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Low prevalence of BDNF rs6265 Met allele carriers among Ethiopian-origin runners

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ABSTRACT:*Ethiopian-origin Jews comprise 1.5% of Israel's population.Most of them immigrate from Ethiopia during the 1980s and 1990s, and experienced slow integration intothe Israeli society, though their assimilation into sports was fast and accomplished. The dominance of Israeli long-distance runners of Ethiopian origin was found tobe related to their divergent genetic basis. The aim of the current study is to explore the prevalence of genetic polymorphisms of the Dopamine and Serotonin systemsamong Ethiopian-origin athletes. 75 non-Ethiopian origin and 37 Ethiopian origin track and field athletes participate in the current study. Genomic DNA was extracted from peripheral venous blood samples and was analyzed for several polymorphisms:HTR2A C/T rs6311, HTR2A T/C rs3742278, BDNF C/T rs6264 and COMT G/A rs4680.The prevalence of Met allele carriers (BDNF C/T rs6265) among Ethiopian-origin was significantly low (8%)compared to non-Ethiopian-origin athletes (33%, p=0.004).These results suggest that the dominance of Israeli long-distance runners of Ethiopian origin might be related to their divergent physiological character-associated genetic predisposition rather to Dopamine and Serotonin genetic polymorphisms and that environmental and epigenetic factors play a pivotal role in the expression of motivation in sports – particularly in long-distance running.*

KEYWORDS:*Runners, Genetic polymorphism, Ethiopian-origin*

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I. INTRODUCTION

The Ethiopian Beta Israel community in Israel comprises slightly more than 1.5% of the nation's population(Israel Central Bureau of Statistics, 2017). Most of them are the immigrants who came to Israel after suffering famine in Ethiopia during the civil war in "Operation Moses" (1984) and "Operation Solomon" (1991), and their progeny.

Similar to other groups of immigrants, the Ethiopian Jews have struggle to integrate into Israeli society(Weil, 1994). They faced language and communication difficulties, as well as discrimination and even racism(Weil, 1999). In addition, they had difficulties to bridge the gap between the agrarian nature of Ethiopia and the industrialized developed nature of Israel(Weil, 1991).Over the years, there has been significant progress in the integration of young Beta Israelis into Israeli society(Almog, 2008), yet Ethiopian-origin Jews still can be described as having low educational attainment and low socio-economic status. The rate of Ethiopians who drop out of school has increased dramatically, as well as the rate of juvenile delinquency, and there are a high number of incidences of depression and suicide among this community(Walsh and Tuval-Mashiach, 2012).

In contrast to their slow and gradual integration into many aspects of Israeli society, the assimilation of the Ethiopian Beta immigrants into sports, in particular track and field, was relatively very fast. During the last 30 years they have had a major influence on the Israeli track and field long-distance record table. For example, 15 of the 30 Israel all-time best male results in marathon (7 out of the first 10!) belong to Ethiopian-origin Israelis**,** and in the half marathon Ethiopian-origin Israeli runners account for 19 of the 30 all-time best male results (8 out of the first 10!). It is still unknown whether this excellent record results from their physiological-metabolic-anatomic characteristics or from motivated behavior, or a combination of these factors.

We recently reported that the dominance of Israeli long-distance runners of Ethiopian origin relates to their divergent genetic basis, which includesnot only a genetic predisposition for endurance, but also speed capabilities and training recovery polymorphisms(Ben-Zaken *et al.*, 2019). However, psychological and cognitive traits such as motivation and mental toughness also play a pivotal role in athletic performance, and perhaps even more so in a population of immigrants who are trying to succeedin their new society. Therefore, genetic polymorphisms related to these traits might also be associated with athletic performance. Although the biological mechanism underlying sport and physical activity motivation is still unknown, it is probably related

to the dopaminergic and serotoninergic systems(Knab*et al.,* 2009; Amy M. Knab and Lightfoot, 2010; Lin and Kuo, 2013). Dopamine (3,4-dihydroxyphenethylamine, DA) and Serotonin (5-Hydroxy-tryptamine, 5-HT) are hormones and neurotransmitters(Carlsson, 1959) within the catecholamine clusterthatplay pivotal roles in motor control, motivation, arousal, cognition, reward, and creativity(Smythies, 2005; Schultz, 2007; Smith *et al.*, 2009; Zabelina *et al.*, 2016).

