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Interaction between SNPs in the *NRF2* gene and elite endurance performance

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Eynon N, Alves AJ, Sagiv M, Yamin C, Sagiv M, Meckel Y. Interaction between SNPs in the *NRF2* gene and elite endurance performance. *Physiol Genomics* 41: 78–81, 2010. First published December 22, 2009; doi:10.1152/physiolgenomics.00199.2009.—Nuclear respiratory factor 2 (NRF2), a member of the Cap-N-Collar family of transcription factors, plays an important role in the mitochondrial biogenesis, and variants of *NRF2* gene have been associated with endurance performance. The aims of the present study were *1*) to compare *NRF2* A/C (rs12594956) and *NRF2* C/T (rs8031031) genotype and allele frequencies between athletes of sports with different demands (endurance vs. sprinters) as well as between competitive levels (elite level vs. national level) and *2*) to analyze the interaction of these two polymorphisms and its influence on the level of endurance performance. One hundred and fifty-five track and field athletes (74 endurance athletes and 81 sprinters) and 240 nonathletic healthy individuals participated in this study. Endurance athletes presented a higher frequency of the AA (rs12594956) and CT (rs8031031) genotypes than sprinters and the control group, as well as higher A and T alleles, respectively. These differences did not appear between the sprinters and control subjects. The odds ratio for harboring the "optimal genotype" (*NRF2* AA + *NRF2* CT) was 4.53 (95% confidence interval 1.23–16.6) in the whole cohort of endurance athletes and 6.55 (95% confidence interval 1.12–38.25) in elite-level endurance athletes, compared with control subjects and both levels of sprinters. In conclusion, our data indicate that the *NRF2* A/C and *NRF2* C/T single nucleotide polymorphisms (SNPs) are associated, separately and in combination, with elite endurance athletes, which supports the notion that these specific gene variants might belong to a growing group of SNPs that are associated with endurance performance.

polymorphisms; sprinters; endurance athletes

ELITE ATHLETES are those who have represented their sport at a major competition: this includes participation in national, international, and world championship events (20). It is now well appreciated that attaining athletic performance status involves multiple genetic factors, with >20 single nucleotide polymorphisms (SNPs) suggested to date as influencing the outcome of elite athletic challenges (6).

The nuclear respiratory factor 2 (NRF2) protein is a member of the Cap-N-Collar transcription factor family that recognizes the antioxidant response element (ARE) in the promoter of target genes (25). NRF2 was discovered as the human homolog of the mouse GA-binding protein (GABP) (23, 24). It was suggested that the *NRF2* gene (GABPB1) encoding the NRF2 protein improves respiratory capacity and increases the rate of ATP production during exercise (12, 19). This is due to its important role in inducing mitochondrial biogenesis (12, 22). In addition, the *NRF2* gene regulates several nuclear genes encoding mitochondrial proteins, including cytochrome *c* and TFAM, as well as regulating heme biosynthesis proteins (9).

A previous study suggested that the β_1-subunit of the *NRF2* gene, located on chromosome 15q21.2, might be linked with elevated maximal oxygen consumption ($\dot{V}O_{2\,max}$) in response to endurance training (5). In an attempt to connect this finding with specific SNPs, He et al. (10) suggested that the AA genotype of rs12594956 in the *NRF2* gene is associated with higher baseline $\dot{V}O_{2\,max}$ in the Chinese Han population. Furthermore, this study acknowledged that a specific ATG haplotype of rs12594956, rs7181866, and rs8031031 is associated with elevated running economy in response to 18 wk of endurance training. A recent study in our laboratory (8) suggested that in Israeli athletes the *NRF2* AG genotype of the *NRF2* intron 3 A/G polymorphism (rs7181866) is associated with endurance and within the endurance group the *NRF2* AG genotype and the G allele are associated with a higher level of endurance performance.

Together, the accumulated data suggest that these specific polymorphisms might be associated with elite endurance performance. Therefore, the aims of the present study were *1*) to compare the frequency distribution of the *NRF2* A/C (rs12594956) and *NRF2* C/T (rs8031031) polymorphisms between athletes of sports with different demands (endurance vs. sprinters) as well as between competitive levels (elite level vs. national level) and *2*) to test the influence of the interaction between the *NRF2* A/C and *NRF2* C/T genotypes on endurance performance.

