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LaGomiCs - Lagomorph Genomics Consortium: An International Collaborative Effort for Sequencing the Genomes of an Entire Mammalian Order

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1 PERSPECTIVES

2

3 **LaGomiCs - Lagomorph Genomics Consortium: an international collaborative effort for**
4 **sequencing the genomes of an entire mammalian order**

5

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24

25 **Running Title: Lagomorph Genomics Consortium**

26 **Abstract**

27 The order Lagomorpha comprises about 90 living species, divided in two families: the pikas
28 (Family Ochotonidae), and the rabbits, hare and jackrabbits (Family Leporidae). Lagomorphs
29 are important economically and scientifically as a major human food resource, valued game
30 species, pests of agricultural significance, model laboratory animals, and key elements in food
31 webs. A quarter of the lagomorph species are listed as threatened. They are native to all
32 continents except Antarctica, and occur up to 5,000 m above sea level, from the equator to the
33 Arctic, spanning a wide range of environmental conditions. The order has notable taxonomic
34 problems presenting significant difficulties for defining a species due to broad phenotypic
35 variation, overlap of morphological characteristics, and relatively recent speciation events. At
36 present, only the genomes of two species, the European rabbit (*Oryctolagus cuniculus*) and
37 American pika (*Ochotona princeps*) have been sequenced and assembled. Starting from a
38 paucity of genome information, the main scientific aim of the Lagomorph Genomics
39 Consortium (LaGomiCs), born from a cooperative initiative of the European COST Action “A
40 Collaborative European Network on Rabbit Genome Biology – RGB-Net” and the World
41 Lagomorph Society (WLS), is to provide an international framework for the sequencing of the
42 genome of all extant and selected extinct lagomorphs. Sequencing the genomes of an entire
43 order will provide a large amount of information to address biological problems not only
44 related to lagomorphs but also to all mammals. We present current and planned sequencing
45 programs and outline the final objective of LaGomiCs possible through broad international
46 collaboration.

47

48 **Keywords:** Comparative genomics; Mammalian evolution; Sequencing data; White Paper;
49 Whole genome sequencing; International consortium.

50 **Introduction**

51 Lagomorphs are such a distinct lineage of mammals that the very word ‘lagomorph’ is a
52 circular reference meaning ‘hare-shaped’. Ancestral lagomorphs evolved following the
53 Cretaceous-Paleogene (K-Pg) boundary 53 million years ago and are in the same major
54 mammalian clade as rodents and primates (Euarchontoglires; O’Leary et al. 2013).

55 The order comprises 91 living species divided into two families (Figure 1; Hoffmann and
56 Smith 2005; Alves and Hacklander 2008): i) the pikas (Family Ochotonidae), and ii) the
57 rabbits, hares and jackrabbits (Family Leporidae). However, the systematics of the order is
58 unclear and currently under review by the IUCN Species Survival Commission (SSC) Global
59 Mammal Assessment and Lagomorph Specialist Group (LSG).

60 The Ochotonidae comprises 30 species of small (70-300 g) egg-shaped mammals with
61 distinct rounded ears and no visible tail. Most of these species are vocal. There are two major
62 groups of pikas (Smith 1988; Smith et al. 1990; Lissovsky 2014): i) those that live in rocks or
63 talus have low reproductive rates and are generally long-lived; are territorial either as
64 individuals or pairs and have extremely low rates of social interaction; and ii) those that live in
65 meadow or steppe habitat and burrow, have high reproductive rates, and are generally short-
66 lived; these species form extended families and are highly social.

67 The family Leporidae comprises 32 species of hares (genus *Lepus*) and 29 species of
68 rabbits (Figure 1). The hares are the largest lagomorphs (2-5 kg), having long ears and hind
69 legs and the rabbits include a range of monotypic genera (Verde Arregoitia et al. 2015), some
70 of which are Evolutionary Distinct and Globally Endangered (EDGE) species. The rabbits also
71 have somewhat long ears, but not as long as the hares, and present a more rounded body type.
72 Other rabbits include a variety of unique forms found around the world: for example, the
73 Riverine rabbit (*Bunolagus monticularis*) in South Africa; the hispid hare (*Caprolagus*
74 *hispidus*) of the Terai region of India and Nepal; the black Amami Island rabbit (*Pentalagus*

75 *furnessi*) that occupies isolated islands in the far south of Japan; the Annamite striped rabbit
76 (*Nesolagus timminsi*) of southeast Asia; and the Volcano rabbit (*Romerolagus diazi*) that lives
77 at high elevations on volcanoes surrounding Mexico City. The only domesticated species of
78 the order, the European rabbit (*Oryctolagus cuniculus*), is the most widespread species globally
79 due to its use by humans (e.g., for meat and fur production, for its role as a biomedical model,
80 and for many biotechnology applications). This species also has the most within-species
81 phenotypic diversity due to artificial selection by humans. There are wild forms (mainly on its
82 native region, the Iberian Peninsula, and southern France) as well as repeated human-mediated
83 dispersal of domesticated rabbits into the wild, in particular on many islands and continents,
84 including Australia and New Zealand, often with devastating consequences for native flora and
85 fauna.

