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**Pitsiladis, YP, Tanaka, M, Eynon, N, Bouchard, C, North, KN, Williams, AG, Collins, M, Moran, CN, Britton, SL, Fuku, N, Ashley, EA, Klissouras, V, Lucia, A, Ahmetov, II, de Geus, E, Alsayrafi, M, Athlome Project Consortium, and Erskine, RM**

**Athlome Project Consortium: a concerted effort to discover genomic and other "omic" markers of athletic performance.**

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### Article

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1 **The Athlome Project Consortium: A Concerted Effort to Discover Genomic and other**  
2 **“OMIC” Markers of Athletic Performance.**

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4  
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41 **Running Head:** The Athlome Project Consortium

42  
43 **Key Words:** Genetics, Performance  
44

45 **The Athlome Project Consortium: A Concerted Effort to Discover Genomic and other**  
46 **“OMIC” Markers of Athletic Performance.**

47

48 **The Athlome Project Consortium\***

49

50 Despite numerous attempts to discover genetic variants associated with elite athletic  
51 performance, injury predisposition and elite/world-class athletic status, there has been limited  
52 progress to date. Past reliance on candidate gene studies predominantly focusing on genotyping a  
53 limited number of single nucleotide polymorphisms (SNPs) or the insertion/deletion variants in  
54 small, often heterogeneous cohorts (i.e., made up of athletes of quite different sport specialties)  
55 have not generated the kind of results that could offer solid opportunities to bridge the gap  
56 between basic research in exercise sciences and deliverables in biomedicine. A retrospective  
57 view of genetic association studies with complex disease traits indicates that transition to  
58 hypothesis-free genome-wide approaches will be more fruitful. In studies of complex disease, it  
59 is well recognized that the magnitude of genetic association is often smaller than initially  
60 anticipated and, as such, large sample sizes are required to identify the gene effects robustly.  
61 Thus, alternative large-scale, collaborative efforts involving well-phenotyped male and female  
62 cohorts from which high-resolution genome-wide data is generated and interrogated using  
63 advanced bioinformatics approaches are necessary for meaningful progress to be made.  
64 Accordingly, a symposium was held in Athens and on the Greek island of Santorini from 14-17th  
65 May 2015 (<http://celebratorysymposium.net>) to review the main findings in exercise genetics and  
66 genomics and to explore promising trends and possibilities. The symposium also offered a forum  
67 for the development of a position stand (the Santorini Declaration). Among the participants,  
68 many were involved in ongoing collaborative studies (e.g., GAMES, Gene SMART, GENESIS  
69 and POWERGENE). A consensus emerged among participants that it would be advantageous to  
70 bring together all current studies and those recently launched into one new large collaborative  
71 initiative, which was subsequently named the *Athlome Project Consortium*.

72

73 At the outset, the Athlome Project aims to collectively study the genotype and phenotype data  
74 currently available on elite athletes, in adaptation to exercise training (in both human and animal  
75 models) and on exercise-related musculoskeletal injuries from individual studies and from  
76 consortia worldwide. To achieve this, several steps are set out:

77

- 78 1. To establish an ethically sound international research consortium (Athlome Project  
79 Consortium) and biobank resource systematically across individual centres;
- 80 2. To discover genetic variants associated with exercise performance, adaptive response to  
81 exercise-training, and skeletal-muscle injuries using the genome-wide association study  
82 (GWAS) approach, targeted sequencing or whole genome sequencing, where possible;
- 83 3. To validate and replicate the genetic markers from the discovery phase across sex and  
84 ethnicity; and
- 85 4. To conduct functional investigations following replicated findings (e.g., study the  
86 replicated SNPs and their linkage disequilibrium regions, *in vitro* expression studies and  
87 knockouts of nearby genes) to better understand the associated biology.