DA is synthesized from l-dihydroxyphenylalanine (l-DOPA), which is synthesized fromthe amino acid tyrosine. Dopaminergic neuronswhich reside in the substantia nigra project to the striatum. These pathways mainly responsible for movement behavior. Dopaminergic neurons which reside from the ventral tegmental nucleus project to the entire cortex. These pathways mainly (involved in cognition and reward responses(Cools and D'Esposito, 2009; Arias-Carrión *et al.*, 2010).

5-HT is synthesized from l-tryptophan. The serotonergic neurons, reside from the median and dorsal raphe nuclei and project to the entire CNS. 5-HT plays pivotal role in the psycho-emotional symptoms of depression and anxiety(Owens and Nemeroff, 1994; Graeff *et al.*, 1996).

The aim of the current study is to explore the prevalence of genetic polymorphisms related to the DA and 5- HTsystems (*HTR2A* C/T rs6311, *HTR2A* T/C rs3742278, *COMT* G/A rs4680 and *BDNF* C/T rs6265) among Ethiopian-origin elite Israeli athletes, and to assess whether motivational-, emotional-, and reward-associated polymorphisms also contribute to their long-distance running success compared to native Israelis of other origins who arelong-distance runners. It was hypothesized thatthe prevalence of genetic polymorphisms related to the DA and SA systems will be significantly higher among Ethiopian-origin elite Israeli athletes compared to Israeli long-distance runners of other ethnic origins.

II. METHODOLOGY

Subjects. One hundred and twelve track and field athletes (92 males and 21 females, age 17-47) participated in the study. Seventy-five athletes (59 males and 16 females) were of non-Ethiopian origin, and 37 athletes (33 males and 4 females)were of Ethiopian origin. The athletes' main event specialties were long-distance runs (5000m to marathon). Participants' achievements were ranked among the top Israeli results, All participantscompeted in national- and/or international-level meets on a regular basis. Forty-eight track and field athletes (22 of non-Ethiopian origin and 26 of Ethiopian origin) were classified as elite athletes (participants and winners in international competitions, in European and World Championships, and in the Olympic Games). Characteristics of the athletes are presented in Table 1. The athletes' main results are presented in Table 2.
The study was approved by the Institutional Review Board of the Hillel Yaffe Medical Center, Hadera, Israel, according to the Declaration of Helsinki. A written informed consent was obtained from all participants.

Table 1.*Athletes' data*

Group	n	M/F	Top/National level	Age(Mean±SD, range)
Ethiopian origin	37	33/4	26/11	32.4±9.5 (18-55)
Non-Ethiopian origin	75	59/16	22/53	32.1±15.0 (18-49)

Table 2.*Athletes' main results [hh:mm:sec]*

Event		Ethiopian Origin	Non-Ethiopian Origin	p
10K	AVG	00:29:28.5	00:30:03.3	0.003
	SD	00:00:51.7	00:00:30.2	
Half Marathon	AVG	01:05:44.0	01:07:54	0.000
	SD	00:01:57.0	00:01:26	
Marathon	AVG	02:19:09.0	02:25:49	0.000
	SD	00:04:39.0	00:03:56	

Genotyping. Genomic DNA was extracted from peripheral venous blood samples using the salting-out procedure. Genotypes were determined by the Taqman allelic discrimination assay. The Assay-by-Design service (https://www.thermofisher.com/il/en/home.html) was used to set up a Taqman allelic discrimination assay for the *HTR2A* C/T rs6311, *HTR2A* T/C rs3742278, *BDNF* C/T rs6264 and *COMT* G/A rs4680. Primers and probe sequences are given in Table 3.

Table 3.*Primers and probe sequences for Taqman allelic discrimination assays*

Primer sequences:		Probe sequences	
Forward	**Reverse**	**Forward: VIC**	**Reverse: FAM**
HTR2A(rs6313 C/T) GCACGATCAGTTCAAGG CAAC	GCTGAGGGTGATGTAGG GATTG	CGAGGCTGACCGAGAG	CCGAGGCTGACTGAGAG
HTR2A (rs3742278 A/T) AGCAGAATCTCCGGACC AGAAAG	CCCATGGATTCAGACTGG ACTT	ACACAGATGGAGGGCC	ACACAGAAGGAGGGCC
COMT (rs46808 G/A) GACGACCTAAGCTGCACT TTTC	GGGCTGATTGGAAACCTT ATTAAGATTG	CTTTAGCAT-GGCAAGAC	CTTTAGCA TCGCAAGAC
BDNF (rs6265, C/T) CCGTTTGTGCAGGGCCTG GCTCTCT	CAGGGTGCTGTCCACACT GGACCCC	CTATCGGGAGGGTTG	CTATCGGAAGGGTTG

