Letter to the editor: A genetic-based algorithm for personalized resistance training

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Abstract

In a recent paper entitled "A genetic-based algorithm for personalized resistance training", Jones et al. [1] presented an algorithm of 15 performance-associated gene polymorphisms that they propose can determine an athlete's training response by predicting power and endurance potential. However, from the design of their studies and the data provided, there is no evidence to support these authors' assertions. Progress towards such a significant development in the field of sport and exercise genomics will require a paradigm shift in line with recent recommendations for international collaborations such as the Athlome Project (see www.athlomeconsortium.org). Large-scale initiatives, involving numerous multi-centre and well-phenotyped exercise training and elite performance cohorts, will be necessary before attempting to derive and replicate training and/or performance algorithms.

Comment

In a recent paper entitled "A genetic-based algorithm for personalized resistance training", Jones et al. [1] proposed an algorithm of 15 performance-associated gene polymorphisms that they assert can determine an athlete's training response by predicting power and endurance potential. Two studies were conducted and involved athletes from several sports (e.g. swimming, ski/snowboard, squash, motorsport, and football players) undergoing an eight-week high- or low-intensity resistance training intervention comprising of one or two training sessions per week; participants continued sport-specific training and competition during the intervention period. The DNAFit Peak Performance Algorithm™ was used to calculate percentage power/endurance score ratio using the 15 gene polymorphisms. Briefly, this involved the summation of assigning a point from 0-4, depending on the putative effect of

each allele on power and/or endurance performance. Based on this derived power/endurance score, subjects were assigned to either an endurance or power genotype training group involving low-intensity or high-intensity resistance training, respectively. The only associations reported were between 5 of the 15 gene polymorphisms and training response as assessed by a countermovement jump (CMJ) and an aerobic-3 min cycle test (Aero3) determined before and after the intervention; albeit none of these associations reached statistical significance. The authors also reported an increase in CMJ and Aero3 performance when assessed within each of the two training groups. On the basis of these results, the authors concluded that the DNAFit Peak Performance Algorithm™ can be used for personalised resistance-training prescription.

It is clear from the study design and the data provided by Jones et al. that there is no evidence to support these authors' assertions. The DNAFit Peak Performance Algorithm™ used by these authors comprises 15 polymorphisms in 14 genes (*ACE*, *ACTN3*, *ADRB2*, *AGT*, *BDKRB2*, *COL5A1*, *CRP*, *GABPB1*, *IL6*, *PPARA*, *PPARGC1A*, *TRHR*, *VDR* and *VEGFA*); most of which have been associated, albeit tentatively with sports performance in the literature (see Table 1 and [2]). To our knowledge, there is no direct evidence linking *CRP* (rs1205) polymorphism to endurance performance (not included in Table 1); this specific polymorphism has recently been linked to a protective effect in the pathogenesis of cardiovascular heart disease in a meta-analysis [3]. The 15 gene polymorphisms have been "identified" primarily using the candidate gene approach and applied to cohorts with small sample sizes [4, 5]. As presented in Table 1, there are positive and negative findings for some genetic markers but few of these polymorphisms have been replicated. Notably, for the *TRHR* gene variant, there is only one study supporting the link with lean body mass variation [6, 7] in 1000 US whites after several replication attempts in three different cohorts consisting of in total over 6000 white US and Chinese participants. The Vitamin D receptor *BsmI* (rs1544410)

polymorphism has also been associated with muscle strength in elderly population in three studies but results remain inconclusive [8]. In contrast, *ACE* I/D and *ACTN3* R577X have been extensively studied and replicated to some degree in different populations [9], these two polymorphisms (together, separately, or part of an algorithm) do not predict training response [2, 10, 11].

