Can we identify a power-oriented polygenic profile?

**Juan R. Ruiz, David Arteta, Amaya Buxens, Marta Artieda, Félix Gómez-Gallego, Catalina Santiago, Thomas Yvert, María Morán, and Alejandro Lucia**

1Department of Biosciences and Nutrition at NOVUM, Unit for Preventive Nutrition, Karolinska Institutet, Huddinge, Sweden; 2Progenika Biopharma, Zamudio, Spain; 3Universidad Europea de Madrid, Madrid, Spain; and 4Centro de Investigación, Hospital 12 de Octubre, Madrid, Spain

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**Methods**

**Subjects**

Written consent was obtained from each subject. The study protocol was approved by the institutional ethics committee (Universidad Europea de Madrid, Madrid, Spain) and was in accordance with the Declaration of Helsinki for Human Research of 1974 (last modified in 2000). The population comprised 253 Spanish (Caucasian for ≥3 generations) healthy men as follows.

**GENETIC ENDOWMENT** is one of the factors that are likely to increase the possibility of one becoming an elite athlete. Being a sports champion is a very complex attribute that results from the combined influence of hundreds of genetic polymorphisms (29). Such a complex trait is difficult to identify with association studies, that is, studies showing between-group differences in the genotypic/allelic frequency of a given polymorphism. New approaches should be identified taking into account the complexity of the question.

One possible approach is conducting genomewide association studies as the one performed by De Moor et al. (6), yet whether their findings can be extrapolated to actual elite (i.e., international level) athletic status is unclear. Using a simpler model, Williams and Folland (39) computed the so-called “total genotype score” (TGS; ranging from 0 to 100), resulting from the accumulated combination of 23 polymorphism that are candidates to explain individual variations in endurance performance. Using a similar model, yet limited to seven well-studied polymorphisms associated with endurance capacity in Caucasians, we determined the actual TGS of the best Spanish male distance runners and road cyclists (29). We showed that the mean TGS of these endurance athletes was significantly higher than that of the Spanish population (70.2 ± 15.6 vs. 60.8 ± 12.1, respectively), suggesting an overall more “favorable” polygenic endurance profile in the athletes group (29).

Less information is available regarding polymorphisms associated with elite athletic status in power/sprint-oriented events such as jumping or sprinting track and field specialties. Therefore, based on the model originally developed by Williams and Folland (39), we determined the theoretically optimal polygenic profile associated with power-oriented sports in a group of power athletes, and in an ethnically and sex-matched endurance athletes and nonathletic control groups (all Spanish Caucasian males). We also determined the probability for the occurrence of Spanish individuals with the “perfect” power polygenic profile.

While recognizing the possibility that several polymorphisms yet to be identified might play a more important role, based on recent published data, we used the six candidate polymorphisms that we believed to be more important at present (at least in Caucasians), for explaining individual variations in power sports performance or power-related phenotypes. The candidate polymorphism included (Table 1): 1) the 287-bp Ins(I)/Del(D) polymorphism (rs1799752) of the angiotensin converting enzyme (ACE) gene (424); 2) the Arg(R)/Thr(T) polymorphism (rs1805086) of the actinin (ACTN3) gene (33); 3) the Met235Thr polymorphism (rs699) of the angiotensinogen (AGT) gene (14); 4) the myostatin (growth and differentiation factor, GDF-8) K153R polymorphism (rs1805086) polymorphism (10, 16, 33); 5) the −174 G/C polymorphism (rs1800795) of the interleukin-6 (IL6) gene (28); and 6) the −786T>C polymorphism (rs2070744) in the 5′-flanking region of the nitric oxide (NO) synthase (NOS3) gene (12).

We hypothesized that the “optimum” polygenic profile differs between power and endurance-oriented athletes owing to the fact that the phenotype traits that determine performance in both types of events are likely different.

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**ACKNOWLEDGMENTS**

*J. R. Ruiz and D. Arteta contributed equally to this study.