The Polymerase Chain Reaction (PCR) mixture included 5ng genomic DNA, 0.125µlTaqMan assay (40*, ABI), 2.5µl Master mix (ABI) and 2.375µl water. PCR was performed in 96 well PCR plates in an ABI 7300 PCR system (Applied Biosystems Inc., Foster City, CA, USA) and consisted of initial denaturation for 5min at 95°C, and 40 cycles with denaturation of 15s at 95°C and annealing and extension for 60s at 63°C. Results were analyzed by the ABI Taqman 7900HT using the sequence detection system 2.22 software (Applied Biosystems Inc., Foster City, CA, USA).

Statistics. The SPSS statistical package, version 20.0, was used to perform all statistical evaluations (SPSS, Chicago, IL, USA). A χ2-test was used to confirm that the observed genotype frequencies were within the Hardy-Weinberg equilibrium, and to compare allele and genotype frequencies between athletes and controls, as well as between athletes from Ethiopian versus non-Ethiopian origin and athletes from different competitive levels. If observed or expected values included a cell with a value of 5, we used Fisher's exact test to compare alleles and genotype frequencies.

III. DISCUSSION

The present study determined the prevalence of dopamine and serotonin polymorphism among Israeli long-distance runners of Ethiopian origin and of non-Ethiopian origin. The main finding of the study is the lower prevalence of the *BDNF* rs6265 Met allele, which is associated with high motivation during exercise (Caldwell, Bryan and Hagger, 2014) among the Ethiopian-origin runners (8% Met allele carriers) compared to non-Ethiopian runners (33% Met allele carriers; p=0.004).

Motivation is conceptualized as the "internal and/or external forces that produce the initiation, intensity, and persistence of behavior." (Levesque *et al.*, 2010). Intrinsic motivation involves performing an activity for one's own pleasure and drive, whereas extrinsic motivation involves engaging in an activity as an external goal – garnering praise and approval, winning a competition, or receiving an award or payment (Levesque *et al.*, 2010). Both types of motivation strongly impact motor performance (Levesque *et al.*, 2010). The identification of the capability to take part in an activity is a challenging task, determined by intrinsic and extrinsic factors as well as by the interaction between them.

Theoretically, studies on the genetics of motivation in sport evolved from two distinguished domains: *sportparticipation* and *sport performance.* However, this discriminationis fallacious. While *sport participation* can be linked directly to the multifactorial trait of motivation, *sport performance* is the outcome of many traits interacting together in a specific context. Therefore, when trying to determine the genetic basis of motivation, it is in fact the genetic basis of motivation toward sport participation, rather than toward sport performance. In other words, everybody is motivated to perform well, but not everyone has the motivation to practice, train, exercise, and put in great effort in order to excel.

Twins' studies have shown that a substantial part of the variation in exercise behavior (Stubbe and de Geus, 2009) and motivational dimensions such as self-efficacy (Waaktaar and Torgersen, 2013), decision making (Tuvblad *et al.*, 2013), and internal motivation (Aaltonen, Kujala and Kaprio, 2014)can be accounted for by genetic factors. However, data from the molecular genetic perspective are scarce. The natural genetic variant candidates related to sport performance motivation are genetic variants related to the dopaminergic system.

The role of the dopaminergic system in motivation and exercise was studied through various paradigms(Knab *et al.*, 2009; Knab and Lightfoot, 2010). The results from these studies imply that the dopaminergic system may play a role in the pleasurable/rewarding feelings associated with voluntary physical activity. Therefore variability in dopaminergic system might contribute to the observed variation in motivation for physical activity and sport participation in animals and humans (Knab and Lightfoot, 2010). Moreover, dopamine and exercise show interconnected interactions, in which exercise induces changes in the dopaminergic system and the dopaminergic system mediates changes in exercise behavior. The support for these interactions comes from anatomical studies, animal models, and the use of exercise in the treatment of depression. From the

anatomical perspective, dopamine functions in both the *striatum*, which is involved in motor activity (Salamone *et al.*, 1989), and the *nucleus accumbens*, which is involved in anticipatory behaviour (Blackburn *et al.*, 1989; Pfaus *et al.*, 1990; Salamone *et al.*, 1994); both areas are integrated by neural connections.

