

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

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5 **Authors:** Yannis P. Pitsiladis^{1*}, Masashi Tanaka², Nir Eynon³, Claude Bouchard⁴, Kathryn N.
6 North⁵, Alun G. Williams⁶; Malcolm Collins⁷; Colin N. Moran⁸, Steven L. Britton⁹, Noriyuki
7 Fuku¹⁰, Euan A. Ashley¹¹, Vassilis Klissouras¹², Alejandro Lucia¹³, Ildus I. Ahmetov¹⁴, Eco de
8 Geus¹⁵, Mohammed Alsayrafi¹⁶

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10

11 **Affiliations:** ¹FIMS Reference Collaborating Centre of Sports Medicine for Anti-Doping
12 Research, University of Brighton, Eastbourne, United Kingdom; ²Department of Longevity and
13 Health, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan; ³Institute of Sport, Exercise,
14 and Active Living (ISEAL), Victoria University, Melbourne, Australia; ⁴Human Genomics
15 Laboratory, Pennington Biomedical Research Center, Louisiana State University, Baton Rouge,
16 United States; ⁵Murdoch Childrens Research Institute, Royal Children’s Hospital, Melbourne,
17 Australia; ⁶Department of Exercise and Sport Science, Manchester Metropolitan University,
18 Crewe, United Kingdom; ⁷Division of Exercise Science and Sports Medicine, Department of
19 Human Biology, University of Cape Town, Cape Town, South African; ⁸Health and Exercise
20 Sciences Research Group, University of Stirling, Stirling, Scotland; ⁹Department of
21 Anesthesiology, University of Michigan Medical School, Ann Arbor, United States; ¹⁰Graduate
22 School of Health and Sports Science, Juntendo University, Chiba, Japan; ¹¹Stanford University
23 Medical Center, Stanford, United States; ¹²Ergophysiology Research Laboratory, Department of
24 Sport Medicine and Biology of Physical Activity, University of Athens, Athens, Greece;
25 ¹³School of Doctorate Studies & Research, Universidad Europea de Madrid, Madrid, Spain; ¹⁴
26 Sport Technology Research Centre, Volga Region State Academy of Physical Culture, Sport and
27 Tourism, Kazan, Russia; ¹⁵VU University and VU Medical Centre, Amsterdam, Netherlands;
28 ¹⁶Anti-Doping Lab Qatar (ADLQ), Doha, Qatar.

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30 ***Corresponding Author:** Professor Yannis P. Pitsiladis
31 Professor of Sport and Exercise Science
32 FIMS Reference Collaborating Centre of Sports Medicine for Anti-
33 Doping Research
34 University of Brighton
35 Eastbourne, BN20 7SN, United Kingdom
36 Email: y.pitsiladis@brighton.ac.uk
37 Telephone: +44 (0) 1273 643707 (Reception)
38 Telephone: +44 (0) 1273 643612 (Office)
39 Fax: +44 (0) 1273 643704

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

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46 **“OMIC” Markers of Athletic Performance.**

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48 **The Athlome Project Consortium***

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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

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

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 ≤ 30 kg/m²).
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 21st 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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430

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433 and Sport of the Russian Federation and the Ministry of Education and Science of the Russian
434 Federation (contract number 02.522.11.2004), the Federal Medical-Biological Agency of the
435 Russian Federation (“Sportgen project”), Republic of Belarus (State program of development of
436 physical culture and sports for 2011-2015) and Royal Society International Joint Project grant
437 from the United Kingdom (code F-90014). **GELAV** (Epigenetics of Lithuanian Athletes from
438 Vilnius) project was developed by the Lithuanian National Olympic Committee and Lithuanian
439 Olympic Sports Centre, while actual research was carried out at the Vilnius University, where
440 Lithuanian athletes DNA samples are stored. We would like to thank Prof. Vaidutis Kučinskas
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443

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495 or SLB brittons@umich.edu for information on the LCR and HCR rats: these rat models are
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502
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526

527 ***The Athlome Project Consortium**

528 **Corresponding author:** Yannis P Pitsiladis¹

529 **Steering Committee:** Yannis P Pitsiladis (Chair), Nir Eynon, Claude Bouchard, Kathryn N
530 North, Alun G Williams, Malcolm Collins, Colin N Moran, Steven L Britton, Noriyuki Fuku,
531 Eco de Geus, Vassilis Klissouras, Euan A Ashley, Alejandro Lucia, Ildus I Ahmetov,
532 Mohammed Alsayrafi and Masashi Tanaka.

