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Can genetic testing predict talent? A case study of five elite athletes

51 Abstract

Purpose: The genetic influence on the attainment of elite athlete status is well-established, with a number of polymorphisms found to be more common in elite athletes than in the general population. As such, there is considerable interest in understanding whether this information can be utilised to identify future elite athletes. Accordingly, the aim of this study was to compare the total genotype scores of five elite athletes to those of non-athletic controls, to subsequently determine whether genetic information could discriminate between these groups, and, finally, to suggest how these findings may inform debates relating to the potential for genotyping to be used as a talent identification tool. Methods: We compared the total genotype scores for both endurance (68 genetic variants) and speed-power (48 genetic variants) elite athlete status of five elite track and field athletes, including an Olympic Champion, to those of 503 Caucasian non-athletic controls. Results: Using the speed-power total genotype score, the elite speed-power athletes scored more highly than the elite endurance athletes. However, using this speed-power score, 68 non-athletic controls registered higher scores than the elite power athletes. Surprisingly, using the endurance total genotype score, the elite speed-power athletes again scored more highly than the elite endurance athletes. Conclusions: These results suggest that genetic information is not capable of accurately discriminating between elite athletes and non-athletic controls, illustrating that the use of such information as a talent identification tool is currently unwarranted and ineffective. Key words: Genetic testing; elite athlete; talent; talent identification; Olympic

99 Introduction

100

101 Over the last thirty years, our appreciation of how genetics influences elite sports 102 performance has grown exponentially, with previous estimates of the heritability of elite 103 athlete status within a population reported to be approximately 66%.¹ Similarly, our understanding of how specific genetic variants, such as ACTN3,² may predispose towards 104 105 elite performance has developed. Such advances have led to speculation that genetic testing may be a viable tool to identify individuals with an increased likelihood of achieving elite 106 107 athlete status in the future, with some direct-to-consumer genetic testing companies already 108 offering this service.³

109

110 However, at present, the scientific consensus suggests that such approaches are ineffective at identifying future talented performers.³ Previously, Williams & Folland⁴ 111 incorporated 23 genetic variants associated with elite endurance performance in a data 112 113 simulation, with subsequent results suggesting that there was only a 0.0005% chance of any 114 single person in the world having the optimal form of all 23 performance-associated variants. 115 A further issue is that, within this simulation, there was considerable similarity in polygenic 116 profiles between individuals, with the clustered distribution of genotype scores limiting the 117 emergence of genetic outliers, who we might reasonably predict are more likely to be elite 118 athletes. Similar findings, relating to muscular strength and power characteristics, have also 119 been demonstrated.⁵ Such issues have also been explored experimentally, most commonly via 120 the use of Total Genotype Scores (TGS). Here, a score is assigned for each genotype of 121 interest, and then summed into a final score for that athlete. For example, Ruiz and 122 colleagues⁶ collected data on elite Spanish endurance athletes and controls. Whilst, on 123 average, the athletes within that cohort had a greater TGS for a panel of seven endurance-124 related polymorphisms than non-athletic controls, there was considerable overlap in score 125 between the populations, thereby illustrating that the predictive capability of this particular 126 TGS was low. Indeed, whilst individuals with a TGS above 74.71 were over five times more 127 likely to be elite athletes, only 43.5% of elite athletes attained such a score. Similar results were reported for elite power athletes;⁷ again, the athletes had a higher average power TGS 128 129 than both controls and endurance athletes, but with a large crossover of standard deviations 130 between the groups, indicating limited sensitivity and specificity. 131

132 Such evidence suggests that utilising a relatively low number of polymorphisms to 133 identify elite athletes is unlikely to provide meaningful insights. However, many more 134 polymorphisms than the 23 or fewer utilised in the studies to date have been associated with 135 elite performance. A recent literature review,⁸ for example, reported that at least 155 genetic 136 markers have been associated with elite athlete status, with further associations emerging since that article's publication.⁹ Additionally, in a recent survey in the UK, 67% of athletes 137 138 and 48% of support staff stated that genetic testing would form a valuable addition to talent identification processes within their sport,¹⁰ suggesting that there is an appetite for such 139 140 information within the sports performance world.

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Despite this apparent enthusiasm, however, further research in this area is clearly
required. Currently, it remains unclear whether genetic information can accurately
discriminate between elite performers and members of the general public. In addressing this
lack of evidence-led insight, within this investigation we used an expanded TGS,
incorporating an increased number of genetic variants, to determine whether such a panel can
reliably distinguish between a sub-population of five elite athletes and a control population of
European Caucasians. To the best of our knowledge, such a large scale TGS has not

149 previously been utilised to identify talented athletes, demonstrating the novelty of such a case 150 study.