88

89 During the development of the initial phase of the Athlome Project in determining the genetic  
90 variations related to elite athletic performance and injury predisposition, epigenomic,  
91 transcriptomic and proteomic analyses need also be carefully planned to strengthen the  
92 understanding of gene functions. Linking these findings with metabolic profiling (the end  
93 products of the cellular processes) is also a future aspiration of the Athlome Project. Another  
94 challenge is to be able to efficiently integrate the multiple “omics” datasets generated from the  
95 different approaches. The ultimate goal of the Athlome Project Consortium is to generate the  
96 ethically sound environment, interest and capacity needed to develop the specialist knowledge to  
97 inform personalized training and injury prevention, as well as doping detection. The following  
98 individual or collaborative studies have agreed to work together in the global partnership that  
99 constitutes the Athlome Project Consortium. The participating cohorts and the focus of each are  
100 depicted in Figure 1.

101

### 102 **Eastern Europe population studies (The Russian and Belarusian cohorts, GELAK, 103 GELAV, and GUAP)**

104 The Russian and Belarusian cohorts, the Genetics and Epigenetics of Lithuanian Athletes from  
105 Kaunas (GELAK) and Vilnius (GELAV), and the Genome of Ukrainian Athletes Project  
106 (GUAP) have consolidated to identify genetic and epigenetic variations associated with high-  
107 level sports performance. The cohort comprises East Europeans (from Belarus, Lithuania,

108 Russia, and Ukraine; in total n = 8,228 athletes and n = 4,121 controls). The athletes are grouped  
109 into international (including participants in Olympics and World Championships), national,  
110 regional, or local/non-competitive categories. These include biathletes, distance runners, cyclists,  
111 triathletes, kayakers, rowers, canoers, modern pentathletes, orienteers, skiers, speed skaters,  
112 short-trackers, walkers, weightlifters, bodybuilders, powerlifters, strongmen, sprint runners ( $\leq$   
113 400 m), sprint swimmers (50 - 100 m), decathletes, heptathletes, combat athletes, field athletes,  
114 bobsleigh athletes, rhythmic and artistic gymnasts, figure skaters, fencers and team ball-sport  
115 players. A portion of the participants have been evaluated with a variety of quantitative  
116 performance- and health-related assessments, including strength/power-related measurements,  
117 agility/speed-related measurements, balance, flexibility and coordination measurements,  
118 endurance-related measurement, skeletal muscle biopsy, and health-related measurements.

119

120 *Principal Investigators:* Ildus I Ahmetov (Volga Region State Academy of Physical Culture,  
121 Sport and Tourism, RUS), Svitlana B Drozdovska (National University of Physical Education of  
122 Ukraine, UKR), Colin N Moran (University of Stirling, GBR), Valentina Ginevičienė (Vilnius  
123 University, LTU), Andrei A Gilep (Institute of Bioorganic Chemistry NASB, BLR).

124

125 **ELITE** [elite.stanford.edu](http://elite.stanford.edu)

126 The Exercise at the Limit – Inherited Traits of Endurance (ELITE) consortium is a global  
127 initiative with the main objective to map the role that genetics plays in athletic ability versus  
128 environmental factors, such as training. Study participant (n > 500) selection is based on a  
129 physiological variable relevant for both health and sport performance, i.e., maximum oxygen  
130 uptake ( $\dot{V}O_2\text{max}$ ). The main inclusion criterion is  $\dot{V}O_2\text{max} > 75$  ml/kg/min for men and > 63  
131 ml/kg/min for women, respectively. The consortium is continuously expanding and is recruiting  
132 athletes from all over the globe (with main focus on Caucasians, North East Africans, East  
133 Asians and South Americans) who are successful in endurance sports (running, cycling, cross  
134 country skiing, triathlon, and rowing). Analyses currently include enhanced whole exome  
135 sequencing and GWAS (1.7 million SNPs). The combination of analytic methods will enable  
136 findings and differentiation between common variants with small effects and novel rare variants  
137 with larger effects. The aim is also to investigate gender and ethnic differences.

138 *Principal Investigators:* Euan A Ashley, C Mikael Mattsson, Matthew Wheeler, Daryl Waggott  
139 (Stanford University, USA).

140

#### 141 **Elite East African athlete cohort**

142 The consortium also aims to study the East African running success by analyzing data from  
143 previously recruited subjects: (i) 76 endurance runners (64 men) and 38 sprint and power event  
144 athletes (18 men) from the Ethiopian national athletics teams, 315 controls from the general  
145 Ethiopian population (281 men), 93 controls from the *Arsi* region of Ethiopia (80 men) and (ii)  
146 291 elite Kenyan endurance athletes (232 men) and 85 control participants (40 men). Seventy  
147 (59 men) Kenyan athletes had competed internationally and achieved outstanding success.