86

87 **Relevance and special features of the order Lagomorpha**

88 *Ecosystem services, conservation and biodiversity*

89 Lagomorphs are herbivores playing crucial roles in ecosystems due to their medium size
90 and their position in the food chain as prey-species. Nevertheless, their diversity in terms of
91 size, behaviour, abundance, and reproductive capacity, among other characteristics, allows
92 them to provide varying ecosystem functions and services. Some species are rare, occur in low
93 number with minor relevance to the ecosystem as a whole, but have intrinsic conservation value
94 as rare or vulnerable species that are often evolutionarily distinct.

95 The order Lagomorpha includes some of the most endangered species of all mammals.
96 Roughly 25% of all extant lagomorphs are listed in a threatened category on the IUCN Red
97 List (Smith 2008). Others, however, are very important as game species or key prey for
98 predators. For example, the European brown hare (*Lepus europaeus*) and the Iberian hare (*L.*
99 *granatensis*) are two major game species in Europe and produce large quantities of healthy

100 game meat. In fact, leporids throughout the world serve as game or subsistence meat. Hares
101 also benefit from human-altered environments and occur in agricultural fields as well as in
102 urban areas.

103 Some lagomorphs are considered keystone species, acting as main drivers of an
104 ecosystem that create opportunities for many other species, some of which are valuable
105 resources for humans (Delibes-Mateos et al. 2011). For example, the European rabbit is a
106 keystone species in the Mediterranean ecosystem in southern Europe, an area defined as a
107 'global biodiversity hotspots' (Myers et al. 2000; Delibes-Mateos et al. 2008). This species is
108 the main prey of the Iberian lynx (*Lynx pardinus*), the world's rarest felid, and 20 other
109 carnivores in the Mediterranean region. Even outside their native range, such as in Sweden, the
110 European rabbit has a recognised importance for threatened plant and insect species (Larsson
111 2006). The snowshoe hare is another example of a lagomorph as a keystone species, with the
112 10-year cycle that dominates 5,000,000 km² of northern forests in North America and includes
113 a host of avian predators, mammalian predators, and secondary prey fluctuating in step with
114 the hare population (Krebs et al. 2001).

115 Pikas are temperate to cold-temperature specialists living primarily at high elevations
116 and/or high latitudes. In contrast to fossil species, extant species are specialists living in
117 extreme environments and are largely heat intolerant (MacArthur and Wang 1973, 1974; Smith
118 1974). As a consequence, they are unable to disperse through warmer environments. Their
119 distribution directly reflects the climatic status of an ecosystem. Studies on the American pika
120 (*Ochotona princeps*) confirm that their temperature sensitivity makes them among the first
121 species to respond to changes in climate, highlighting them as excellent indicators of global
122 warming (Smith et al. 2004; Ray et al. 2012). Genetic evidence has revealed both highly
123 restricted dispersal and putative signatures of selection in response to rapidly changing
124 environments (Henry et al. 2012; Henry and Russello 2013; Lemay et al. 2013).

125 Species Distribution Modelling using climatic, topographical and habitat variables for all
126 lagomorph species under past and current climate scenarios and projected into future climatic
127 conditions suggest more than two-thirds of lagomorph species will be impacted (Leach et al.
128 2015). Thirty-six lagomorph species are predicted to experience range loss, 48 poleward
129 movements, and 51 elevational increases. Thirty-five species are predicted to undergo
130 poleward movements or elevational increases *and* range declines. Small-bodied species
131 (predominately pikas) are more likely to exhibit range contractions and upward elevational
132 shifts but little poleward movement, whilst fecund species are most likely to shift latitudinally.
133 The average poleward shift for the order Lagomorpha has been estimated at 1.1° with an
134 elevational upward shift of 165 m. These are much greater changes than those calculated in a
135 meta-analysis collating information on a wide variety of taxonomic groups (Parmesan and
136 Yohe 2003). This vulnerability to climate change makes the Lagomorpha an ideal order to
137 study not only because they are potentially at the greatest threat of extinction, but also because
138 they will be an effective indicator species displaying changes that we may expect to see in less
139 vulnerable groups as local temperatures increase.