- 151
- 152 Methods

153154 Participants

The participants were five former or current high-level athletes. All participants gave written, informed consent for their genotype results and identity to be shared here. All participants read the final version of this manuscript prior to submission, and consented to its publication, and their naming within this publication. The study protocol was approved by the University of Central Lancashire Ethics Committee, in accordance with the Declaration of Helsinki

- 160 (Ethics Board number BAHSS 575)
- 161

Participant A (Andrew Steele) is a former 400m runner. He competed at one Olympic
Games, winning a medal in the 4x400m relay. His personal best time is 44.94s, and he was a
high-level athlete for approximately 11 years.

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Participant B (Greg Rutherford) is a former long jumper. He has competed at three
Olympic Games, winning a Gold and a Bronze medal. His personal best distance is 8.51m,
and he was a high-level athlete for approximately 13 years.

Participant C (Craig Pickering) is a former sprinter. He competed at one Olympic
Games, and has a World Championships Bronze medal in the 4x100m relay. His personal
best 100m time is 10.14s, and he was a high-level athlete for approximately 7 years.

Participant D (Tom Lancashire) is a middle-distance runner, competing primarily over
1500m, the distance at which he was selected for an Olympic Games. His personal best
1500m time is 3:33:96, and he was a high-level athlete for approximately 13 years.

Participant E (Andrew Lemoncello) is a long-distance runner, with a Marathon
personal best time of 2:13:40. He competed at two World Championships, and one Olympic
Games, and was a high-level athlete for approximately 12 years.

182 All participants are of primarily European Caucasian ethnicity, although Participant183 D's mother is Mauritian.

184185 Genetic Testing

186 Each participant volunteered a saliva sample, which was collected through sterile and 187 self-administered buccal swabs. The samples were sent to AKESOgen, Inc (Peachtree 188 Corners, GA, USA), where DNA was extracted from the saliva samples using Qiagen 189 chemistry on an automated Kingfisher FLEX instrument (Thermo Fisher Scientific, 190 Waltham, MA, US), following the manufacturer's recommended protocols and standard 191 operating procedures. PicoGreen and Nanodrop measurements were taken to measure the 192 quality and quantity of the DNA. Input to the custom testing array occurred at 200ng in 193 20µL. Amplification, fragmentation, and resuspension was performed using Biomek FXP 194 following Affymetrix's high throughput protocol for Axiom 2.0. Hybridization was performed for 24 hours at 48°C in a Binder oven, and staining and scanning of the arrays was 195 196 performed using GeneTitan instrumentation (Thermo Fisher Scientific, Waltham, MA, US), 197 all following the same Affymetrix high throughput Axiom 2.0 protocol. Data analysis was

then performed using a raw CEL file data input into the Affymetrix Axiom Analysis Suite(Affymetrix, Santa Clara, CA, US).

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201 Creation of Total Genotype Scores

In order to best examine the potential use of genetic information in identifying elite athletes, polymorphisms previously linked to elite speed-power and elite endurance athlete status were collated through a structured literature search.

205 206 Speed-Power Athlete Status: A total of 48 genetic variants associated with power 207 athlete status were identified from two review articles.^{8,11} Of these 48, one marker (*IL1RN*) 208 could not be genotyped due to lack of coverage on the AKESOgen chip array. A further SNP, 209 rs2854464 in ACVR1B, was added to the panel based on subsequent research.¹² Three 210 additional SNPs in the carnosine genes CNDP1 and CNDP2, associated with elite power 211 athlete status⁹ were also not present on the chip array, and so were not assessed. 212 Mitochondrial DNA (mtDNA) was not assessed. The effect allele of one SNP, rs11091046 in 213 AGTR2, was reversed given the findings of a recent meta-analysis.¹³ Accordingly, 48 genetic 214 variants were utilised in the power TGS within this study.

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Endurance Athlete Status: A total of 68 genetic variants associated with endurance
athlete status were identified from two review articles.^{8,11} Of these, the genotype of 5
(*ADARA2A* 6.7/6,3kb, *BDKRB2* +9/-9, *COL5A1* rs71746744, *NOS3* 4A/4B, *PPP3R1* 5I/5D)
could not be determined due to insufficient coverage. We also added rs10497520 *TTN* to the
TGS.¹⁴ mtDNA was not assessed. Accordingly, 64 genetic variants were utilised in the
endurance TGS within this study.