It is widely acknowledged that a single gene or a combination of a few genes (using genotype score) may explain a very low percentage of sports performance variation, for example, a 2-3% of sprinting performance variability may be explained by *ACTN3* genotype [11, 12]. Nevertheless, a recent meta-analysis of genome-wide association studies and their replications reported that common genetic variants could not discriminate elite endurance athletes from respective control populations (GENATHLETE, Japan, Australia, Poland, Russia, Spain, Kenya, and Ethiopia) [13]. Therefore, the research evidence to date to support the selection of any polymorphism is weak [11, 14, 15]. Timmons et al. and Bouchard et al. were the first to investigate training response using genome-wide exploration. Timmons et al. reported a discovery of 29 transcripts that predicted maximum oxygen uptake ($\dot{V}O_2max$) training response, and these transcripts contained 11 single-nucleotide polymorphisms (SNPs) explaining 23% of the variance in gains in $\dot{V}O_2max$ [16]. Bouchard et al. used data from the HERITAGE study (Health, Risk factors, Training and Genetics) and identified a set of 21 SNPs accounting for 49% of the variance in $\dot{V}O_2max$ trainability [17]. However, none of the training-associated SNPs reported by Timmons et al. [16] were replicated by Bouchard et al. [17], nor were any of the "putative" training-associated SNPs reported in either study used in the DNAFit Peak Performance Algorithm™. The study by Jones et al. also highlights a number of methodological problems typically associated with the sport and exercise genomics literature [18] such as small sample size, sports variation and low number of training sessions. For example, both experiments in the Jones et al. employed very small sample sizes of 28 and

39 participants, respectively. Although authors stated that the sample sizes used were sufficient after power calculation, details of the power calculation were not provided and is most unlikely given the data presented and on the basis of other studies [19-21]. Progress towards developing training and/or performance algorithms will require a paradigm shift in line with recent recommendations for international collaborations [22] such as the Athlome Project (see www.athlomeconsortium.org). Such large-scale initiatives, designed specifically to overcome many of the limitations of small single-site studies will be necessary before attempting to derive and replicate training and performance algorithms.

In conclusion, while it is widely acknowledged that a favourable genotype combined with suitable training will enhance trainability and sporting performance, to date few (i.e. *ACTN3* and *ACE*) polymorphisms have been associated with an acceptable level of replication with endurance or power athletic performance, and none of these associations are strong enough to predict elite sports performance or trainability [14, 23, 24]. Currently, there is lack of scientific evidence supporting the predictive values of genetic tests (direct-to-consumer) for prescription of exercise training programmes, or for that matter, talent identification. Further studies with replication are needed in order for genetic variants to be used in personalised training prescription. As stated by Webborn et al., research findings should not be misinterpreted for commercial purposes. Jones et al. [1] are premature in their attempt to demonstrate that a genetic test using DNAfit Peak Algorithm™ can determine the training response by predicting power and endurance potential. There are important limitations in their study design and interpretation of their results. Their suggestion of using a somewhat ambiguous algorithm to prescribe individualised training is premature. While acknowledging the difficulties in translating research discoveries, it is the responsibility of researchers to be cautious and not to over-interpret their research findings as this can motivate unsubstantiated commercial exploitation. Sarzynski et al. recently developed a framework for translating

research discoveries that included useful information on sample size requirements and preferred technologies for discovery and replication phases of genetic research with particular reference to exercise genomics[25].