Address for reprint requests and other correspondence: J. R. Ruiz, Dept. of Biosciences and Nutrition at NOVUM, Unit for Preventive Nutrition, Karolinska Institutet, Huddinge 14157, Sweden (e-mail: ruizj@ugr.es).
Table 1. Studied polymorphisms and genotype frequencies in Spanish population, Spanish endurance elite athletes, and power elite athletes

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Gene (peptide-dipeptidase A)</th>
<th>Polymorphism</th>
<th>Genotypes (2=“Optimal” Power Genotype)</th>
<th>In Spanish controls</th>
<th>In Spanish endurance elite athletes</th>
<th>In Spanish power elite athletes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin I-converting enzyme</td>
<td>287-bp Ins(I)/Del(D) (rs1799752)</td>
<td>0 = II, 1 = ID, 2 = DD</td>
<td>44, 43, 13</td>
<td>44, 36, 20</td>
<td>40, 49, 11</td>
</tr>
<tr>
<td>ACTN3</td>
<td>Actinin, alpha 3</td>
<td>Arg(R)/Gln(Q) (rs1815739)</td>
<td>0 = XX, 1 = RX, 2 = RR</td>
<td>13, 58, 29</td>
<td>29, 46, 25</td>
<td>13.2, 43.4, 43.4</td>
</tr>
<tr>
<td>AGT</td>
<td>Angiotensinogen</td>
<td>Met235Thr (rs699)</td>
<td>0 = TT, 1 = TC, 2 = CC</td>
<td>34, 50, 16</td>
<td>16, 50, 34</td>
<td>33.3, 31.7, 34.9</td>
</tr>
<tr>
<td>GDF-8</td>
<td>Myostatin (growth and differentiation factor)</td>
<td>Lys(K)/Arg(R) (rs1805086)</td>
<td>0 = RR, 1 = RK, 2 = KK</td>
<td>0, 8, 92</td>
<td>0, 10, 90</td>
<td>0.7, 92.5</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleukin 6</td>
<td>−174 G/C (rs1800795)</td>
<td>0 = CC, 1 = GC, 2 = GG</td>
<td>12, 46, 42</td>
<td>15, 43, 42</td>
<td>9, 26, 65</td>
</tr>
<tr>
<td>NOS3</td>
<td>Nitric oxide synthase 3</td>
<td>−866 T/C (rs2070744)</td>
<td>0 = CC, 1 = TC, 2 = TT</td>
<td>21, 45, 34</td>
<td>27, 40, 33</td>
<td>15, 28, 57</td>
</tr>
</tbody>
</table>

The group comparisons of genotypic and allelic frequency of these polymorphisms have been published elsewhere (Refs. 13, 14, 28).

1) Fifty-three elite power (track and field) athletes aged 20–33 yr, including the best Spanish jumpers (n = 13) and sprinters (n = 40) in recent years, formed one study group. Thirteen of them were Olympians during the period 2000–2008. Their mean (SD) maximal oxygen uptake (V\textsubscript{O2max}) was 60.3 (5.5) ml·kg\textsuperscript{-1}·min\textsuperscript{-1}.

2) One hundred endurance elite athletes aged 20–39 yr were another study group. This sample included 50 elite endurance runners (the top Spanish runners during the 1999–2009 period) and 50 professional road cyclists who were all Tour de France finishers. Their V\textsubscript{O2max} was 73.7 ± 5.7 ml·kg\textsuperscript{-1}·min\textsuperscript{-1}.

3) One hundred healthy nonathletic controls aged 19–32 yr (V\textsubscript{O2max}: 50.1 ± 2.6 ml·kg\textsuperscript{-1}·min\textsuperscript{-1}) formed a third study group. All were undergraduate Physical Education students from the same university (Universidad Europea de Madrid, Madrid, Spain). Inclusion criteria for this group were to be free of any diagnosed cardiorespiratory disease and not to be engaged in competitive sports or in formal, supervised exercise training (i.e., performing less than 3 structured weekly sessions of strenuous exercise as running, swimming, bicycling, or weight lifting).

The test protocols for V\textsubscript{O2max} determination are explained in detail elsewhere (28). The athlete sample size, especially for power athletes, is limited as we wanted to ensure that we gathered only the best track and field power athletes and the best endurance Spanish athletes in recent years.