223 Scoring

224 For each genetic variant, a score of 0, 1 or 2 was given depending on the genotype of 225 the athlete. A score of 2 represents the possession of two alleles associated with elite athlete 226 status (e.g. CC for ACTN3 rs1815739 within the power TGS); a score of 1 represents carriage 227 of one such allele (e.g. CT for ACTN3 rs1815739 within the power TGS); and a score of 0 228 represents the possession of no elite athlete-associated alleles for that genetic variant (e.g. TT 229 for ACTN3 rs1815739 within the power TGS). For each trait, the scores were then summated, 230 divided by the total possible score, and multiplied by 100 to get a percentage. This method is 231 identical to that utilised in previously published research utilising a TGS to explore elite 232 athlete status.⁴⁻⁷ The analysis was carried out in Excel 16.13.1 (Microsoft, Redmond, WA, 233 USA).

234235 Control Population

In order to develop an adequate control population, genotype scores for 503 European Caucasians were downloaded from e!GRCh37 (<u>http://grch37.ensembl.org/index.html</u>) into a spreadsheet for analysis. For each genetic variant, a score of 0, 1, or 2 was given as per the speed-power and endurance TGS detailed previously. The sum of scores for each variant was then calculated, and converted into the TGS% as per the previously detailed method. Additionally, the mean and standard deviation score for this reference population were

- 242 calculated.243
- 244 **Results**
- 245
- 246 TGS Scores

247	Table 1 shows the results of all five participants' speed-power TGS, as well as the
248	mean score expected in European Caucasians. The three speed-power athletes had the highest
249	TGS, whilst the two endurance athletes had the lowest. This trend held up in comparison to
250	the mean score for European Caucasians, with the speed-power athletes having a higher score
251	than the mean, and the endurance athletes a lower score than the mean. Table 1 also
252	demonstrates the results of the endurance TGS. Here, the two endurance athletes still have
253	the lowest TGS – lower than the elite speed-power athletes and the mean for European
254	Caucasians.
255	
256	Insert Table 1 around here
257	
258	Comparison to previously published TGS
259	The next stage of our analysis was to calculate the TGS from previously published
260	research by Ruiz and colleagues. ^{6,7} The results for both the speed-power and endurance TGS
261	developed by Ruiz are shown in table ?
262	
263	
265	Insert Table 2 around here
265	
266	
267	Non-athlete Control Results
268	We then calculated the frequency distributions for 503 non-athletic Caucasian
269	controls for both the power (figure 1) and endurance (figure 2) TGS. In general, the results of
270	the controls are fairly tightly distributed around the mean Within the power TGS no
270	narticipants fell below a score of 26% or above a score of 53% Similarly within the
271	endurance TGS no participant had a score below 34% or above 55%
272	
273	
275	Insert Fig 1 around here
276	
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278	Insert Fig 2 around here
279	
280	Discussion
281	
282	Using a 48 SNP TGS of speed-power associated SNPs, we found a general trend for
283	the elite speed-power athletes to score more highly (range 42.7-44.8%) than the elite
284	endurance athletes (37.5%) in our cohort. The mean score for our control population of
285	European Caucasians was 39.4%: lower than the scores achieved by the speed-power
286	athletes, but higher than the elite endurance athletes. These outcomes may appear to
287	provisionally support the use of genetic information to identify talented performers: however.
288	both endurance athletes and two of the three power athletes were within one standard
289	deviation of the non-athletes mean score. Indeed, in the 503 European reference samples
290	utilised, 68 individuals had higher speed-power TGSs than athlete A, the highest scoring
291	athlete in our cohort. The highest score in the control population was a TGS of 50% just over
292	2SDs greater than the mean.
293	
294	The results for the 64 SNP endurance TGS further demonstrated the lack of utility of
295	genetic testing for talent identification. Here, all three speed-power athletes (range -43.8 -
296	47.7%) out-scored the endurance athletes $(39.8 - 42.2\%)$, who in turn scored lower than the

mean for European Caucasians (43.8%). The SD for scores in the 503 European reference
samples was 3.8%, with 82 control participants having an endurance score >1SD outside of
the mean. The highest score was 54.6%.