References

1. Jones N KJ, Suraci B, Collins DJ, de Lorenzo D, Pickering C, Grimaldi KA. A genetic-based algorithm for personalized resistance training. Biol Sport. 2016;33(2):117-26.
2. Wang G, Padmanabhan S, Wolfarth B, Fuku N, Lucia A, Ahmetov, II, Cieszczyk P, Collins M, Eynon N, Klissouras V, Williams A, Pitsiladis Y. Genomics of elite sporting performance: what little we know and necessary advances. Advances in genetics. 2013;84:123-49.
3. Hernández-Díaz Y, Tovilla-Zárate CA, Juárez-Rojop I, Baños-González MA, Torres-Hernández ME, López-Narváez ML, Yañez-Rivera TG, González-Castro TB. The role of gene variants of the inflammatory markers CRP and TNF-α in cardiovascular heart disease: systematic review and meta-analysis. Int J Clin Exp Med. 2015;8(8):11958-84.
4. Pitsiladis Y, Wang G, Wolfarth B, Scott R, Fuku N, Mikami E, He Z, Fiuza-Luces C, Eynon N, Lucia A. Genomics of elite sporting performance: what little we know and necessary advances. British journal of sports medicine. 2013;47(9):550-5.
5. Tanaka M, Wang G, Pitsiladis YP. Advancing sports and exercise genomics: moving from hypothesis-driven single study approaches to large multi-omics collaborative science. Physiological genomics. 2016;48(3):173-4.
6. Roth SM. Genetic aspects of skeletal muscle strength and mass with relevance to sarcopenia. Bonekey Rep. 2012;1:58.

7. Liu XG, Tan LJ, Lei SF, Liu YJ, Shen H, Wang L, Yan H, Guo YF, Xiong DH, Chen XD, Pan F, Yang TL, Zhang YP, Guo Y, Tang NL, Zhu XZ, Deng HY, Levy S, Recker RR, Papasian CJ, Deng HW. Genome-wide association and replication studies identified TRHR as an important gene for lean body mass. Am J Hum Genet. 2009;84(3):418-23.

8. Garatachea N, Lucía A. Genes and the ageing muscle: a review on genetic association studies. Age (Dordr). 2013;35(1):207-33.

9. Ma F, Yang Y, Li X, Zhou F, Gao C, Li M, Gao L. The association of sport performance with ACE and ACTN3 genetic polymorphisms: a systematic review and meta-analysis. PloS one. 2013;8(1):e54685.

10. Guth LM, Roth SM. Genetic influence on athletic performance. Current opinion in pediatrics. 2013;25(6):653-8.

11. Webborn N, Williams A, McNamee M, Bouchard C, Pitsiladis Y, Ahmetov I, Ashley E, Byrne N, Camporesi S, Collins M, Dijkstra P, Eynon N, Fuku N, Garton FC, Hoppe N, Holm S, Kaye J, Klissouras V, Lucia A, Maase K, Moran C, North KN, Pigozzi F, Wang G. Direct-to-consumer genetic testing for predicting sports performance and talent identification: Consensus statement. British journal of sports medicine. 2015;49(23):1486-91.

12. Moran CN, Yang N, Bailey ME, Tsiokanos A, Jamurtas A, MacArthur DG, North K, Pitsiladis YP, Wilson RH. Association analysis of the ACTN3 R577X polymorphism and complex quantitative body composition and performance phenotypes in adolescent Greeks. Eur J Hum Genet. 2007;15(1):88-93.

13. Rankinen T, Fuku N, Wolfarth B, Wang G, Sarzynski MA, Alexeev DG, Ahmetov, II, Boulay MR, Cieszczyk P, Eynon N, Filipenko ML, Garton FC, Generozov EV, Govorun VM, Houweling PJ, Kawahara T, Kostryukova ES, Kulemin NA, Larin AK, Maciejewska-Karlowska A, Miyachi M, Muniesa CA, Murakami H, Ospanova EA, Padmanabhan S, Pavlenko AV, Pyankova ON, Santiago C, Sawczuk M, Scott RA, Uyba VV, Yvert T, Perusse

L, Ghosh S, Rauramaa R, North KN, Lucia A, Pitsiladis Y, Bouchard C. No Evidence of a Common DNA Variant Profile Specific to World Class Endurance Athletes. PloS one. 2016;11(1):e0147330.

14. Camporesi S, McNamee MJ. Ethics, genetic testing, and athletic talent: children's best interests, and the right to an open (athletic) future. Physiological genomics. 2016;48(3):191-5.

15. Eynon N, Hanson ED, Lucia A, Houweling PJ, Garton F, North KN, Bishop DJ. Genes for elite power and sprint performance: ACTN3 leads the way. Sports medicine. 2013;43(9):803-17.