Genotypes

We selected those genetic polymorphisms for which an association with power performance was previously shown in publications using Caucasian elite power athletes as subjects (13, 14, 28). We also included the most common functional polymorphism of the myostatin gene in Caucasians given the important role that myostatin plays in modulating muscle phenotypes (16) (Table 1). The putative influence(s) of the studied gene/polymorphisms in elite endurance/power sports performance (or in important exercise/performance related phenotypes) is detailed below.

1) The ACE I/D polymorphism (rs1799752) is arguably the most extensively studied genetic variation with regard to exercise-related phenotypes. It is related to cardiovascular and skeletal muscle function, but also to skeletal muscle hypertrophy as angiotensin-converting enzyme catalyzes the synthesis of ANG II, which acts as a skeletal muscle growth factor (17, 42). While the I allele has been associated with elite endurance performance, e.g., in runners (19), the D allele, which is associated with higher circulating ANG II, might favor performance in power-oriented sport events (4, 24).

2) The ACTN3 R577X polymorphism (rs1815739) of the actinin, alpha 3 (ACTN3) gene encodes for the synthesis of α-actinin-3, a protein necessary for producing fast, powerful sarcomeric contractions in type II skeletal muscle fibers (22). This polymorphism is associated with elite power/sprint performance (8, 9, 20, 25–27, 32), with the α-actinin-3 deficient (XX) genotype virtually precluding top-level (Olympic class) power performance, at least in women (42).

3) The Met235Thr polymorphism (rs699) of the AGT gene is associated with elite power sports performance, with the C allele exerting a favorable effect probably owing to higher ANG II levels (14). Overall, both ACE and AGT genes play a crucial role in the renin-angiotensin-aldosterone system, which modulates important cardiac and muscle phenotypes during exertion in humans.

4) The GDF-8 gene is a strong candidate for explaining human variability in skeletal muscle phenotypes, e.g., strength (16). It encodes myostatin, a skeletal muscle-specific secreted peptide that functions to limit muscle growth (21). In transgenic animal models, prolonged absence of myostatin reduces sarcopenia (34) and systemic treatment with myostatin inhibitors seems to increase muscle size (38). Several polymorphisms and mutations have been identified in the GDF8 gene with diverse functional consequences. Of the identified polymorphisms, the Lys(K)153Arg(R) variation located in exon 2 (rs1805086, 2379 A>G replacement) is a candidate to influence skeletal muscle phenotypes. Although controversy exists (18), the rs1805086 polymorphism is associated with muscle strength in Caucasians, with the R allele [present in 3–4% of the population (3, 10, 18)] exerting a negative influence (10, 16, 33).

5) The IL6 −174 G/C polymorphism (rs1800795) is associated with power sports performance, with the G allele exerting a favorable effect (vs. no effect on endurance performance) (28). This in turn could be due to the improved muscle repair response after eccentric damage that is associated with the G allele (40).

6) The gene, NOS3, encoding NO synthase is a candidate for explaining human individual variability in health- and exercise-related phenotypes (2). In contrast with other linked polymorphisms (∼922A/G and −1468T/A) that are not associated with changes in gene transcription, the −786C→mutation of the NOS3 −786 T/C polymorphism (rs2070744) results in significantly reduced gene promoter activity and reduced endothelial NO synthesis (23). The rs2070744 polymorphism is associated with elite power sports performance (12). The wild-type T allele, which is associated with increased gene promoter activity and higher endothelial NO synthesis compared with the mutant (C) allele (23), would exert its favorable effect in power performance through the muscle hypertrophic stimulus brought about by NO-mediated vasodilatation (12).

Genotype Analysis

We obtained DNA from all subjects’ blood or saliva samples over years 2004 to 2008. All genotyping procedures were in accordance with stringent recommendations for replicating human genotype-phenotype association studies (5) and were performed in the same laboratory (Progenika Biopharma, Parque Tecnológico de Zamudio, http://jap.physiology.org/ Downloaded from by 178.220.32.2 on August 28, 2017
Table 2. Probability of possessing perfect genetic profile by number of polymorphisms in Spanish population