148

149 *Principal Investigators:* Yannis Pitsiladis (University of Brighton, GBR), Robert Scott  
150 (University of Cambridge, GBR).

151

#### 152 **GAMES**

153 An international consortium (GAMES) was established to compare allele frequencies between  
154 elite endurance athletes and ethnicity-matched controls. GWASs were undertaken on two cohorts  
155 of elite endurance athletes (GENATHLETE and Japanese endurance runners) and their  
156 respective controls, from which a panel of 45 candidate SNPs was identified. These markers  
157 were tested for replication in seven additional cohorts of endurance athletes and controls from  
158 Australia, Ethiopia, Japan, Kenya, Poland, Russia and Spain. The study is based on a total of  
159 1,520 endurance athletes (835 of them had competed in World Championships or Olympic  
160 Games) and 2,760 controls.

161

162 *Principal Investigators:* Claude Bouchard, Tuomo Rankinen (Pennington Biomedical Research  
163 Centre, Louisiana State University, USA), Noriyuki Fuku (Juntendo University, JPN), Yannis  
164 Pitsiladis (University of Brighton, GBR), Bernd Wolfarth (Humboldt University, DEU),  
165 Alejandro Lucia (Universidad Europea de Madrid, SP).

166

#### 167 **GENATHLETE**

168 The study was launched in 1993 with the aim of identifying DNA variants that are present at

169 different frequencies between elite endurance athletes and sedentary controls. Male endurance  
170 athletes and controls were recruited from Canada, Finland, Germany and the USA. The cohort  
171 assembled to date includes 315 elite endurance athletes and 320 matched controls. Selection  
172 criteria for the all-male endurance athlete sample include that they had to be athletes of national  
173 or international caliber with a  $\dot{V}O_2\text{max}$  of at least 75 ml/kg/min. The mean value for the 315  
174 athletes is currently 79 ml/kg/min while the mean for the 320 control subjects reached 40  
175 ml/kg/min. Multiple candidate genes have been studied using the resources of GENATHLETE.  
176 A genome-wide screen for common variants has been performed on GENATHLETE (see  
177 GAMES cohort above) and further studies are focusing on nuclear and mitochondrial DNA  
178 sequencing.

179  
180 *Principal Investigators:* Claude Bouchard, Tuomo Rankinen (Pennington Biomedical Research  
181 Centre, Louisiana State University System, USA), Bernd Wolfarth (Department of Sports  
182 Medicine, Charite Medical School, Berlin, Germany), Louis Perusse (Laval University, Quebec,  
183 Canada), Rainer Rauramaa (University of Eastern Finland, Kuopio, Finland).

## 185 **GENESIS**

186 The GENetics of Elite Status In Sport (GENESIS) consortium aims to identify molecular genetic  
187 characteristics associated with successful sports performance. The cohort (current  $n > 1,200$ ) is  
188 mainly composed of UK athletes. Sports include marathon running and other track-and-field  
189 athletics, cycling and team sports (e.g. soccer). The RugbyGene Study is a major subcomponent  
190 of GENESIS and focuses on rugby (both union and league codes). Objectives of GENESIS are:  
191 (i) to increase current cohort size substantially; (ii) to apply hypothesis-free approaches to  
192 identify molecular genomic markers; (iii) to expand GENESIS from genomics to other “omics”;  
193 and (iv) to combine the “omics” data with athlete health and performance data to maximize  
194 practical impact of GENESIS.

195  
196 *Principal Investigators:* Alun G Williams, Stephen H Day, Georgina K Stebbings (Manchester  
197 Metropolitan University, GBR), Robert M Erskine (Liverpool John Moores University, GBR),  
198 Hugh E Montgomery (University College London, GBR).