Animal models show that dopamine-depleted animals lack the motivation for doing more effortful tasks (Salamone, Cousins and Bucher, 1994; Cousins *et al.*, 1996). Complementary to this finding, it was found that exercise alleviates symptoms of depression (Duman *et al.*, 2008), and that trained animals showed increased D2 (MacRae *et al.*, 1987) and D1 receptors (Liste *et al.*, 1997). Similarly, human exercise training studies show parallel changes in the dopamine system in response to exercise (Knab and Lightfoot, 2010). Knab and Lightfoot (Knab and Lightfoot, 2010)introduced a model linking the dopaminergic system with regulation of physical activity, through a combination of motor movement and motivational/rewarding components. According to this model, physical activity can cause changes in neuronal signalling and dopamine level.

Catechol-O-methyltransferase (COMT) is one of the main enzymes involved in DA degredation(Lachman *et al.*, 1996), and thus acts as an important regulator of CNS DA levels in the CNS (Gogos *et al.*, 1998). The *COMT* gene is located on chromosome 22q11. The Val158Met (rs4680) single nucleotide polymorphism (SNP) in *COMT* gene is a G to A nucleotide substitution, which results in the replacement of the amino acid valine (Val) by the amino acid methionine (Met), and therefore the activity of COMT enzyme decreases by approximately 35–50% (Lachman *et al.*, 1996; Chen *et al.*, 2004). As a result, G/G (Val/Val) gene carriers have the higher activity of COMT enzyme and the lower levels of DA (Lachman *et al.*, 1996; Nackley *et al.*, 2009).

In the present study, no differences were found in the prevalence of the examined genetic polymorphisms related to the dopaminergic system between the Ethiopian-origin and non-Ethiopian-origin long-distance runners. This suggests that successful long-distance runners need to be highly motivated, regardless of their ethnic background. It is also possible that other environmental and epigenetic factors, and not necessarily genetics per se, had contributed to a different extent to the motivation of each group (e.g. understanding that sports excellence in particular in a member of a low socio-economic status immigrant population, is perhaps the best way – or even the only way – to improve the economic and social status of the individual and his or her family).

5-HT has long been implicated in a wide variety of emotional, cognitive. and behavioral control processes. However, its precise contribution is still not well understood. Several genetic polymorphisms that modulate neurotransmitters' functioning that may influence the regulation of the 5-HT system, and subsequently affect behavior and cognition. The rs6313 SNP is a synonymous substitution located in exon 1 of the gene, where it is involved in coding the 34th amino acid serine. This rs6313 SNP was found to be associated with novelty-seeking and impulsiveness (Salo *et al.*, 2010), and has been shown to transcriptionally modulate the expression of this gene (Parsons *et al.*, 2004; Myers *et al.*, 2007), with the minor allele T reducing expression of the *HTR2A* mRNA compared to the C allele. It is evident that during prolonged exercise increased brain serotonergic activity might augment lethargy and cause a loss of drive (Meeusen *et al.*, 2006). T allele carriers have a lower expression of SR, which protects them against fatigue and consequently enables them to perform better in aerobic tasks compared to non-carriers. *HTR2A* rs3742278 was previously described as related to panic disorder(Unschuld*et al.*, 2007) and binge/purge subtypes of anorexia nervosa (Kiezebrink *et al.*, 2010). No differences in the prevalence of this serotonin-associated polymorphism was found in the present study between long-distance runners of Ethiopian and non-Ethiopian origin.

