates glutamate and dopamine release, with associated effects on insomnia and pain (Fried et al., 2017; Urry et al., 2015). The antagonism of adenosine receptors by caffeine could differ by ADORA2A genotype, resulting in altered dopamine signaling (Yang et al.,2010). Dopamine has been associated with motivation and effort in exercising individuals, and this may be a mechanism by which differences in response to caffeine are manifested (Salamone et al., 2018; Meeusen et al., 2013; Salamone et al., 2009). One study has observed the effect of ADORA2A genotype (rs5751876) on the ergogenic effects of caffeine under exercise situations (Loy et al., 2015). Twelve female subjects underwent a double-blinded, crossover trial comprising two 10-minute cycling time trials following caffeine ingestion or placebo. Caffeine benefitted all six subjects with the TT genotype but only one of the six C allele

carriers. Further studies are required to confirm these preliminary results and include a larger sample to distinguish any effects between the different C allele carriers (i.e., CT vs. CC genotypes). Sleep is recognized as an important component of physiological and psychological recovery from, and preparation for, high intensity training in athletes (Robson-Ansley et al., 2009; Reilly et al., 2007). The ADORA2A rs5751876 genotype has also been implicated, by both objective and subjective measures, in numerous parameters of sleep quality after caffeine ingestion in several studies (Nunes et al., 2017; Bodenmann et al., 2012; Byrneet al., 2012; Retey et al., 2007). Adenosine promotes sleep by binding to its receptors in the brain, mainly A1 and A2A receptors, and caffeine reverses these effects by blocking the adenosine receptor, which promotes wakefulness (Nunes et al., 2017). This action, as well as the potency of caffeine to restore performance (cognitive or physical) in situations, such as highway-driving during the night (Philip et al., 2006), support the notion that the adenosine neuromodulator/receptor system plays a major role in sleep–wake regulation. This action of caffeine may also serve athletes well under conditions of jetlag, and irregular or early training or competition schedules. Psychomotor speed relies on the ability to respond, rapidly and reliably, to randomly occurring stimuli which is a critical component of most sports (Drummond et al., 2005). Genetic variation in ADORA2A has been shown to be a relevant determinant of psychomotor vigilance in the rested and sleep-deprived state and modulates individual responses to caffeine after sleep deprivation (Bodenmann et al., 2012). In support of this notion, individuals who had the TT genotype for ADORA2A rs5751876 consistently had faster response times (in seconds) than C allele carriers after ingesting 400mg caffeine during a sustained vigilant attention task after sleep loss (Bodenmann et al., 2012).Consistent with the "adenosine hypothesis" of sleep where the accumulation of adenosine in the brain promotes sleep, caffeine prolongs the time to fall asleep, decreases the deep stages of non-rapid-eye movement (nonREM) sleep, reduces sleep efficiency, and alters the waking and sleep electroencephalogram (EEG) frequencies, which reliably reflect the need for sleep (Landolt et al., 2004 & 1995). Although additional research in this area is warranted, genetic variation appears to contribute to subjective and objective responses to caffeine on sleep. Carriers of the ADORA2A (rs5751876) C allele have greater sensitivity toward caffeine induced sleep disturbance compared to those with the TT genotype (Retey et al., 2007). Thus, it seems that persons with the TT genotype for the rs5751876 SNP in the ADORA2A gene may have better performance outcomes, faster response times and less sleep disturbance following caffeine ingestion.

Conclusion: The research in the field of genetics and sports nutrition (i.e. gene-diet interaction) is linking genetic variation to nutritional or supplemental needs of athletes with a focus on sport performance.

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