199



200 **Gene SMART Study** [www.vu.edu.au/speed-gene](http://www.vu.edu.au/speed-gene)

201 The Gene SMART (Skeletal Muscle Adaptive Response to Training) study aims to identify the  
202 gene variants that predict the skeletal muscle response to both a single bout and 4 weeks of High-  
203 Intensity Interval Training (HIIT) in three different training centres. While the lead training and  
204 testing centre is located in Victoria University, Melbourne, two other centres have been launched  
205 at Bond University, Australia and the University of Sao Paulo, Brazil. A fourth centre  
206 (University of Brighton, UK) will focus on the omics analyses. The cohort is comprised of  
207 moderately-trained, healthy male participants (aged 20-45 years, body mass index  $\leq 30$  kg/m<sup>2</sup>).  
208 Participants are undergoing similar exercise testing and exercise training in three different  
209 laboratories. Dietary habits are assessed by questionnaire and nutritionist consultation. Activity  
210 history is assessed by questionnaire and current activity level is assessed by activity monitoring.  
211 A number of muscle and blood analyses are to be performed, including genotyping,  
212 mitochondrial respiration, transcriptomics, proteomics, and enzymes activity before, during and  
213 after training, where appropriate. Currently ~40 participants have finished the study and the aim  
214 is to train a total of 250 participants. The Gene SMART also includes baseline and post-training  
215 testing and sampling for all participants.

216

217 *Principal Investigators:* David Bishop, Nir Eynon (Victoria University, AUS).

218

219 **GOINg**

220 The recently established Genomics Of INjuries (GOINg) consortium aims to identify DNA  
221 variants that modify the risk of anterior cruciate ligament (ACL) injuries. It is the only  
222 consortium within the Athlome Project to specifically investigate exercise-associated  
223 musculoskeletal injuries. The plan is to screen current known loci for ACL injury susceptibility  
224 in larger data sets in an attempt to determine if they remain as susceptibility loci across all  
225 populations using the hypothesis-driven candidate gene case-control study design. Care will be  
226 taken to use the same criteria to accurately phenotype, with respect to ancestry, sporting and  
227 occupational details, injury profile and mechanism(s) of injury, other injury history and family  
228 history, as well as, other appropriate medical history and medication use. The actual functional  
229 significance of the identified variants will also be investigated. This initial phase will be  
230 followed by sequencing and the research objectives will be eventually expanded to include other

231 “omics”. Thus far, ACL rupture consortium has collected DNA samples and clinical, as well as  
232 physical and occupational activity information from subjects from South Africa, Poland,  
233 Australia, Russia and Italy.

234  
235 *Principal Investigators:* Malcolm Collins, Alison September, Michael Posthumus (University of  
236 Cape Town, ZAF), Nir Eynon (Victoria University, AUS), Pawel Cieszczyk (University of  
237 Szczecin, POL).

238

### 239 **J-HAP**

240 The Japanese Human Athlome Project (J-HAP) focuses on the study of genes associated with  
241 physical performance and its related phenotypes (e.g., muscle mass, muscle fiber type,  $\dot{V}O_2\text{max}$ ).  
242 The cohort is comprised of Japanese athletes (currently > 2,400, mainly international and  
243 national levels) and healthy Japanese controls (currently > 1,000). These athletes are mainly  
244 track-and-field athletes and swimmers competing in endurance- and sprint/power-oriented events.  
245 Multiple “omics” approaches will be used to determine genes in talent identification in the  
246 Japanese population. Among the collected Japanese athletes’ and controls’ samples,  
247 approximately 200 muscle biopsies were obtained from both athletes and controls in order to  
248 investigate genetic variants associated with muscle fibre type distribution.

249

250 *Primary Investigators:* Noriyuki Fuku (Juntendo University, JPN), Naoki Kikuchi (Nippon Sport  
251 Science University, JPN), Eri Miyamoto-Mikami (The National Institute of Fitness and Sports in  
252 Kanoya, JPN).