Brain-derived neurotrophic factor, also known as BDNF, is a member of the neurotrophin family of growth factors, which are related to the canonical nerve growth factor (Levesque *et al.*, 2010). The trophic effect of BDNF on dopamine neurons is well established (Zhou, Bradford and Stern, 1994a; Zhou, Bradford and Stern, 1994b). BDNF is expressed by dopamine neurons of substantia nigra pars compacta, where it plays a critical role in cellular functions (Im *et al.*, 2010) and survival(Hyman *et al.*, 1991), synaptic plasticity (Fritsch *et al.*, 2010), dopamine release modulation (Blöchl and Sirrenberg, 1996; Goggi *et al.*, 2002), neuronal firing (Shen, Altar and Chiodo, 1994), striatal re-innervation (Yurek *et al.*, 1996), dopamine phenotype induction (Zhou, Bradford and Stern, 1994a; Zhou, Bradford and Stern, 1997), and dopamine D3 receptor expression (Guillin *et al.*, 2001; Sokoloff *et al.*, 2002).

The *BDN*F val66met SNP is a common, functional polymorphism results in a valine (val) to methionine (met) amino acid substitution at codon66. Carriers of at least one copy of the met allele had lower neuronal expression of BDNF compared to non-carriers (Egan *et al.*, 2003), as well as smaller hippocampal volume (Pezawas *et al.*, 2004), and impaired memory and hippocampal activation (Egan *et al.*, 2003), and more positive mood response to a bout of moderate-intensity exercise (65 % of VO2max) (Bryan *et al.*, 2007). The BDNF genotype has also been shown to moderate the response to exercise intervention (Bryan *et al.*, 2007), since subjects with the met allele in the intervention group increased their aerobic exercise the most, while control participants with the met allele exercised the least. The affective response to exercise influences future exercise motivation and participation (Williams *et al.*, 2008, 2012; Kwan and Bryan, 2010a; Kwan and Bryan,

2010b). It was found that regular exercising individuals with at least one copy of the met allele reported greater increases in intrinsic motivation during exercise, and were more likely to continue to exercise when given the option to stop (Caldwell, Hooper, Bryan and Hagger, 2014). In the present study, long-distance runners of Ethiopian origin had a significantly lower prevalence of the *BDNF* Met allele compared to non-Ethiopian runners and even to the controls. The results suggest that this genetic difference might be beneficial for increased motivation and performance for the non-Ethiopian origin long-distance runners.

IV. FINDINGS

The complete data on allele and genotype frequencies are presented in Table 4. The genotype subtype did not differ by age or gender. All genotypes were in agreement with the Hardy-Weinberg equilibrium for both Ethiopian-origin,non-Ethiopian origin, and controls (*HTR2A* rs6313: p = 0.716 for Ethiopian origin, p = 0.288 for non-Ethiopian;*HTR2*A rs3742278: p = 0.999 for Ethiopian origin, p = 0.541 for non-Ethiopian; *COMT* rs4680: p = 0.408 for Ethiopian origin, p = 0.999 for non-Ethiopian origin; and BDNF rs6265: p = 0.834 for Ethiopian origin, p = 0.065 for Non-Ethiopian origin.

Table 4. ***Genotype and allele frequencies (%)***

SNP	Non-Ethiopian Origin			Ethiopian Origin			p
	Top level	National level	Total	Top level	National level	Total	
N	22	53	75	26	11	37	
HTR2A (rs6313 C/T)							
CC	5(23)	10(19)	15(20)	6(23)	5(55)	11(30)	
CT	9(41)	31(58)	40(53)	12(46)	4(36)	16(30)	
TT	8(36)	12(23)	20(27)	8(31)	2(9)	10(24)	
C allele	19(43)	51(48)	70(47)	24(46)	14(64)	38(51)	
T allele	25(57)	55(52)	80(53)	28(54)	8(36)	36(49)	
HTR2A (rs3742278 T/C)							
TT	17(77)	39(73)	56(74)	16(61)	7(64)	23(62)	
TC	5(23)	12(23)	17(23)	8(31)	4(36)	12(32)	
CC	0(0)	2(4)	2(3)	2(8)	0(0)	2(6)	
T allele	39(89)	90(85)	129(86)	40(77)	18(82)	58(78)	
C allele	5(11)	16(15)	21(14)	12(23)	4(18)	16(22)	
*COMT (*rs46808 G/A)							
GG	5(23)	17(32)	22(29)	7(27)	2(18)	9(24)	
AA	13(59)	18(34)	31(42)	10(38)	4(36)	14(38)	
AG	4(18)	18(34)	22(29)	9(35)	5(46)	14(38)	
G allele	23(52)	52(49)	75(50)	24(46)	8(36)	32(43)	
A allele	21(48)	54(51)	75(50)	28(54)	14(64)	42(57)	
BDNF (rs6265, C/T)							
CC	14(64)	36(68)	50(67)	24(92)	10(91)	34(92)	1,2,3
CT	7(32)	14(26)	21(28)	1(4)	1(9)	2(5)	
TT	1(4)	3(6)	4(5)	1(4)	0(0)	1(3)	
C allele	35(80)	86(81)	121(81)	49(94)	21(95)	70(95)	
T allele	9(20)	20(19)	29(19)	3(6)	1(5)	4(5)	