140

141 ***Local adaptation***

142 Lagomorphs are adapted to a broad range of environments and thus have been able to
143 achieve a worldwide distribution. In contrast to pikas that are cold-temperature and hypoxia
144 specialists, hares have a wide range of remarkable adaptations permitting them to occupy
145 habitats from extremely arid conditions to Arctic tundra. For example, some boreal species (*L.*
146 *americanus* and *L. timidus* among others) undergo seasonal coat colour change from a brown
147 summer morph to a white winter pelage in adaptation to seasonal snowpack conditions, a trait
148 with limited phenotypic plasticity (Zimova et al. 2014). However, global warming may
149 endanger the survival of these species (Mills et al. 2013). As a consequence, many boreal

150 lagomorph species may act as important markers of climate change because of mismatching
151 between the coat colour and the timing of snowfall in the autumn and snowmelt in the spring
152 (Mills et al. 2013). *Lepus timidus* is particularly well adapted to cold habitats, and mitogenomic
153 analyses suggest that mitochondrial DNA (mtDNA) may have played a role in this adaptation,
154 with several instances of positive selection identified in genes encoding proteins of the
155 oxidative phosphorylation chain (Melo-Ferreira et al. 2014c). Other species are well adapted
156 to hot climates (e.g., the long eared *L. californicus* and *L. callotis*). Additional ecological
157 features contribute to make lagomorphs of particular relevance for the study of diurnal,
158 crepuscular or nocturnal habits, quick movements, reproduction features, parental care,
159 behaviour, and disease resistance among other biological features. These considerations make
160 lagomorphs invaluable models to study the architecture of adaptive evolution and the nature of
161 ecological specialization.

162

163 ***Phylogenetics, speciation, and hybridization***

164 Pikas, hares, and cottontails are notoriously difficult groups in terms of taxonomic
165 classifications and definition of species, mainly due to broad phenotypic variation within taxa,
166 overlap of morphological characters across taxa, and the relatively recent speciation events in
167 some genera. Molecular markers, initially mtDNA and more recently multi-locus approaches
168 have been used to disentangle questions related to phylogenetics and classification within the
169 different groups (Matthee et al. 2004; Lanier and Olson 2009; Melo-Ferreira et al. 2012, Melo-
170 Ferreira et al. 2015). However, these studies have often uncovered extensive sharing of genetic
171 variation among species, complicating phylogenetic inference based on a comparatively small
172 number of loci. These findings are largely influenced by the retention of ancestral
173 polymorphisms and incomplete lineage sorting across the history of the group, but also, in
174 some cases, due to secondary introgression across historical or current hybrid zones (Thulin et

175 al. 2006; Melo-Ferreira et al. 2005, 2012, 2014a, 2014b). Indeed, several lagomorph systems
176 have become textbook models for speciation and hybridization studies (e.g., *O. cuniculus*,
177 Carneiro et al. 2013, 2014a, 2014b; *L. europaeus/timidus/granatensis*, Alves et al. 2008, Melo-
178 Ferreira et al. 2011, 2012; *S. transitionalis/obscures/floridanus*, Litvaitis et al. 2008). At this
179 point, more data and studies are needed to better resolve lagomorph systematics and evolution.

180

181 ***Palaeontology and ancient DNA***

182 Extant and extinct species provide complementary information on the biological
183 diversity and evolutionary mechanisms that have occurred and are still occurring within the
184 order Lagomorpha (Ge et al. 2013). Among European taxa, the relatively recent extinction of
185 *Prolagus* is of particular interest for palaeobiogeographical and biochronological research.
186 *Prolagus* is one of several ochotonids that populated Europe during the last 25 millions of
187 years, and was remarkable due to its longevity, extraordinary abundance and geographical
188 distribution (López Martínez 2001). There is sufficient archaeological evidence (Vigne et al.
189 1981; Angelone et al. 2008) as well as testimonies from historians (e.g., Polybius) that *Prolagus*
190 survived in Corsica and Sardinia until the classical epoch. The availability of archeological
191 specimens attributed to *Prolagus sardus* can provide genomic information from this extinct
192 species. Moreover, genetic analyses of ancient specimens of *L. europaeus* and *L. timidus* would
193 allow a better understanding of the adaptive process that led to high altitude specialization of
194 the latter. This information will assist in predicting the possible evolutionary responses to
195 climate change, providing an important evolutionary context for the contemporary
196 management of lagomorph species.