<table>
<thead>
<tr>
<th>Polymorphisms Influencing Power Performance</th>
<th>New Gene Included at Each Stage</th>
<th>Typical Frequency of “Optimal” Genotype in Spanish Population, %</th>
<th>Probability of Possessing a “Perfect” Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%Chance</td>
<td>Approximate odds ratio</td>
</tr>
<tr>
<td>1</td>
<td>ACE</td>
<td>13</td>
<td>13.0</td>
</tr>
<tr>
<td>2</td>
<td>ACTN3</td>
<td>28</td>
<td>3.8</td>
</tr>
<tr>
<td>3</td>
<td>AGT</td>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td>4</td>
<td>GDF-8</td>
<td>90</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>IL-6</td>
<td>42</td>
<td>0.3</td>
</tr>
<tr>
<td>6</td>
<td>NOS3</td>
<td>34</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Data obtained from a data set of 50,000 hypothetical Spanish individuals, each with a randomly generated genetic profile (for all 6 polymorphisms) based on the typical frequency of each genotype. See text for gene abbreviations.

RESULTS

We calculated the mean and kurtosis statistics of the TGS obtained in the three study groups and that extrapolated for the Spanish population. We compared the TGS of power athletes, endurance athletes, and controls with a one-factor ANOVA test and used Tukey post hoc test for between-group comparisons. We evaluated the ability of the TGS to correctly classify potential elite power athletes from nonathletes (0 = nonathlete, 1 = elite power athlete) by receiver operating characteristic (ROC) curves (43). We calculated the area under the ROC curve (AUC) and 95% confidence intervals (95% CI). Finally, we used binary logistic regression to study the relationship between TGS and elite power athletic status. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS, v. 16.0 for WINDOWS, SPSS, Chicago, IL).

The genotype frequencies for the three study groups are shown in Table 1. The typical frequency of “optimal” genotype of each polymorphism in Spanish (Caucasian) population is shown in Table 2. The probability of a given Spanish (Caucasian) individual possessing an “optimal” polygenic profile for power athletic status was 13% when considering just one polymorphism (the DD genotype for the ACE gene) and it was reduced to ~3.8% when adding a second polymorphism (the RR genotype for the ACTN3 gene). When considering all polymorphisms, the typical frequency of each genotype for the Spanish population observed in our laboratory (Table 1). Finally, we examined the distribution of TGSs within this virtual population.

Statistical Analysis

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polymorphisms, the probability of possessing an optimal polygenic profile was ~0.2% (i.e., 1 in 500 Spanish individuals).

The mean TGS was significantly higher in elite power athletes compared with controls and endurance athletes, whereas it did not differ between the latter two groups (Fig. 1). A total of five power athletes (9.4% of the group total, all sprinters) had a TGS of 100, vs. 0 subjects in the other two groups (Table 3). Of note is that, however, none of the five power athletes with a TGS of 100 were among the very best Spanish sprinters (i.e., no national champion). The ROC analysis showed a significant discriminating accuracy of TGS in identifying an elite power athlete (AUC = 0.624; 95% CI: 0.525–0.723; P = 0.012; sensitivity = 0.528, specificity = 0.841) (Fig. 2). The corresponding TGS value at this point was 70.83. Logistic regression analysis showed that subjects with TGS above 70.83 had a slightly increased odds ratio (OR) of being an elite power athlete compared with those with a TGS below this value (OR: 1.381; 95% CI: 0.985–1.935; P = 0.061).

The frequency distributions of TGSs derived from a model sample of 50,000 randomly selected Spanish (Caucasian) individuals and that obtained from 100 Spanish healthy controls, 100 Spanish elite endurance athletes, and 53 Spanish elite power athletes are depicted in Fig. 3. The distribution in power athletes was shifted to the right compared with the other groups.

DISCUSSION

This is the first attempt to determine, using actual data and the TGS model, the polygenic profile that is more suitable for attaining the “power” end of the human exercise performance continuum. Our main findings are as follows.

1) The TGS mean was shifted to the right in power athletes compared with controls and athletes who are in the “opposite” (“endurance”) end point of the sports performance continuum. Importantly, for the six polymorphisms we studied, endurance athletes and controls had similar TGSs. Our data, together with recent findings showing a mean “endurance” TGS also shifted to the right in elite endurance athletes (70.2 ± 15.6 vs. 62.4 ± 11.5 for the endurance and control group, respectively) (29), support the notion that it might be possible to identify an “optimal” polygenic profile for each of the two “extreme” sports phenotypes, i.e., power- and endurance-oriented, respectively.