533

534 **Consortium Group: University of Brighton, GBR:** Yannis P Pitsiladis¹ (Principal
535 Investigator), Nick Webborn¹, Guan Wang¹; **Victoria University, AUS:** Nir Eynon² (Principal
536 Investigator), David J Bishop² (Principal Investigator), Ioannis Papadimitriou², Xu Yan², Oren
537 Tirosh², Jujiao Kuang²; **Pennington Biomedical Centre, USA:** Claude Bouchard³, Tuomo
538 Rankinene³, Mark Sarzinsky³; **Stanford University, USA:** Euan A Ashley⁴, C Mikael
539 Mattsson⁴, Matthew Wheeler⁴, Daryl Waggott⁴; **Bond University, AUS:** Nuala M Byrne⁵;
540 **University of Sao Paulo, BRA:** Guilherme G Artioli⁶; **University of Cape Town, ZAF:**
541 Malcolm Collins⁷ (Principal Investigator), Alison September⁷, Michael Posthumus⁷, Willem van
542 der Merwe⁷; **Gdansk University of Physical Education and Sport, POL; University of**
543 **Szczecin, POL:** Pawel Cieszczyk^{8,9} (Principal Investigator), Agata Leonska-Duniec^{8,9}, Krzysztof
544 Ficek⁹, Agnieszka Maciejewska-Karłowska⁹, Marek Sawczuk⁹, Marta Stepien-Slodkowska⁹;
545 **Epworth Healthcare Melbourne, AUS:** Julian Feller¹⁰; **Aspetar, QAT:** Paul Dijkstra¹¹; **Ural**
546 **State University of Physical Culture, RUS:** Aleksandr M Chmutov¹², Dmitry A Dyatlov¹²,
547 Evgeniy F Orekhov¹², Yuliya E Pushkareva¹², Irina A Shvedkaya¹²; **University of Cagliari,**
548 **ITA:** Myosotis Massidda¹³, Carla M Calò¹³; **Manchester Metropolitan University, GBR;**
549 **University College London, GBR; Liverpool John Moores University, GBR:** Alun G
550 Williams^{14,15} (Principal Investigator), Stephen H Day¹⁴, Georgina K Stebbings¹⁴, Robert M
551 Erskine^{15,16}, Hugh E Montgomery¹⁵; **Murdoch Childrens Research Institute, AUS:** Kathryn N
552 North¹⁷ (Principle Investigator), Fleur C Garton¹⁷, Peter Houweling¹⁷; **Ghent University, BEL:**
553 Wim Derave¹⁸, Audrey Baguet¹⁸; **Universidad Europea de Madrid, ESP:** Alejandro Lucia¹⁹,
554 Carlos A Muniesa¹⁹; **University of Foggia, ITA:** Francesco Sessa²⁰, Annamarie Petito²⁰;
555 **Nottingham Trent University, GBR:** Craig Sale²¹, David C Hughes²¹; Ian Varley²¹ (Principal
556 Investigator); **VU University Amsterdam, NLD:** Eco de Geus²² (Principal Investigator), Dorret
557 Boomsma²², Meike Bartels²², Gareth E Davies²² **Vilnius University, LTU; Lithuanian**