197

198 ***Diseases***

199 Lagomorphs are carriers of pathogens with zoonotic potential (e.g., Tularemia) or may
200 act as reservoirs and/or asymptomatic hosts and carriers of new, emerging and/or potential
201 zoonotic infections and infestations (i.e., Lyme borreliosis, Crimean-Congo haemorrhagic
202 fever, tick borne encephalitis, paratuberculosis, etc.). The role of different lagomorphs in
203 Europe including the native *Lepus* spp. and *O. cuniculus* as well as the imported species such
204 as *Sylvilagus floridanus*, also may be linked to the presence of new vectors (mosquitoes, sand-
205 flies, ticks, etc.) and to changing climate conditions or different ways of dissemination and
206 diffusion of pathogens that on the whole have determined new epidemiological patterns. In
207 particular, rabbits may act as sentinels of zoonotic infections because they are reared in
208 industrial units for meat production as well as in small rural operations, used as laboratory
209 animals and kept as pets, all the while being present simultaneously in the wild (Shaughnessy
210 et al. 2013).

211 There is evidence from the literature that the susceptibility to diseases, especially viral
212 diseases such as European brown hare syndrome, rabbit haemorrhagic disease, and
213 myxomatosis, may be linked to genetic factors (Nyström et al. 2011; Abrantes et al. 2012; Kerr
214 2012; Lopes et al., 2014a) that are likely different between breeds/populations and even
215 differentially expressed at an individual level. In particular, the study of cell receptors for
216 pathogens may lead to improvements in our understanding of pathogenesis of infections
217 including to what extent affected hosts develop innate and adaptive immunity that confers
218 resistance to diseases. A better understanding of the processes involved (including interactions
219 with other factors and organisms) should provide new insights into disease control. These
220 studies are particularly important since there are several examples of viral species jump.
221 Indeed, it has been shown that *Sylvilagus* is susceptible to European brown hare syndrome and
222 *Lepus granatensis*, *L. capensis* and *L. corsicanus* are susceptible to rabbit hemorrhagic diseases
223 (Puggioni et al., 2013; Camarda et al., 2014; Lopes et al., 2014b; Lavazza et al., 2015).

224 Furthermore, direct epidemiological insights may result from the biological similarities
225 between lagomorph and human diseases.

226 Rabbits and hares, which are present in the wild as large populations, offer the
227 opportunity to perform large-scale analyses of natural ecosystems and to repeat them at regular
228 intervals to follow the dynamics of the host and parasite genotypes under selection and co-
229 evolution. Specifically, the role of density and frequency-dependent selection in host parasite
230 co-evolution may be addressed, for example, in *S. floridanus*. This species facilitated the spread
231 of exotic nematodes and one exotic flea in the population of autochthonous lagomorphs in
232 Europe (Meneguz and Tizzani 2002; Tizzani et al. 2011). These imported parasites offer a
233 robust epidemiological model to study the effects of pathogens in non-coevolved hosts.

234

235 *Animal models*

236 The European rabbit is one of the most used experimental animals for biomedical
237 research, particularly as a widely-used bioreactor for the production of polyclonal and
238 monoclonal antibodies. Studies of the rabbit immune system have greatly contributed to our
239 knowledge of the structure, function, and regulation of antibodies (reviewed in Pinheiro et al.
240 2011). However, many unique physiological features of the rabbit (like human but unlike
241 rodents) have also made it an excellent species for investigating a number of aspects of human
242 diseases such as cardiovascular disease, atherosclerosis, respiratory disease, immune-related
243 diseases, osteoarthritis, ocular research, and Alzheimer's disease and reproductive physiology
244 (Fan et al. 2015). Because of their short life spans, short gestation periods, high numbers of
245 progeny, low cost, and availability of genomic and proteomic information, rabbits usually serve
246 to bridge the gap between smaller rodents (mice and rats) and larger animals (dogs and
247 monkeys) and play an important role in many translational research activities such as pre-
248 clinical testing of drugs and diagnostic methods for patients. One of the best contributions made

249 by rabbits in the history is the discovery of statin, the most potent lipid-lowering drug which is
250 currently prescribed for more than 30 million cardiovascular disease patients in the world.
251 From the point of view of therapeutic development, it has become evident that many human
252 diseases cannot be properly investigated by rodents such as psychological stress (Nalivaiko
253 2011) and sepsis (Seok et al. 2013). Many clinical trials failed possibly because the initial
254 concepts were mainly based on mouse studies. Therefore, rabbit serves as an alternative animal
255 model for human diseases to solve those specific questions, which cannot be conducted by
256 rodents. Transgenic rabbits along with the advent of knock-out rabbits will pave a novel way
257 for the development of both therapeutic and diagnostic strategies in the future (Fan and
258 Watanabe 2003; Yang et al. 2014).