MATERIALS AND METHODS

Participants. The study followed recent recommendations for replicating genotype-phenotype association studies (7). We did not perform genotyping in two independent laboratories with different methodologies. One hundred and fifty-five track and field athletes (119 men and 36 women, age 35.9 ± 12.2 yr) volunteered to participate in the study. We included athletes in the study sample only if they had participated in national/international track and field championships. The control group consisted of 240 nonathletic healthy individuals (167 men and 73 women) who were randomly selected from the Israeli population. Control subjects were not engaged in physical activity on a regular basis. We divided the athletes into two groups: *1*) an endurance-type group that included 74 long-distance runners (60 men and 14 women) whose main events were the 10,000-m run and the marathon and *2*) a sprint-type group that included 81 sprinters (59 men and 22 women) whose main events were the 100- to 200-m dash and long jump. According to their individual best performances, we further divided the athletes within each group into two subgroups: elite level (those who had represented Israel in world track and field championships or in the Olympic Games; 28 men and 18 women) and national level (91 men and 18 women). All participants, athletes and nonathletes, were Israeli Caucasians for at least three generations, with an equivalent ratio of mixed Jews coming from Arab countries

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(non-Ashkenazi) and Jews coming from Europe (Ashkenazi) (2:1, respectively). The study was approved by the Helsinki Committee, the formal ethics committee of the Hillel Yaffe Medical Center, Hadera, Israel, according to the Declaration of Helsinki. Written informed consent was obtained from each participant.

Genotyping. We extracted genomic DNA from peripheral EDTA-treated anticoagulated blood with a standard protocol. Genotyping of *NRF2* A/C (rs12594956) and C/T (rs8031031) was performed with polymerase chain reaction (PCR). A 407-bp fragment of the *NRF2* A/C (rs12594956) polymorphism was amplified with primers *NRF2*-F 5′-TAAAATGAATAAAGGTGGGGGT-3′and *NRF2*-R 5′-TAAGAGTGGAAGGGTGGAGAA-3′. PCR was performed by denaturation at 94°C for 5 min, 34 cycles of denaturation at 94°C for 1 min, annealing at 53°C for 1 min, and extension at 72°C for 1 min, and a final extension step of 10 min at 72°C. The amplified fragment subsequently underwent digestion by *Mfe*I (New England Biolabs, Beverly, MA) in a condition recommended by the supplier. The digested products were then electrophoresed in a 2% agarose gel. This method yields 277-bp and 130-bp fragments in the presence of the A allele and a 407-bp fragment in the presence of the C allele. The *NRF2* C/T (rs8031031) polymorphism was amplified with primers F-5′-CTAAAATGTGAGGGAAGGAAGA-′3 and R-5′-ATAGAGAGATAGGACTAAGGAC-′3. PCR was performed by denaturation at 94°C for 5 min, 34 cycles of denaturation at 94°C for 1 min, annealing at 57°C for 1 min, and extension at 72°C for 1 min, and a final extension step of 10 min at 72°C. The amplified fragment subsequently underwent digestion by *Rsa*I (New England Biolabs). This method yields a 208-bp fragment in the presence of the C allele and 158- and 50-bp fragments in the presence of the T allele. To ensure proper internal control, for each genotype analysis we used positive and negative controls from different DNA aliquots that were previously genotyped with the same method, according to recent recommendations for replicating genotype-phenotype association studies (7). The restriction fragment length polymorphism (RFLP) results were scored by two experienced and independent investigators who were blind to the participants' data.

Data analysis. The SPSS statistical package, version 17.0, was used to perform all statistical evaluations (SPSS, Chicago, IL). Allele frequencies were determined by gene counting. A Pearson χ^2-test, Yates corrected χ^2-test, or Fischer exact test was used to confirm that the observed genotype frequencies were in Hardy-Weinberg equilibrium and to compare the *NRF2* A/C and *NRF2* C/T alleles and genotype frequencies between athletes and control subjects. One of these tests was also used to examine the interaction between the *NRF2* A/C and *NRF2* C/T genotypes in relation to endurance performance and in relation to the endurance athletes' level of performance. A logistic regression analysis was set in order to calculate the odds ratio for the interaction of both polymorphisms in endurance athletes, in sprinters, and in control subjects. The level of significance was set at $P < 0.05$.