253

### 254 **NTR**

255 The Netherlands Twin Register (NTR) is a population-based cohort recruiting both newborn and  
256 adult multiples and their family members with continuous longitudinal data collection. In the  
257 past 25+ years, around 40% of all twins and multiples in the Netherlands have taken part in the  
258 NTR research projects. Family members and spouses of twins also took part, leading to a total of  
259 over 185,000 participants across multiple research projects. The longitudinal information that has  
260 been collected extends from genotype to biomarkers, gene expression to rich behavioral  
261 information including biennial reports on (competitive) sports participation and performance

262 level and on injuries related to sports. In its sports research track, NTR aims to understand the  
263 interplay between genetic and environmental factors shaping individual differences in sports  
264 participation and performance. In the NTR, participants are recruited as newborns and followed  
265 into young adulthood, 520 have played competitively at a regional and 189 at a national level.  
266 Main sports that Dutch adolescents/young adults engage in are swimming, tennis, bicycling,  
267 soccer and field hockey. The longitudinal data collection of the NTR is ongoing and securely  
268 funded for the next 5 years.

269

270 *Principal Investigators:* Eco de Geus, Meike Bartels (VU University and VU medical centre,  
271 NLD).

272

### 273 **POWERGENE**

274 The POWERGENE consortium aims to characterise the elite sprint/power athlete genotype. The  
275 internationally competitive (Olympic/World championship qualifiers) sprint/power athletes are  
276 from: Australia, Belgium, Greece, Italy, Jamaica, Japan, Lithuania, Poland, Spain, the U.S.A.,  
277 Brazil, and Russia. They will be compared with sub-elite athletes (national qualifiers), endurance  
278 athletes, team athletes and controls. The current cohort consists of female (n = 264) and male (n  
279 = 481) specialist power athletes across three major ethnicities (i.e., European, West African and  
280 East Asian ancestries). Sprint/power athletes include those individuals competing in track ( $\leq$  800  
281 m) and field (jump, throw) events, cycling (track), swimming ( $\leq$  200 m), gymnastics (artistic),  
282 weightlifting, judo, speed-skating and power lifting. Endurance athletes (n = 586) include track  
283 and road running specialists ( $>$  800 m), rowers, cyclists, swimmers ( $>$  200 m), triathletes and  
284 ironmen. Team sports (n = 862) include football (soccer), cricket, hockey, volleyball and  
285 basketball.

286

287 *Principal Investigators:* Yannis Pitsiladis (University of Brighton, GBR), Kathryn North  
288 (Murdoch Childrens Research Institute, AUS), Nir Eynon (Victoria University, AUS).

289

### 290 **Super-athletes: Genes and Sweat**

291 The study aims to (i) identify genetic variants associated with elite athletic performance, (ii)  
292 study potential ethnic differences, and (iii) study the functional significance of the identified

293 variants. A GWAS will be carried out in 3,000 consented elite athletes, tested negative for  
294 doping substances at the Anti-Doping Laboratories, Federazione Medico Sportiva Italiana  
295 (FMSI) and Anti-Doping Lab Qatar (ADLQ), using Illumina genotyping technologies.  
296 Examining genotype frequency distribution of elite athletes from European countries (where  
297 most of FMSI samples will be obtained) against those from South Asian and African countries  
298 (where most of ADLQ samples are expected to be obtained) would help to identify potential  
299 ethnic differences in the genetic predisposition to athletic performance. Subsequently, urine  
300 metabolome in a subset of these athletes (1,000 subjects) will be performed, and will be related  
301 to the athlete's sporting discipline.

302

303 *Principal Investigators:* Mohamed El-Rayess, Costas Georgakopoulos, Mohammed Alsayrafi  
304 (ADLQ, QAT), Francesco Botre (FMSI, ITA), Karsten Suhre (Weill Cornell Medical College in  
305 Qatar, QAT), Mike Hubank (University College London, GBR).

306

### 307 **Epigenetics of Elite Athletic Performance**

308 It is clear from animal and human studies that epigenetic marks play a role in the modulation of  
309 gene expression in relevant tissues. There also are indications that epigenetic marks can be  
310 altered by acute and chronic exercise in skeletal muscle and adipose tissue where they have been  
311 studied. Thus individual differences in any exercise-related traits can potentially be explained by  
312 not only the impact of DNA sequence variation on biology and behavior but also by the effects  
313 of epigenomic signaling on gene expression. We are formulating the hypothesis that elite athletic  
314 performance is influenced by epigenomic alterations, facilitating morphological, physiological,  
315 metabolic, cognitive, emotional and behavioral changes that empower the athlete to push  
316 performance beyond existing boundaries. We envisage testing this hypothesis by recruiting twin  
317 athletes competing at the Olympic or World Championship levels.