259 Thus, comparative analysis of the rabbit genome with other Lagomorphs will provide an
260 informative context for the rabbit genome and will increase the utility of the rabbit as a
261 biological model. The study of epigenetic changes in regulatory genes may reveal a major way
262 that animals adapt to environmental challenges (Zhang and Meaney 2010) and lagomorph
263 genome sequencing could identify comparable critical genes and their promoters in rodents,
264 primates, and lagomorphs.

265 Pikas are considered interesting models to study biological mechanisms related to
266 hypoxia from different perspectives. Although pikas are associated with cold environments,
267 not all species evolved at high elevations. Identifying genes responsible for hypoxia tolerance
268 will reveal if lower elevation species may be limited in their ability to shift their ranges in
269 response to climate change due to a lack of hypoxia adaptations. In addition, comparative
270 analyses within the genus *Ochotona* will reveal information about adaptation and resistance to
271 hypoxia with potential applications to the biomedical field.

272 Pikas also constitute a potential mammalian model for investigating biotic responses to
273 climate change. The latitudinal and elevational distributions of the American pika, in particular,

274 provide interesting opportunities for testing theoretical predictions associated with the roles of
275 historical processes and contemporary forces in shaping genome-wide patterns of neutral and
276 adaptive genetic variation.

277

278 **Status of Lagomorph genomics**

279 The genomes of two lagomorph species, the European rabbit and American pika, have
280 been preliminarily sequenced and assembled by the Broad Institute in the framework of the
281 Mammalian Genome Project (Lindblad-Toh et al. 2011). The European rabbit genome has been
282 subsequently improved and used to infer information about the domestication process of this
283 species (Carneiro et al. 2014b). These assemblies are publicly available in the ENSEMBL and
284 NCBI databases. The first release of the low-coverage 1.93X assembly (OchPri2.0,
285 http://www.ensembl.org/Ochotona_princeps/Info/Index) of the *O. princeps* genome has been
286 recently improved by the Broad Institute (OchPri3.0). The European rabbit genome (second
287 assembly: OryCun2, GCA_000003625.1) was sequenced to a 6.51-fold coverage (~7X).
288 Approximately 82% of its 2.74 Gb has been anchored to chromosomes
289 (http://www.ensembl.org/Oryctolagus_cuniculus/Info/Index). For the Ochotonidae 273,670
290 sequences are already deposited in GenBank and EMBL databases (20 Sept. 2015), most of
291 which (99.47%) are from *O. princeps* whose genome still includes many unassembled
292 scaffolds. The Leporidae accounts for 2,259,925 entries (20 Sept. 2015), most of which
293 (99.54%) are from *O. cuniculus*.

294 Transcriptome data have so far been reported for just a few species. For example, in the
295 American pika RNA-seq data have been obtained for animals from high and low elevation sites
296 (Lemay et al. 2013). Also, RNA-seq data from *Lepus granatensis* has been included in a study
297 about the efficacy of natural selection in vertebrates and invertebrates (Gayral et al. 2013). A

298 microarray designed for *O. cuniculus* was used to quantify transcript abundance in snowshoe
299 hares (Lavergne et al. 2014).

300 Collectively, however, these data indicate that genomic information in the Lagomorpha
301 is still in its infancy, despite the large number of biological questions that can be addressed by
302 research efforts in this field.

303

304 **The Lagomorph Genomics Consortium (LaGomiCs)**

305 *Overview and aims*

306 Sequencing the genomes of all extant species of a mammalian order will provide a unique
307 opportunity to address a large number of biological problems not only related to lagomorphs
308 but also related to all mammals. Indeed, it is currently one of the few orders that have a
309 relatively small number of species that would feasibly permit comprehensive genome
310 sequencing. As outlined, lagomorphs possess many advantageous characteristics to address a
311 broad array of biologically significant topics. A comparative genomic analysis will provide
312 basic information on genome evolution and possibilities to analyse the detailed properties
313 differentiating a unique mammalian order. These data will potentially elucidate features of the
314 ancient lagomorph genome. In addition, sequencing genomes of this order will establish
315 sequence-based rules to clarify the complex systematics within the Lagomorpha providing
316 information for conservation prioritization.