301 The comparison to the previously published TGS utilised by Ruiz and colleagues^{6,7} 302 provides some interesting results. In our cohort, the elite endurance athletes scored more 303 highly on Ruiz and colleagues'⁶ endurance TGS (64 and 71%) than our speed-power athletes. 304 This is the opposite result to that seen when utilising the larger scale TGS developed for our 305 study. This potentially suggests that the utilisation of fewer genetic variants within a TGS 306 may enhance the predictive ability of such a model, potentially because the selected variants 307 have a greater effect size, or that the reported effects in the literature are correct, and not 308 spurious. Larger sample sizes are required to further test this. Regarding the power TGS, the 309 athletes in our cohort all scored lower than the mean power score in the Ruiz and colleagues⁷ 310 cohort; two just outscored the mean for European Caucasians, whilst participant C-a 311 European medalist over the 60m sprint—scored below the mean for European Caucasians, 312 and was outscored by participant E, the long-distance runner. Again, this is in contrast to our 313 results, where the speed-power athletes all outscored the endurance athletes, suggesting that 314 the larger scale TGS is potentially more sensitive in determining speed-power athlete status. 315

- 316 The two genetic variants most well-associated with elite athlete status are ACE and 317 ACTN3.^{2,15,16} Regarding ACTN3, the C allele of rs1815739 is consistently associated with elite speed-power athlete status, with two recent meta-analyses^{17,18} finding that individuals 318 319 with the TT genotype were significantly less likely to achieve elite speed-power athlete status 320 compared to those with at least one C allele. The three speed-power athletes within our 321 cohort exhibit the full range of ACTN3 genotypes (data not shown). Participant B, the highest 322 achieving of our cohort, possesses the CC genotype. Participant C, the short sprinter, 323 possesses the CT genotype, whilst Participant A, the Olympic 400m relay medallist, is a TT 324 genotype. This latter result is somewhat surprising given that this genotype is considered 325 unfavourable for elite speed performance, a result which has also been demonstrated in 400m 326 runners.¹⁶ Furthermore, the endurance athletes in this cohort possessed the CT and CC 327 genotype respectively, both of which might be considered slightly unfavourable for elite 328 endurance performance.¹⁷ This relationship, however, appears complex and poorly 329 understood; whilst some studies suggest an association between the ACTN3 T allele and elite 330 endurance status², others do not.¹⁹
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The genotype results for *ACE* were similarly heterogenous (data not shown). For this genetic variant, the D allele is considered favourable for elite speed-power athlete status,^{17,18} with the I allele favourable for elite endurance athlete status.¹⁷ Within our speed-power cohort, two athletes had the ID genotype, and one the II genotype; neither is considered optimal for elite speed performance. Conversely, both endurance athletes had the favourable II genotype.

Non-athletic controls exhibited extensive similarities in polygenic profiles, with a
minimal spread of results across individuals. This similarity in polygenic profiles in nonathletes has previously been reported with a lower number of generic variants for both
endurance⁴ and strength/power⁵ phenotypes. Within this case study, none of the elite athletes
were significant outliers in terms of TGS%, demonstrating that, for the polymorphisms
tested, genetic information is not sufficient to discriminate between elite athletes and nonathletic controls.

347 Would genetic testing have helped identify these athletes at a young age?

348 Based on these results, it seems unlikely that genetic testing of these athletes during 349 their teenage years would have correctly identified them as potential future elite athletes 350 relative to a group of non-athletes. In fact, it's unlikely that this information would have proved more useful than traditional talent identification methods. Participant A, for example, 351 352 was English Schools 400m Champion at age 16. Participant B is the British under-20 Long 353 Jump record holder and former European under-20 Champion, Participant C won multiple 354 national age group titles at under-15 and under-17, and the European under-20 355 Championships. Participant D won multiple junior national titles, and Participant E also won 356 national age-group championships. Consequently, given the failure of genetic information to provide insights over and above that provided by inspecting results and observing 357 358 performances, the practical utility of such tests for the specific purpose of talent identification 359 is not supported by these case study results. In addition, the utilisation of genetic testing in 360 under-18s is ethically troubling, with a number of key researchers recommending against such practice.^{3,20,21} 361

362

363 Limitations

364 There are some limitations to the present study that must be considered when 365 interpreting the results. Firstly, we were unable to collect data on mitochondrial DNA 366 (mtDNA). Mitochondrial haplotypes have been associated with elite athlete status, with different variations conferring an advantage or disadvantage in achieving elite athlete status 367 for both speed-power and endurance athletes.^{8,22-24} Furthermore, we were unable to collect 368 369 genotype data for a small number of polymorphisms, due to a lack of coverage on the testing 370 array. There is the potential that the athletes in this study may have held favorable versions of 371 these variants, which would have increased their scores. Nevertheless, even given these 372 limitations, the genotype panel created for use in this study represents the most 373 comprehensive gene score to appear in the published literature with regards to elite athlete 374 status. Furthermore, we utilised an unweighted TGS, with each variant having a score of 0, 1, 375 or 2 depending on genotype. A weighted TGS, with genetic variants with demonstrably larger 376 effect sizes getting a greater score, may have proved more accurate. However, at present, 377 very few genetic variants associated with elite athlete status have been adequately replicated, 378 making the development of such a weighted, multi-variant TGS difficult to achieve. 379