16. Timmons JA, Knudsen S, Rankinen T, Koch LG, Sarzynski M, Jensen T, Keller P, Scheele C, Vollaard NB, Nielsen S, Akerstrom T, MacDougald OA, Jansson E, Greenhaff PL, Tarnopolsky MA, van Loon LJ, Pedersen BK, Sundberg CJ, Wahlestedt C, Britton SL, Bouchard C. Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. Journal of applied physiology. 2010;108(6):1487-96.

17. Bouchard C, Sarzynski MA, Rice TK, Kraus WE, Church TS, Sung YJ, Rao DC, Rankinen T. Genomic predictors of the maximal O(2) uptake response to standardized exercise training programs. Journal of applied physiology. 2011;110(5):1160-70.

18. Pitsiladis Y, Wang G. Necessary advances in exercise genomics and likely pitfalls. Journal of applied physiology. 2011;110(5):1150-1.

19. Tabor HK, Risch NJ, Myers RM. Candidate-gene approaches for studying complex genetic traits: practical considerations. Nature reviews Genetics. 2002;3(5):391-7.

20. Long AD, Langley CH. The power of association studies to detect the contribution of candidate genetic loci to variation in complex traits. Genome research. 1999;9(8):720-31.

21. Lalouel JM, Rohrwasser A. Power and replication in case-control studies. American journal of hypertension. 2002;15(2 Pt 1):201-5.

171 22. Bouchard C. Exercise genomics-a paradigm shift is needed: a commentary. British
172 journal of sports medicine. 2015;49(23):1492-6.
173 23. Collins M, September AV, Posthumus M. Biological variation in musculoskeletal
174 injuries: current knowledge, future research and practical implications. British journal of
175 sports medicine. 2015;49(23):1497-503.
176 24. Mattsson CM, Wheeler MT, Waggott D, Caleshu C, Ashley EA. Sports genetics
177 moving forward: lessons learned from medical research. Physiological genomics.
178 2016;48(3):175-82.
179 25. Sarzynski MA, Loos RJ, Lucia A, Pérusse L, Roth SM, Wolfarth B, Rankinen T,
180 Bouchard C. Advances in Exercise, Fitness, and Performance Genomics in 2015. Medicine
181 and science in sports and exercise. 2016.
182 26. Ahmetov II, Fedotovskaya ON. Current Progress in Sports Genomics. Adv Clin
183 Chem. 2015;70:247-314.

Table 1. Gene variants for endurance and power/strength athlete status (Adapted from [26]).

Gene	Polymorphism	Endurance related marker	Power/ strength-related marker	Endurance		Power/Strength	
				Number of studies with positive results	Number of studies with negative or controversial results	Number of studies with positive results	Number of studies with negative or controversial results
ACE	Alu I/D (rs4646994)	I	D	16	12	7	7
ACTN3	R577X (rs1815739 C/T)	577X	Arg577	4	14	12	5
ADRB2	Gly16Arg (rs1042713 G/A)	16Arg	Gly16	2	1	1	-
	Gln27Glu (rs1042714 C/G)	-	27Glu	-	-	1	-
AGT	Met235Thr (rs699 T/C)	-	235Thr	-	-	2	-
BDKRB2	rs1799722 C/T	rs1799722 T	-	1	-	-	-
COL5A1	rs12722 C/T (BstUI)	rs12722 T	-	2	-	-	-
GABPB1 (NRF2)	rs7181866 A/G	rs7181866 G	-	2	1	-	-
IL6	-174 C/G (rs1800795 C/G)	-	rs1800795 G	-	-	2	1
PPARA	rs4253778 G/C	rs4253778 G	rs4253778 C	5	-	2	1
PPARGC1A	Gly482Ser (rs8192678 G/A)	Gly482	-	4	3	-	-
VEGFA	rs2010963 G/C	rs2010963 C	-	1	-	-	-