317 The Lagomorph Genomics Consortium (LaGomiCs; Figure 2) was born from a
318 cooperative initiative of the European COST Action TD1101, “A Collaborative European
319 Network on Rabbit Genome Biology – RGB-Net” 2011-15
320 (http://www.cost.eu/COST_Actions/bmbs/TD1101; <http://www.biocomp.unibo.it/rabbit/>) and
321 the World Lagomorph Society (WLS; <http://www.worldlagomorphsociety.org/>).

322 Its main scientific aim is to provide an international research framework whose final
323 objective is the sequencing of the genomes of all extant and selected extinct lagomorph species
324 over the next 5 years. Initially, a priority list of proposed species to be sequenced has been
325 prepared (Table 1) considering the availability of samples, research priorities, and key
326 questions attached to the proposed species. This list covers the whole Order and includes
327 endangered species, species with taxonomic problems, and the most representative species of
328 the different taxa.

329 The main political aim of LaGomiCs is to coordinate research efforts to avoid the
330 duplication of activities, facilitate the exchange of data and analyses, and efficiently maximize
331 the scientific impact of these genomic resources. LaGomiCs facilitates the coordination of
332 scientists with overlapping biological interests focused on lagomorph species and welcomes
333 the further development of research questions based on the interest of additional contributors.

334

335 *Strategic issues*

336 The sequenced genomes of the European rabbit and American pika will provide key
337 resources to facilitate broad-scale genomic research projects of lagomorph species. To this aim,
338 current or future projects are expected to produce next generation sequencing (NGS) data from
339 additional lagomorphs. Table 2 shows a list of sequencing programs in species of this order,
340 partially overlapping the priority list (Table 1). These programs confirm the emerging interests
341 of the lagomorph research community in developing the resources necessary to address
342 biological questions from a genomic perspective.

343 The cooperation of national and international funding agencies as well as coordinated
344 activities among research groups will ensure that the necessary resources to achieve the
345 scientific aim of the LaGomiCs are secured. RGB-Net and the WLS will provide the strategic
346 framework to carry out cooperative activities, exploit common interests, prepare research

347 programs, and apply to research agencies. LaGomiCs will follow protocols and methodologies
348 already proposed by the 10K Genome Project, considering the strategic and key issues of
349 sampling and storage of biological material needed for the project and all other steps that should
350 be completed to reach its goal (Genome 10K Community of Scientists 2009; Koefli et al. 2015).

351

352 ***Sampling and storage of biological material***

353 Sequencing the genome of all lagomorph species requires an important preliminary step
354 of collection of biological samples. Sampling will be coordinated by LaGomiCs according to
355 specific standards and rules that all contributing scientists should follow. Samples will be
356 registered in the Biosamples database, which is a freely available service provided by EMBL-
357 EBI (<http://www.ebi.ac.uk/biosamples/index.html>). The purpose of the Biosamples database is
358 to provide a central point of access to information about any biological sample, which may
359 then be referenced by other external databases (e.g., the ENA database).

360 An example of a Biosamples record can be seen here:

361

362 <http://www.ebi.ac.uk/biosamples/sample/SAMEA1145802>

363 Sample Accession: SAMEA1145802

364 Name : source GSM570796 1

365 Sample Description :

366 Organism : *Oryctolagus cuniculus*

367 characteristic[cell type] : stomach cells

368 characteristic[strain] : Dutch rabbit

369 comment[Sample_source_name] : rabbit stomach cell

370 comment[Sample_description] : Gene expression in rabbit stomach cells

371

372 The 'Sample Accession' is a stable identifier, which will be assigned to a sample when
373 it is registered to the database. This accession will then be used within the consortium to track

374 samples at every stage of analysis. Following the accession, the record consists of a set of
375 attributes composed of key/value pairs. The choice of attributes is flexible as it is possible to
376 annotate samples according to information available (e.g., cell type, sex, location, age, health,
377 and a textual description of the sample).

378 Furthermore, Biosamples records may be collected together into one or more ‘groups’,
379 which also may have attributes, and are identified by a group accession identifier (e.g.
380 <http://www.ebi.ac.uk/biosamples/group/SAMEG64149>). Creating a LaGomiCs group for the
381 consortium will allow easy access to the complete set of Biosamples associated with the
382 project.

383 In addition to using the Biosamples resource, the consortium also will hold its own
384 central record of samples held by consortium members. The central record will reference
385 Biosamples accession identifications, and can track other consortium-relevant information,
386 such as whether the sample may be shared by the owner with consortium members.