318

319 *Principal Investigators:* Vassilis Klissouras (University of Athens, GRC), Yannis Pitsiladis  
320 (University of Brighton, GBR).

321

### 322 **Rat models of exercise and health (LCR-HCR rat model)**

323 The purpose of the Low Capacity Rats-High Capacity Rats (LCR-HCR) model is to serve as a  
324 resource for the in-depth study of rat models to resolve the extremes of exercise and health. By  
325 connecting clinical observation with a theoretical base, the working hypothesis is that: *variation*  
326 *in capacity for energy transfer is the central mechanistic determinant between disease and*  
327 *health (energy transfer hypothesis)*. As an unbiased test of this hypothesis, this study showed that  
328 two-way artificial selective breeding of rats for low and high intrinsic endurance exercise  
329 capacity also produced rats that differed for numerous disease risks, including the metabolic  
330 syndrome, premature aging, fatty liver disease, obesity, and Alzheimer's disease. Exercise  
331 capacity is a result of intrinsic capacity plus adaptation to all aspects of physical activity. To  
332 capture this biology, rats for low and high response to 8 weeks of treadmill running exercise  
333 were selectively bred. Thus, the study has models that represent the 4 "corners" of exercise  
334 capacity. These contrasting animal model systems may prove to be translationally superior  
335 relative to more widely used simplistic models for understanding disease conditions. The rat  
336 models may be deeply explored to discover causal mechanisms and develop effective  
337 therapeutics. These rats are being studied at over 50 institutions in 11 countries.

338

339 *Principal Investigators:* Steven Britton, Lauren Koch (University of Michigan, USA).

340

#### 341 **1000 Athlome Project**

342 The 1000 Athlome Project aims to sequence 1000 genomes of sprinters and distance runners of  
343 West and East African descent. Phase 1 of the project has already commenced and involves the  
344 sequencing of 12 sprinters and 12 distance runners of the highest level (i.e. world record holders,  
345 Olympians and World Champions). Phase 2 (2016-2018) will involve increasing the sample size  
346 for sequencing to 100 genomes. The pool of the runners to be sequenced will be expanded to  
347 1000 by 2020 (Phase 3). An important aim of this sequencing project is to document the  
348 genotype distribution of elite east and west African athletes. The large amount of genotype data  
349 to be generated from the 1000 Athlome project will serve 1) as a reference panel for future  
350 performance studies, and 2) to guide other extreme phenotype studies in medical science.

351

352 *Principal Investigators:* Masashi Tanaka (Tokyo Metropolitan Institute of Gerontology, JPN),  
353 Yannis Pitsiladis (University of Brighton, GBR).

354

355 **Ethical Principles for Athlome biobanking**

356 The rise of biobanking has brought about a whole range of issues that are not all wholly relevant  
357 to the Athlome project. Nevertheless, certain key principles must be noted here that will inform  
358 the governance framework for Athlome: (i) the consortia are global in reach but there is no  
359 universal agreement on the precise nature of ethically justifiable governance for biobanking; (ii)  
360 given the globality of the consortia, no single regional (e.g., European, American) framework  
361 ought to be adopted; (iii) a general framework drawing on widely shared principles should be  
362 discussed and adopted. Chief among the concerns, but only one among several, is the problem of  
363 consent.

364

365 Each of the projects that comprise Athlome are existing bio-guardians with a duty to protect the  
366 rights of participants who have contributed their samples to the individual projects noted above.  
367 The collection, storage, access to and use by researchers of those samples has been approved by  
368 relevant regulatory authorities (e.g., IRBs, RECs National Health Services Research Ethics  
369 Services) appropriate to the lead institution of the individual projects/consortia. Existing  
370 procedures do not currently extend to the sharing of samples beyond the study, since consent  
371 models are prospective (i.e. they guide future actions of researchers) and typically entail a form  
372 of specificity and the specific consent obtained varies between project partners. No retrospective  
373 consent is feasible and this is a widely shared problem for biobank development. Since the form  
374 of collaboration Athlome envisages was not laid out before participants gave their consent, it  
375 might be concluded that the sharing of data beyond the original research group and its stated  
376 purposes invalidates that consent. The problem for Athlome is not an uncommon one for biobank  
377 collaborations since it seeks retrospective extension of the consent model.