[1]$\chi^2(2) = 8.646$, p=0.013 genotypes frequency, Ethiopian-origin athlete vs. non-Ethiopian origin athletes
[2]$\chi^2(2) = 6.846$, p=0.032 genotypes frequency, top-level Ethiopian-origin athlete vs. top-level non-Ethiopian originathletes
[3]$\chi^2(2) = 8.408$, p=0.004 Met allele carriers, Ethiopian-origin athlete vs. non-Ethiopian originathletes

HTR2A C/T rs6311, *HTR2A* T/C rs3742278 and *COM*T G/A rs4680 genotype and allele frequencies did not significantly differ between Ethiopian-origin athletes andnon-Ethiopian-origin athletes (p>0.05). However, *BDN*F C/T rs6265 genotype frequencies differed significantly between Ethiopian-origin and non-Ethiopian-origin athletes (p=0.013), with a low prevalence of Met allele carriers among Ethiopian-origin (8%) compared to non-Ethiopian-origin athletes (33%, p=0.004) (Fig. 1).

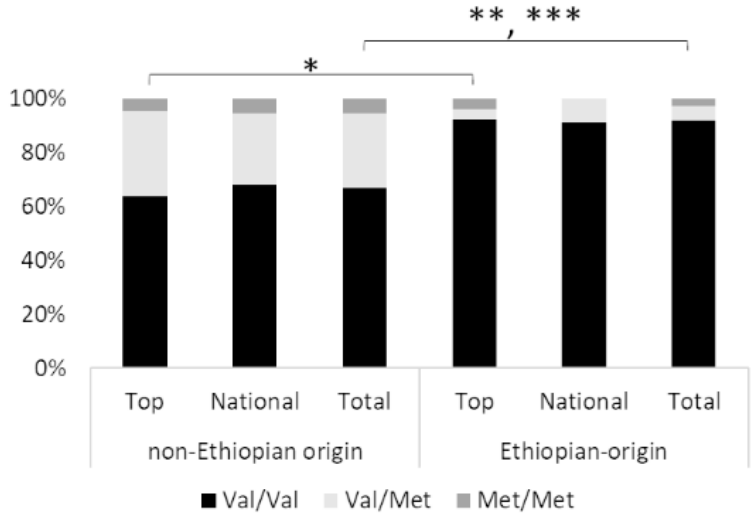

Fig. 1. BDNF Val/Met rs6265 polymorphism among athletes

$*\chi^2(2) = 8.646$, p=0.013 genotypes frequency, Ethiopian-origin athlete vs. non-Ethiopian n athletes
$**\chi^2(2) = 6.846$, p=0.032 genotypes frequency, top-level Ethiopian-origin athlete vs. top-level non-Ethiopian origin athletes
$***\chi^2(1) = 8.408$, p=0.004 Met allele carriers, Ethiopian-origin athlete vs. non-Ethiopian origin athletes

V. CONCLUSIONS

The present study examined whether the dominance of Israeli long-distance runners of Ethiopian origin is related to several genetic polymorphisms related to the dopamine and serotonin systems and to motivation. None of the SNPs tested were advantageous among the Ethiopian-origin runners, and in fact the BANF polymorphism was even more potentially beneficial for the non-Ethiopian-origin long-distance runners. These findings suggest that the dominance of Israeli long-distance runners of Ethiopian origin relates mainly to a divergent genetic physiological basis/ which includes endurance and also speed capabilities and training recovery polymorphisms (Ben-Zaken *et al.*, 2019). It is also possible that other motivational genetic polymorphisms that were not examined in the present study would reveal different results. Finally, it is possible that environmental and epigenetic factors are equally, and perhaps even more, important for the expression of motivation in sports, particularly in long-distance running. Further research is definitely required to better understand this understudied area in competitive sports.

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