387

388 *Sequencing approaches and data analysis*

389 Next generation sequencing technologies will provide cost effective approaches that can
390 produce sufficiently reliable sequence data useful for assembling mammalian genomes.
391 Methods for sequencing and assembling mammalian genomes with NGS data are reasonably
392 well established, although still challenging (Nagarajan and Pop 2013). Generation and analysis
393 of genome sequences will be most efficient if, to the extent possible, the methods are uniform
394 across all species.

395 For each species, a minimum number of sequences should be produced to build a *de novo*
396 assembly independent from other species. Species in the lagomorph clade are sufficiently
397 divergent so that it is inappropriate to use inter-species sequence alignment or any low-
398 coverage sequencing strategy.

399 In addition, the sequencing strategy should be tailored for the specific assembly tool to
400 be used in the next downstream steps. The Allpaths-LG assembler is currently a forerunner in
401 successfully producing mammalian genomes from NGS reads (Gnerre et al. 2011), and should
402 be used preferentially for the LaGomiCs project. Allpaths-LG requires the following
403 sequencing data as its input:

404

- 405 1. Paired end Illumina sequencing of 180 bp fragments to a ~45x depth of coverage across the genome.
- 406 2. Mate pair Illumina sequencing of multiple libraries with long inserts in the range 3 kb - 8 kb, totalling to
407 a ~45x depth of coverage.

408

409 The genome assemblies produced from the Allpaths-LG strategy will be sufficient for
410 most downstream analyses. However, assemblies could optionally be improved for key
411 lagomorph species by sequencing of fosmid libraries (Gnerre et al. 2011) or using optical
412 mapping data (Dong et al. 2013) and other sequencing approaches and technologies allowing
413 the sequencing of long reads (Pedleton et al. 2015). RNA-seq data will be obtained from tissue
414 samples from key species and used to facilitate annotation of assembled genomes.

415 The likely advent of new sequencing and assembly technologies during the course of this
416 project will facilitate higher quality assemblies and reduce the necessary effort. Once the
417 genome assemblies have been generated, a host of additional analyses can be addressed
418 including genome annotation, evolution, and speciation. Having genomic resources for an
419 entire order of species will support novel analytical approaches to address ecological and
420 evolutionary questions.

421

422 *In-depth characterization of the transcriptome for genome annotation*

423 To identify all poly-adenylated transcripts in a genome, a variety of adult, embryonic,
424 and developmental tissues (10-15 tissues; e.g. blood, brain, heart, kidney, liver, lung, ovary,

425 skeletal muscle, and skin), from multiple individuals/species will be collected and used for
426 RNA-Seq and transcriptome assembly. Initial target species will be those most easily accessible
427 for the collection of fresh tissues for RNA storage and isolation. The resulting transcriptome
428 will be rich in alternative isoforms and yield an accurate picture of tissue distribution for both
429 coding and non-coding transcripts.

430 RNA-Seq libraries from each tissue will be constructed using a strand-specific dUTP
431 protocol as described by Levin et al. (2010). Sequencing can be carried out on
432 machines/platforms yielding a minimum of 50 Million 101 bp pair-end reads per tissue. PolyA
433 isolation step will be performed to maximize the breadth of protein-coding transcripts
434 sequenced (Di Palma, personal communications). Strand specificity is useful for all RNA-
435 sequencing and because it allows the determination of the orientation of transcripts it is
436 particularly important for RNA-sequencing used in annotation.

437 Reads will be aligned to the genome using a gene annotation system (Curwen et al. 2004).
438 Protein-coding gene models will be annotated by combining alignments of UniProt (UniProt
439 Consortium 2013) vertebrate/mammalian protein sequences and RNAseq data. In parallel,
440 reads from each tissue will also be assembled separately using Trinity *de novo* transcriptome
441 assembler (Grabherr et al. 2011). As Trinity uses no reference genome for the assembly
442 process, it will serve as a validation step for the transcriptome. The annotation will be further
443 expanded (as needed) by syntenically mapping using the species Ensembl gene set and the
444 protein coding genes from the expanded Rabbit annotation (Ensembl/Broad Institute) with the
445 synteny aligner Satsuma (Grabherr et al. 2010) and a specially developed local aligner
446 (Broad/Uppsala, Di Palma personal communications). This will further characterize non-
447 coding transcripts, missed protein coding genes, and alternative isoforms as well as antisense
448 transcripts.