558 **Olympic Sports Centre, LTU:** Valentina Ginevičienė^{23,24} (Principal Investigator), Audronė
559 Jakaitienė²³, Vaidutis Kučinskas²³, Linas Tubelis²⁴, Algirdas Utkus²³; **Lithuanian University of**
560 **Educational Sciences, LTU:** Kazys Milašius²⁵ (Principal Investigator), Linas Tubelis²⁵;
561 **University of Stirling, GBR:** Colin N Moran²⁶ (Principal Investigator); **Lithuanian Sports**
562 **University, LTU:** Tomas Venckunas²⁷, Albertas Skurvydas²⁷, Arvydas Stasiulis²⁷; **University**
563 **of Glasgow, GBR:** Dalia Malkova²⁸, Richard Wilson²⁸; **University of Michigan, USA:** Steven
564 L Britton²⁹ (principal investigator), Lauren G Koch²⁹ (principal investigator); **Juntendo**
565 **University, JPN:** Noriyuki Fuku³⁰ (Principal Investigator), Hirofumi Zempo³⁰, Hisashi Naito³⁰,
566 Noriko Ichinoseki-Sekine; **Nippon Sport Science University, JPN:** Naoki Kikuchi³¹; **National**
567 **Institute of Fitness and Sports in Kanoya, JPN:** Eri Miyamoto-Mikami³², **National Institute**
568 **of Health and Nutrition, NIBIOHN, JPN:** Haruka Murakami³³, Motohiko Miyachi³³; **Japan**
569 **Institute of Sports Sciences, JPN:** Hideyuki Takahashi³⁴, Nao Ohiwa³⁴, Takashi Kawahara³⁴;
570 **Toyo University, JPN:** Hiroyasu Tsuchie³⁵; **University of Nagasaki, JPN:** Takuro Tobina³⁶;
571 **The Open University of Japan, JPN:** Noriko Ichinoseki-Sekine³⁷; **Fukuoka University, JPN:**
572 Hiroaki Tanaka³⁸; **Waseda University, JPN:** Koji Kaneoka³⁹; **Nippon Sport Science**
573 **University, JPN:** Koichi Nakazato⁴⁰; **Sport Technology Research Centre Kazan, RUS;**
574 **Kazan State Medical University, RUS:** Ildus I Ahmetov^{41,42} (Principal Investigator), Emiliya S
575 Egorova⁴², Leysan J Gabdrakhmanova^{41,42}, Alina A Arkhipova⁴², Alyona V Borisova⁴², Rashid T
576 Gabbasov⁴², Albina A Stepanova⁴¹, Ravil I Kashapov⁴¹; **St Petersburg Research Institute of**
577 **Physical Culture, RUS:** Victor A Rogozkin⁴³ (Principal Investigator); Irina V Astratenkova⁴³,
578 Anastasiya M Druzhevskaya⁴³, Olga N Fedotovskaya⁴³, Natalya D Golberg⁴³, Albina M
579 Hakimullina⁴³; **Research Institute for Physical-Chemical Medicine Moscow, RUS:** Elena S
580 Kostryukova⁴⁴, Dmitry G Alexeev⁴⁴, Edward V Generozov⁴⁴, Dmitry S Ischenko⁴⁴, Nickolay A
581 Kulemin⁴⁴, Andrey K Larin⁴⁴, Elena A Ospanova⁴⁴, Alexander V Pavlenko⁴⁴, Vadim M
582 Govorun⁴⁴; **The National Academy of Sciences of Belarus, BLR:** Andrei A Gilep⁴⁵ (Principal
583 Investigator), Irina L Gilep⁴⁵, Irina V Haidukevich⁴⁵, Irina L Rybina⁴⁵; **National University of**
584 **Physical Education and Sport of Ukraine, UKR:** Svitlana B Drozdovska⁴⁶ (Principal
585 Investigator), Victor E Docenko⁴⁶, Vladimir N Ilyin⁴⁶; **M.Akmullah Bashkir State Pedagogical**
586 **University, RUS:** Eugeny Lekontsev⁴⁷; **Moscow Department of Physical Culture and Sport,**
587 **RUS:** Egor B Akimov⁴⁸; **Anti-Doping Lab Qatar, QAT:** Mohamed El-Rayess⁴⁹, Costas
588 Georgakopoulos⁴⁹, Mohammed Alsayrafi⁴⁹, **FMSI, ITA:** Francesco Botre⁵⁰, **Weill Cornell**