2) We found that the possibility of a given Spanish (Caucasian) individual existing with a theoretically “optimal” polygenic profile for power sports performance (using the 6 polymorphisms we studied) is of only ~0.2%, whereas 9.4% of the power athlete group had a TGS of 100. Further, an individual with a TGS ≥ 71 has a slightly increased possibility of becoming an elite power athlete than one with a TGS below this value. The inclusion of new polymorphisms in the model would probably increase this value.

Table 3. Distribution [n(%)] of nonathletes (controls), elite endurance athletes, and elite power athletes, and with an “optimal” power genotype for 1 up to 6 polymorphisms

<table>
<thead>
<tr>
<th>Number of “Optimal” Power Genotypes</th>
<th>Controls (n = 100)</th>
<th>Endurance (n = 100)</th>
<th>Power (n = 53)</th>
<th>P Value (Overall)</th>
<th>P Value (C vs. P)</th>
<th>P Value (E vs. P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0 (0.0%)</td>
<td>P = 0.001</td>
<td>P = 0.002</td>
<td>P = 0.007</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>17</td>
<td>4 (7.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>31</td>
<td>15 (28.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>29</td>
<td>13 (24.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>16</td>
<td>9 (17.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>4</td>
<td>7 (13.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
<td>5 (9.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C indicates controls; P, power; E, endurance.
in the near future will likely limit the possibility of finding individuals with a “perfect” TGS, whereas it will increase the accuracy of the model.

To determine the best possible combination of genetic polymorphisms that allows for excelling in power sports is of potential interest, both from a sports performance and a more health-oriented perspective. The sports performance of the human species seems to be close to its physiological limits (i.e., ~1 generation away), with the current World records approaching their predicted maximum (1). For instance, we are close to our locomotory limits in sprint races, considerably reducing the ability of natural or artificial selection to produce faster athletes (7). Given the theoretical difficulty to find more powerful athletes in the next generations, and ethics apart, sports professionals could be interested in identifying those athletes who are endowed with the most suitable polygenic profile to excel in competitive power sports. Furthermore, identification and understanding of the gene combinations associated with muscle power-related phenotypes is of overall health interest as sarcopenia (i.e., significant loss of muscle mass and strength) is a growing problem in the ageing population of the Western world (3), and muscular strength is a predictor of adulthood mortality (30, 31).

Elite athletes with a pure power-oriented phenotype as the ones studied here are seldom gathered in genotype:phenotype association studies, and the majority of studies in the field have typically focused on endurance-related phenotype traits. The “optimum” genotype profile does probably differ between endurance- and more power-oriented sports because the phenotype traits that determine performance in both types of events are likely different. This is illustrated in the sport of Decathlon, which comprises mostly power (throwing, sprinting, and jumping events) but also an endurance-oriented event as is the 1,500 race; the performance of the world best competitors in 100-m sprint or the long jump is negatively correlated with performance in the 1,500-m race (36). There seems to exist a “trade-off,” achieved through human evolution by balancing natural selection, between sprint and endurance phenotypic traits; as such, an individual would be inherently predisposed toward performance in either sprint/power or endurance events (11). In our study, the TGS was higher in power athletes than in both endurance athletes and nonathletic population. The possibility of a given Spanish (Caucasian) individual existing with a theoretically “optimal” polygenic profile for power sports performance and for the polymorphisms we studied is of only 0.2% (i.e., 1 in 500 Spanish individuals), yet 9.4% of power athletes had a “perfect” TGS of 100. Of note is that we are still far for computing a screening test for children (or anyone else) to accurately predict future athletic success.

The inclusion of new polymorphisms in the model will likely reduce the possibly of finding individuals with a “perfect” TGS, while increasing the accuracy of our present predictions. Moreover, it must be kept in mind that, beyond genetic endowment or complex gene-gene and gene-environment interactions, there are numerous other contributors to the “complex trait” of being an athletic champion that are difficult to quantify, e.g., technique, motivation, socioeconomic factors, or simply opportunity.

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DISCLOSURES
No conflicts of interest are declared by the authors.

REFERENCES