In addition, the comparison population utilised within this study was an anonymous group of 503 European Caucasians. One issue with using such a group is that the identities of the participants is unknown; there is the possibility that this group was comprised of a large number of elite athletes, which would have skewed the results, although this is very unlikely. Finally, the sample sized utilised within this study is extremely limited, with further research with larger numbers of athletes required.

386

387 Practical Applications

388 389 It seems clear that, at present, genetic testing cannot adequately discriminate between 390 elite athletes and non-athletes. In the current study, the TGS scores of five elite athletes did 391 not deviate substantially from average population scores, nor did they reach the thresholds 392 typically seen in elite athletes from other published TGS-elite athlete status associations,^{6,7} 393 although the number of genetic variants used within these earlier studies was very small. 394 Indeed, within this present cohort, and utilising a larger-scale TGS, all three of the elite 395 power athletes had a higher endurance score than both the middle-distance and long-distance runners. As a result, it appears that current commercially available genetic tests purporting to
 assist in the talent identification process have minimal utility,²¹ and should not be used.³

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399 Athletic success is predicated on a wide variety of capacities. In the future, as a 400 greater number of genetic variants associated with elite athlete status are identified, especially in areas involved in the psychological,^{25,26} anatomical,²⁷ and skill acquisition²⁸ aspects 401 402 associated with elite athlete status, it is feasible that the predictive ability of future TGSs may 403 improve. Such improvements could be further facilitated by the use of weighted algorithms, 404 where genetic variants with relatively larger effect sizes achieve a higher relative score 405 compared to variants with a smaller effect size. However, at present, and as clearly illustrated 406 by this case study involving highly elite athletes, the similarity of polygenic profiles within 407 populations limits the capacity of genetic information to adequately discriminate between the 408 general population and high performing athletes. For further insights into the limitations of 409 genetic testing for talent identification, interested readers are directed to reviews by Webborn 410 and colleagues³ and Pickering et al.²¹

- 411 412
- Conclusion
- 413

The results of this study suggest that, at present, the ability to utilise genetic information to identify talented performers holds limited predictive utility. The reasons for this are potentially varied, but include a limited understanding of the genetic variants that predispose to elite performance, the importance of non-genetic factors in the talent development process, and a similarity of polygenic profiles amongst athletes and controls.

- 419420 Footnotes
- 420 421

422 Supplementary files: S1 – List of SNPs included within the TGS utilised within this study.
423
424

425 Funding: Genetic testing for this case study was provided free of charge by DNAFit Life426 Sciences, a genetic testing company.

427
428 Competing interests: CP is a former employee of DNAFit Life Sciences, a genetic testing
429 company. He received no payment for carrying out this work, which was undertaken as part
430 of his doctoral studies. JK has no competing interests relevant to the content of this article to
431 declare. The results of the current study do not constitute endorsement of the product by the
432 authors or the journal.

433

434 Data availability: Athlete genotype data, other than that reported here, cannot be shared due
435 to the terms of the ethics approval. Genotypes of the non-athletic controls are publicly
436 available.

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545 Figure Captions





Fig. 1 Frequency distribution of power TGS% for non-athletic controls



Fig. 2 Frequency distribution of endurance TGS% for non-athletic controls

Participant	Α	В	С	D	Ε	European Average
Speed TGS	44.8	43.8	42.7	37.5	37.5	39.4
Endurance	46.9	47.7	43.8	42.2	39.8	43.8
TGS						

567 Table 1 – Comparison of athletes' scores in both the speed and endurance TGS utilised

within this study, against the European Average score.

Participant	Α	B	С	D	Ε	European	Ruiz	Ruiz
						Average	Endurance	Power
Ruiz	66.7	66.7	50	50	58.3	62.5	60	70
Power								
TGS ⁷								
Ruiz	57.1	42.9	57.1	64.3	71.4	60.7	70.2	
Endurance								
TGS ⁶								

Table 2 – Overview of the athletes' scores on previously published research by Ruiz and colleagues^{6,7}.