589 **Medical College in Qatar, QAT: Karsten Suhre⁵¹, University College London, GBR: Mike**
590 **Hubank⁵²; University of Athens, GRC: Vassilis Klissouras⁵³; University of Humboldt and**
591 **Charite Medical University, DEU: Bernd Wolfarth^{54,55}; Army Recruiting and Training**
592 **Division, GBR: Julie P. Greeves⁵⁶; Canadian Sport Institute Pacific, CAN: Trent**
593 **Stellingwerff⁵⁷; Cardiff Metropolitan University, GBR: Craig Ranson⁵⁸; University of East**
594 **Anglia, GBR: William D Fraser^{59,60}; Institute of Health and Biomedical Innovation,**
595 **Queensland University of Technology, AUS: Rebecca Grealy⁶¹, Lyn Griffiths⁶¹; University of**
596 **Cambridge, GBR: Robert Scott⁶²; The Swedish School of Sport and Health Sciences, SWE:**
597 **C Mikael Mattsson⁶³; Tokyo Metropolitan Institute of Gerontology, JPN: Masashi**
598 **Tanaka^{64,65}; Physiology Laboratory of the Urals Research Center for Radiation Medicine**
599 **of the Federal Medical-Biological Agency of Russia, RUS: Vladimir P Pushkarev⁶⁶.**

600
601 **Affiliations:** ¹ FIMS Reference Collaborating Centre of Sports Medicine for Anti-Doping
602 Research, University of Brighton, Eastbourne, United Kingdom; ² Institute of Sport, Exercise,
603 and Active Living (ISEAL), Victoria University, Melbourne, Australia; ³ Human Genomics
604 Laboratory, Pennington Biomedical Research Center, Louisiana State University, Baton Rouge,
605 United States; ⁴ Stanford University Medical Center, Stanford, United States; ⁵ Bond Institute of
606 Health and Sport (BIHS), Bond University, Gold Coast, Australia; ⁶ Laboratory of Applied
607 Nutrition and Metabolism, School of Physical Education and Sport, University of Sao Paulo, Sao
608 Paulo, Brazil; ⁷ Division of Exercise Science and Sports Medicine, Department of Human
609 Biology, University of Cape Town, Cape Town, South African; ⁸ Department of Tourism and
610 Recreation, Academy of Physical Education and Sport, Gdansk, Poland; ⁹ Department of
611 Physical Culture and Health Promotion, University of Szczecin, Szczecin, Poland; ¹⁰ Epworth
612 Healthcare, Melbourne, Australia; ¹¹ Department of Sport Medicine, Aspetar, Doha, Qatar; ¹²
613 Genetic laboratory, Ural State University of Physical Culture, Chelyabinsk, Russia; ¹³
614 Department of Environmental and Life Science, University of Cagliari, Cagliari, Italy; ¹⁴
615 Department of Exercise and Sport Science, Manchester Metropolitan University, Crewe, United
616 Kingdom; ¹⁵ Institute of Sport, Exercise and Health (ISEH), University College London, London,
617 United Kingdom; ¹⁶ Research Institute for Sport and Exercise Sciences (RISES), Liverpool John
618 Moores University, Liverpool, United Kingdom; ¹⁷ Murdoch Childrens Research Institute, Royal
619 Children's Hospital, Melbourne, Australia; ¹⁸ Department of Movement and Sports Sciences,