Table 1. *Genotype distribution of NRF2 A/C and NRF2 C/T SNPs in all groups*

	n	Genotype		
NRF2 A/C		AA	AC	CC
Endurance	74	43 (58)*†	27 (37)*†	4 (5)*†
Sprinters	81	28 (35)	38 (47)	15 (18)
Control	240	102 (43)	111 (46)	27 (11)
NRF2 C/T		CC	CT	TT
Endurance	74	66 (89)‡§	8 (11)‡§	0 (0)
Sprinters	81	80 (99)	1 (1)	0 (0)
Control	240	231 (96)	9 (4)	0 (0)

Data are presented as absolute and relative (within parentheses) values. NRF2, nuclear respiratory factor 2; SNP, single nucleotide polymorphism. *χ^2 = 11.10, degrees of freedom (df) = 2, P = 0.004 for genotype frequencies in endurance athletes vs. sprinters; †χ^2 = 6.17, df = 2, P = 0.046 for genotype frequencies in endurance athletes vs. control subjects; ‡χ^2 = 6.48, df = 1, P = 0.011 for genotype frequencies in endurance athletes vs. sprinters; §χ^2 = 5.50, df = 1, P = 0.019 for genotype frequencies in endurance athletes vs. control subjects.

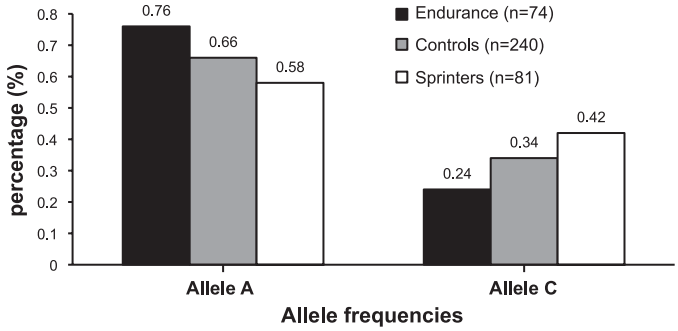

Fig. 1. Allele frequencies (in percentage) of nuclear respiratory factor 2 (*NRF2*) A/C in sprinters, endurance athletes, and control subjects. *χ^2 = 11.7, degrees of freedom (df) = 2, P = 0.003 for allele frequencies in endurance athlete, sprinters, and control subjects.

RESULTS

The complete data on genotype distribution of the *NRF2* A/C and C/T polymorphisms are shown in Table 1. The genotype subtype of the *NRF2* A/C and C/T did not differ by sex in the athlete group or in the control group ($P > 0.01$). *NRF2* A/C and C/T genotype and allele frequencies met Hardy-Weinberg expectations in the endurance athletes, sprinters, and control subjects ($P > 0.01$). Since the Israeli population includes Caucasians who are mixed non-Ashkenazi and Ashkenazi, we confirmed that there was an equivalent ratio of non-Ashkenazi and Ashkenazi descent in each group (2:1) and that there were no differences across *NRF2* genotype between non-Ashkenazi and Ashkenazi descendants ($P > 0.01$). Genotype distribution (see Table 1) and allele frequencies (see Fig. 1 and Fig. 2) of the *NRF2* A/C and the *NRF2* C/T SNPs were significantly different between the groups of endurance athletes, sprinters, and control subjects, with a higher frequency of the A allele and the CT genotype among the endurance athletes. However, the sprinters' genotype distribution was similar to those of the control group [χ^2 = 3.392, degrees of freedom (df) = 2, P = 0.183 for NRF2 A/C and χ^2 = 1.270, df = 1, P = 0.260 for NRF2 C/T]. A comparison between elite-level and national-level endurance

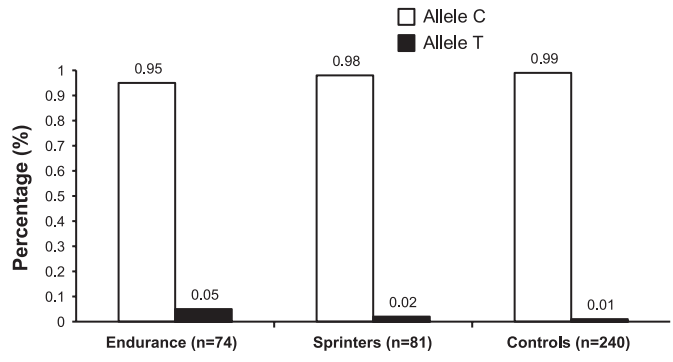

Fig. 2. Allele frequencies (in percentage) of *NRF2* C/T in sprinters, endurance athletes, and control subjects. *χ^2 = 8.85, df = 2, P = 0.012 for allele frequencies in endurance athlete, sprinters, and control subjects.