378

379 An ethical solution to this problem and related consent problems for new participants is to  
380 consider the use of a technique such as “broad consent”. The nomenclature here is important  
381 since this notion is variously described as “broad consent”, “blanket consent”, “future consent”,  
382 “hypothetical consent”, “passive/tacit/silent consent”, or “waived consent” (4,5). This would  
383 entail asking participants to agree to future unspecified uses of their data that are  
384 und(er)determined in the consent process and relevant forms (6). Without sufficient grasp of the

385 uses of the data or with whom it might be shared, this process fails the test of “comprehension” a  
386 user must understand sufficiently what they are agreeing to (3). Another possibility going  
387 forward would be “meta-consent” where consent is sought for broad categories of unspecified  
388 future research (7,8). Others have argued with respect to biobanking that the ethical issues  
389 entailed (e.g., privacy, confidentiality, ownership of access to the data) may be sufficiently  
390 assuaged by rigorous anonymization (1) and associated practices of data storage, though this is  
391 far from universally agreed upon (2).

392  
393 The Athlome project will develop principles and protocols for safeguarding participants rights to  
394 access, confidentiality, privacy of data, and assurances that there is no significant mission drift of  
395 the kind of which is permitted under some conceptions of broad consent (or its similes). This  
396 would, for example, prohibit commercialization of participants’ data. In order to preserve the  
397 integrity of this process and the principles, rigorous anonymisation processes will be developed  
398 by a partner institution that does not have any direct role in data collection, storage or analysis.  
399 This will assure independence and integrity to the process. This is especially important in this  
400 case since some of the research participants are public figures, which increases the likelihood  
401 that someone might be interested in re-identifying their data and genomic sequences. The  
402 independent institution would also have an oversight of each new proposal for the Athlome  
403 project going forward in order to ensure compliance with those principles and protocols.

404  
405 In conclusion, by presenting the main study cohorts and projects that are currently included in  
406 the Athlome consortium it is our intention to show a global view not only of the main studies and  
407 initiatives that will be performed in the foreseeable future in the field of sports genomics (and  
408 that are likely to provide new exciting findings); we also wish to motivate potential collaboration  
409 initiatives with other research groups worldwide. International collaborations are likely to go  
410 well beyond the study of sports performance per se. Indeed, the Athlome consortium presents a  
411 unique chance to study the biology of the best elite athletes across most ethnicities, which is  
412 profoundly interesting from a medical point of view. World-class athletes represent the actual  
413 end-point of the human continuum of fitness-related phenotypes. In this regard, there is growing  
414 evidence (coming from both human and rodent study approaches – such as those included in the  
415 consortium) that not only physical activity levels but also individual fitness levels (a trait which

416 has a strong genetic component independent of activity levels) are inversely associated with the  
417 risk of major cardiometabolic diseases of western civilization, several cancer types and  
418 Alzheimer’s disease. Thus, studying the genes of elite athletes offers a unique chance to gain  
419 insight into important medical, including genetic predisposition (or resilience) to chronic disease.  
420 Indeed, the “rare-common” strategy, underpinned by ethically sound research governance, is a  
421 valuable approach model to examine general mechanisms of disease pathophysiology, with  
422 world-class athletes representing the “rare” (“super-fit”) human phenotype. Finally, identifying  
423 genetic markers of exercise capacity, adaptation to exercise programmes and in the  
424 predisposition to injury is certain to provide useful information to prescribe personalised exercise  
425 interventions in the context of 21<sup>st</sup> century medicine, which should not be based only on  
426 identifying new drug targets but also on implementing lifestyle interventions for disease  
427 prevention at the individual level.

428

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669



670 Figure Legends:

671

672 **Figure 1. The Athlome Project Consortium.** Genomic, epigenomic, transcriptomic, proteomic  
673 and metabolomic studies are being conducted by the participating centres to address questions in  
674 the three main research areas: elite performance, training response, and injury. Future  
675 investigations planned include genetically modified studies.

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Athlome Project Consortium