620 Ghent University, Ghent, Belgium; ¹⁹School of Doctorate Studies & Research, Universidad
621 Europea de Madrid, Madrid, Spain; ²⁰ Medical Genetics Unit, Department of Medical Sciences
622 and Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy; ²¹
623 Musculoskeletal Physiology Research Group, Sport, Health and Performance Enhancement
624 Research Centre, Nottingham Trent University, Nottingham, United Kingdom; ²² VU University
625 and VU Medical Centre, Amsterdam, Netherlands; ²³ Department of Human and Medical
626 Genetics, Vilnius University, Vilnius, Lithuania; ²⁴ Lithuanian Olympic Sports Centre, Vilnius,
627 Lithuania; ²⁵ Department of Sport Teaching Methods, Lithuanian University of Educational
628 Sciences, Vilnius, Lithuania; ²⁶ Health and Exercise Sciences Research Group, University of
629 Stirling, Stirling, Scotland; ²⁷ Lithuanian Sports University, Kaunas, Lithuania; ²⁸ School of
630 Medicine, University of Glasgow, Glasgow, Scotland; ²⁹ Department of Anesthesiology,
631 University of Michigan Medical School, Ann Arbor, United States; ³⁰ Graduate School of Health
632 and Sports Science, Juntendo University, Chiba, Japan; ³¹ Sports Training Center, Nippon Sport
633 Science University, Tokyo, Japan; ³² Department of Sports and Life Science, National Institute
634 of Fitness and Sports in Kanoya, Kagoshima, Japan; ³³ Department of Health Promotion and
635 Exercise, National Institute of Health and Nutrition, Tokyo, Japan; ³⁴ Department of Sports
636 Science /Medical Centre, Japan Institute of Sports Sciences, Tokyo, Japan; ³⁵ Faculty of Law,
637 Toyo University, Tokyo, Japan; ³⁶ Faculty of Nursing and Nutrition, University of Nagasaki,
638 Nagasaki, Japan; ³⁷ Faculty of Liberal Arts, The Open University of Japan, Chiba, Japan; ³⁸
639 Institute for Physical Activity, Fukuoka University, Fukuoka, Japan; ³⁹ Faculty of Sports
640 Sciences, Waseda University, Saitama, Japan; ⁴⁰ Department of Exercise Physiology, Nippon
641 Sport Science University, Tokyo, Japan; ⁴¹ Sport Technology Research Centre, Volga Region
642 State Academy of Physical Culture, Sport and Tourism, Kazan, Russia; ⁴² Laboratory of
643 Molecular Genetics, Kazan State Medical University, Kazan, Russia; ⁴³ Sports Genetics
644 Laboratory, St Petersburg Research Institute of Physical Culture, St Petersburg, Russia; ⁴⁴
645 Research Institute for Physical-Chemical Medicine, Moscow, Russia; ⁴⁵ Institute of Bioorganic
646 Chemistry NASB, Minsk, Belarus; ⁴⁶ National University of Physical Education and Sport of
647 Ukraine, Kiev, Ukraine; ⁴⁷ M. Akmulla Bashkir State Pedagogical University, Ufa, Russia; ⁴⁸
648 Centre for Sports Innovation Technologies and National Teams of the Moscow Department of
649 Physical Culture and Sport, Moscow, Russia; ⁴⁹ Anti-Doping Lab Qatar (ADLQ), Doha, Qatar; ⁵⁰
650 Anti-Doping Lab, Federazione Medico Sportiva Italiana (FMSI), Italy; ⁵¹ Department of

651 Physiology and Biophysics, Weill Cornell Medical College in Qatar, Doha, Qatar; ⁵² Centre for
652 Translational Omics, University College London, London, United Kingdom; ⁵³ Ergophysiology
653 Research Laboratory, Department of Sport Medicine and Biology of Physical Activity,
654 University of Athens, Athens, Greece; ⁵⁴ Department of Sports Sciences, University of
655 Humboldt, Berlin, Germany; ⁵⁵ Laboratory of Sports Medicine, Charite Medical University,
656 Berlin, Germany; ⁵⁶ Department of Occupational Medicine, Headquarters Army Recruiting and
657 Training Division, United Kingdom; ⁵⁷ Canadian Sport Institute Pacific, Pacific Institute for
658 Sport Excellence, Victoria, British Columbia, Canada; ⁵⁸ Sports injury Research Group, Cardiff
659 School of Sport, Cardiff Metropolitan University, Cardiff, Wales, United Kingdom; ⁵⁹ Norwich
660 Medical School, University of East Anglia, United Kingdom; ⁶⁰ Norfolk and Norwich University
661 Hospital, Norwich, United Kingdom; ⁶¹ Genomics Research Centre, Institute of Health and
662 Biomedical Innovation (IHBI), Queensland University of Technology, Brisbane, Australia; ⁶²
663 MRC Epidemiology Unit, University of Cambridge, Cambridge, United Kingdom; ⁶³ Åstrand
664 Laboratory of Work Physiology, The Swedish School of Sport and Health Sciences, Stockholm,
665 Sweden; ⁶⁴ Department of Longevity and Health, Tokyo Metropolitan Institute of Gerontology,
666 Tokyo, Japan; ⁶⁵ Department of Clinical Laboratory, Tokyo Metropolitan Geriatric Hospital,
667 Tokyo, Japan; ⁶⁶ Physiology Laboratory of the Urals Research Center for Radiation Medicine
668 of the Federal Medical-Biological Agency of Russia, Chelyabinsk, Russia.

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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