Table 2. *NRF2 A/C and C/T genotype and allele frequencies in sprinters and endurance athletes according to their level of competition*

Athlete Group	Competitive Level	*n*	Genotype			Allele Frequencies	
NRF2 A/C			AA	AC	CC	Allele A	Allele C
Endurance	Elite level	20	13 (65.0)	6 (30.0)	1 (5.0)	32 (80.0)*	8 (20.0)*
	National level	54	30 (55.5)	21 (38.9)	3 (5.6)	81 (75)	27 (25)
Sprinters	Elite level	26	7 (26.9)	10 (38.5)	9 (34.6)	24 (46.2)	28 (53.8)
	National level	55	21 (38.2)	28 (50.9)	6 (10.9)	70 (63.6)	40 (36.4)
NRF2 C/T			CC	CT	TT	Allele C	Allele T
Endurance	Elite level	20	17 (85.0)	3 (15.0)	0 (0)	37 (92.5)	3 (7.5)
	National level	54	49 (90.7)	5 (9.3)	0 (0)	103 (95.3)	5 (4.6)
Sprinters	Elite level	26	25 (96.2)	1 (3.8)	0 (0)	51 (98.1)	1 (1.9)
	National level	55	55 (100)	0 (0)	0 (0)	110 (100)	0 (0)

Data are presented as absolute and relative (within parentheses) values. *$\chi^2 = 8.56$, df = 2, $P = 0.014$ for allele frequencies in endurance vs. sprinter in elite-level athletes and $\chi^2 = 3.58$, df = 2, $P = 0.167$ for allele frequencies in endurance vs. sprinter in national-level athletes.

athletes (see Table 2) revealed that the A allele of the *NRF2* A/C SNP was more frequent in elite endurance athletes than in elite sprinters ($P = 0.014$). The *NRF2* AA+*NRF2* CT genotype was found to be the "optimal genotype" for endurance athletes compared with the other genotypes (see Table 3).

The odds ratio of finding the optimal genotype (*NRF2* AA+*NRF2* CT) was 4.53 (95% confidence interval 1.23–16.6) in endurance athletes after adjusting for sex, compared with the other participants. The odds ratio of finding the optimal genotype was 6.55 (95% confidence interval 1.12–38.25) in elite-endurance athletes compared with the other participants.

DISCUSSION

In the present study the frequency distribution of *NRF2* A/C and *NRF2* C/T genotypes was assessed in elite endurance and sprint athletes. Our main findings were that *1*) the *NRF2* A allele and the *NRF2* C/T genotype were significantly more frequent among endurance athletes and *2*) the combined *NRF2* AA+*NRF2* C/T genotype was more frequent in endurance athletes than in the sprinters group and the control group. These findings suggest that harboring this specific genotype might increase the probability of being an endurance athlete.

The *NRF2* gene plays a significant role in the induction of mitochondrial biogenesis (12, 22). The process of mitochondrial biogenesis is complex. The major steps involved in this process include signaling events leading to transcription, brought about by each exercise bout, and transcriptional regulation of nuclear genes, such as *NRF2*, mainly mediated by peroxisome proliferator-activated receptor γ coactivator 1α (*PPARGC1A*) (1, 11). Since a functional polymorphism in the *PPARGC1A* gene (e.g., Gly482Ser, rs8192678) was found to be associated with elite Israeli (8), Spanish (15) and Russian (2) endurance athletic status, it could be that the *PPARGC1A-NRF2* gene pathway is important in the process of becoming an elite endurance athlete.

Table 3. *Combined NRF2 A/C and NRF2 C/T SNP genotype frequencies within endurance athletes, sprinters, and control group*

NRF2 A/C	NRF2 C/T	Endurance Athletes ($n = 74$)	Sprinters ($n = 81$)	Control ($n = 240$)
AA	CC	37 (50)	27 (33.3)	98 (40.8)
AA	CT	6 (8.1)*	1 (1.2)	4 (1.7)
AC	CC	25 (33.8)	38 (47)	107 (44.6)
AC	CT	2 (2.7)	0 (0)	4 (1.7)
CC	CC	4 (5.4)†	15 (18.5)	26 (10.8)
CC	CT	0 (0)	0 (0)	1 (4)

Data are presented as absolute and relative (within parentheses) values. $\chi^2 = 22.4$, df = 10, $P = 0.013$ for overall combined genotype distribution. *$\chi^2 = 6.9$, df = 2, $P = 0.03$ for genotype frequencies differences in *NRF2* AA+CT ("optimal" genotype for endurance athletes) vs. other genotypes between endurance athletes, sprinters, and control subjects; †$\chi^2 = 6.8$, df = 2, $P = 0.034$ for genotype frequencies differences in *NRF2* CC+CC ("not preferred" genotype) vs. other genotypes between endurance athletes, sprinters, and control subjects.

The A allele and the CT genotype of the *NRF2* A/C and C/T SNPs, respectively, were more frequent in the group of endurance athletes. A specific comparison between the subgroups of elite and national endurance athletes revealed that 80% of the elite-level endurance athletes were carrying the A allele of the *NRF2* A/C SNP, compared with only 46% of the elite-level sprinters. It is clear that individuals exist who have combinations of genotypes at multiple distinct loci that generate athletic performance (20). In the present study, it was found that >8% of the endurance athletes carried the "optimal" AA+CT genotype, belonging to two separate SNPs in the *NRF2* gene. Thus it appears that *NRF2* A/C together with *NRF2* C/T belong to a growing group of SNPs previously found to be associated with endurance performance (6). This assumption is supported by a previous study that reported a remarkable increase in muscle NRF2 protein levels 12–18 h after an acute bout of endurance exercise (4). Another study reported that the *PPARGC1A* gene induced a two- to threefold increase in the expression of the *NRF2* gene in response to endurance exercise (3). These findings lead us to believe that the *NRF2* AA and *NRF2* CT genotypes may stimulate a greater increase in *NRF2* protein and/or mRNA levels, and thus possessing the AA+CT genotype might confer an advantage to endurance athletes but not to sprinters.

Further explanations for the advantage attained by a higher expression of *NRF2* might come from its pivotal role in inducing antioxidative enzymes (13). *NRF2* has been shown to play a key role in inducing many antioxidative enzymes (such as heme oxygenase-1) and diverse defensive genes against oxidative stress (13, 18). *NRF2* also regulates cytoprotective enzymes that eventually provide multiple layers of protection during cellular insults, collectively favoring cell survival (19).

It is unclear how these specific SNPs influence the regulation of *NRF2* gene and/or protein expression, since these particular

SNPs are located in an intron region of the gene, and their functionality needs to be elucidated (10). Recently, genome-wide association analysis identified loci for type 2 diabetes and triglyceride levels within the intron region of several unsuspected genes (21). It should be noted that mutations positioned in a noncoding region, such as *NRF2* A/C and *NRF2* C/T, might regulate the alternative splicing of mRNA, leading to expression differences and hence an effect on mitochondrial biogenesis (10). For instance, one study has shown that sequences in the intron region of the apolipoprotein A-II gene (*Apo-II*) modulate *Apo-II* exon 3 splicing (17).

It has been suggested that genetic association studies be interpreted with caution (14), because as with any statistical analysis the possibility of false positive results attributable to chance cannot be diminished. This is particularly true in studies involving multiple gene-trait analyses (16). In an attempt to avoid a false positive result, this study compared two groups of "extreme" phenotype cohorts (i.e., groups of people who exhibit extreme levels of a given outcome trait). This kind of comparison can maximize statistical power in studies that seek to test hypotheses of genetic association (15).

In conclusion, our data indicate that there is an association between the *NRF2* A/C and *NRF2* C/T SNPs, separately and together, and elite endurance athletes. Our findings support the concept that these specific SNPs might belong to a growing group of SNPs associated with endurance performance at the elite level.

DISCLOSURES

The authors are not aware of financial conflict(s) with the subject matter or materials discussed in this manuscript with any of the authors, or any of the authors' academic institutions or employers.

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References 13, 18, 19, and 25 were cited in error. These studies (Kobayasahi and Yamamoto, *Antioxid Redox Signal* 7: 385–394, 2005; Numazawa and Yoshida, *J Toxicol Sci* 29: 81–89, 2004; Osburn and Kensler, *Mutat Res* 659: 31–39, 2008; Yu and Kensler, *Mutat Res* 591: 93–102, 2005) deal with the transcription factor Nrf2. The Nfr2 is a completely different protein from the nuclear respiratory factor 2 (NRF-2), the protein encoded by the *NRF2* gene that we studied here. The Nfr2 is involved in antioxidant defense, whereas the NRF-2 plays a pivotal role in mitochondrial biogenesis. These references were erroneously cited in the second paragraph of the INTRODUCTION (1st sentence), and in the 4th paragraph of the DISCUSSION.

The authors regret these errors. We are however confident that the aforementioned errors do not actually diminish the scientific contribution of our study nor affect the conclusions reached.