449

450 *A database of well-annotated genes of the Lagomorpha*

451 After the RNA-seq based genome annotation, the next step will be to provide annotation
452 of protein functions of the new genomes. Automated annotation will be obtained using the
453 University of Bologna Biocomputing Group annotation systems. This method is based on a
454 large-scale genome cross comparison and a non-hierarchical clustering procedure
455 characterized by a metric that after statistical validation transfers knowledge within a set of
456 sequences in a cluster that includes homologous and orthologous genes (Piovesan et al. 2011;
457 Radivojac et al. 2013). The annotation system will be specifically implemented as to contain
458 all lagomorph gene sequences with links to all the available information on model animals
459 making the structural location of the different variants among species apparent.

460

461 *Data storage, ownership, and release policies*

462 Genomics as a field has benefited tremendously from pre-publication release of sequence
463 data and has a long history of developing forward-looking community-based policies in this
464 area including the 1996 Bermuda Agreement, the 2003 Fort Lauderdale Agreement, and the
465 2009 Toronto Statement. These approaches have allowed for the field to expand quickly and
466 have driven many discoveries. LaGomiCs will follow these strategic release policies providing
467 beneficial information to the lagomorph scientific community.

468 LaGomiCs will use the European Nucleotide Archive (ENA) to deposit its nucleotide
469 sequence data (<http://www.ebi.ac.uk/ena/about/about>). ENA is a service provided by EMBL-
470 EBI, which both stores nucleotide sequence data and records information relating to the
471 experimental workflow that produced the sequence data. Submitting sequence data to the ENA
472 is a central and mandatory step of a research project, as it satisfies the rules set by scientific
473 publishers to make research data freely available to the scientific community. Sequences
474 submitted at an early stage to the ENA databases by the LaGomiCs consortium may be held

475 privately until a nominal publication date, after which it would be made freely available.
476 Specifically, LaGomiCs will use the Sequence Read Archive (SRA) to deposit its raw
477 sequencing data and EMBL-Bank to deposit assembled sequences of the lagomorph genomes.

478 In addition, a UCSC Track Data Hub will be made available for the community through
479 a hosting institution. Track hubs are web-accessible directories of genomic data that can be
480 viewed on the UCSC Genome Browser alongside native annotation tracks. The data underlying
481 the tracks in the hub would reside on the selected institute's servers. The tracks would be both
482 publicly available and linked through both the institute's website and the UCSC Genome
483 Browser.

484 Additionally, a Memorandum of Understanding (MoU) will be produced to regulate the
485 sharing and storage of samples, the sharing and use of unpublished data and resources,
486 including publication policy, following standards already proposed in genomic projects and
487 open access policies.

488

489 *A portal for lagomorph genomic resources and international collaborations*

490 LaGomiCs has established a website to house all useful content and contacts
491 (<http://biocomp.unibo.it/lagomics/>) to foster the growth of the lagomorph research community
492 interested in lagomorph genomics and to provide a virtual meeting point to share information
493 and initiatives. LaGomiCs also has established a collaborative connection with the Genome
494 10K project with the specific intention to coordinate sequencing initiatives to avoid duplication
495 of efforts and to increase the transparency of the need for genomic resources in lagomorph
496 species.

497

498 *Science outreach and education*

499 Lagomorphs are well known species, both from a historical and contemporary
500 perspective. Several species are present in folklore and mythology from different countries
501 while others are popular in literature or as cartoon figures. They also are charismatic creatures,
502 easily creating empathy with both adults and children. Such characteristics make lagomorphs
503 excellent vehicles for science communication and education. For example, American pikas are
504 at the center of multiple citizen science programs at the regional (e.g., North Cascades National
505 Park, Washington, USA) and global (e.g., Worldwide Pika Project;
506 <http://www.adventurescience.org/pika.html>) scales. Moreover, they are a focal species for
507 ScienceLIVE (<http://www.science-live.org/>), an organization that facilitates understanding of
508 science by connecting field researchers to the general public. Knowledge generated within the
509 framework of this project can thus be used to contribute to the public understanding of science,
510 from basic biological disciplines to more complex or sensitive topics.

511

512 **Conclusions**

513 The sequencing of the genome of all lagomorphs is particularly challenging due to the
514 difficulties in organizing appropriate sampling and coordinating data production and data
515 analysis. **However, we are able to take advantage of what has already been done in this field**
516 by several groups and what specific local projects will obtain in the future. An international
517 framework is needed to collect and combine efforts that, on the whole, will obtain the
518 sequencing of the genome of all species of an entire mammalian order. Different expertises are
519 needed to fully exploit sequence-derived information that might address biological problems
520 not only related to lagomorphs but also to all mammals. The LaGomiCs is open to all
521 contributors who are willing to share their experience, expertise, specialization, and resources
522 in all fields relevant for reaching the final aim.

523

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529

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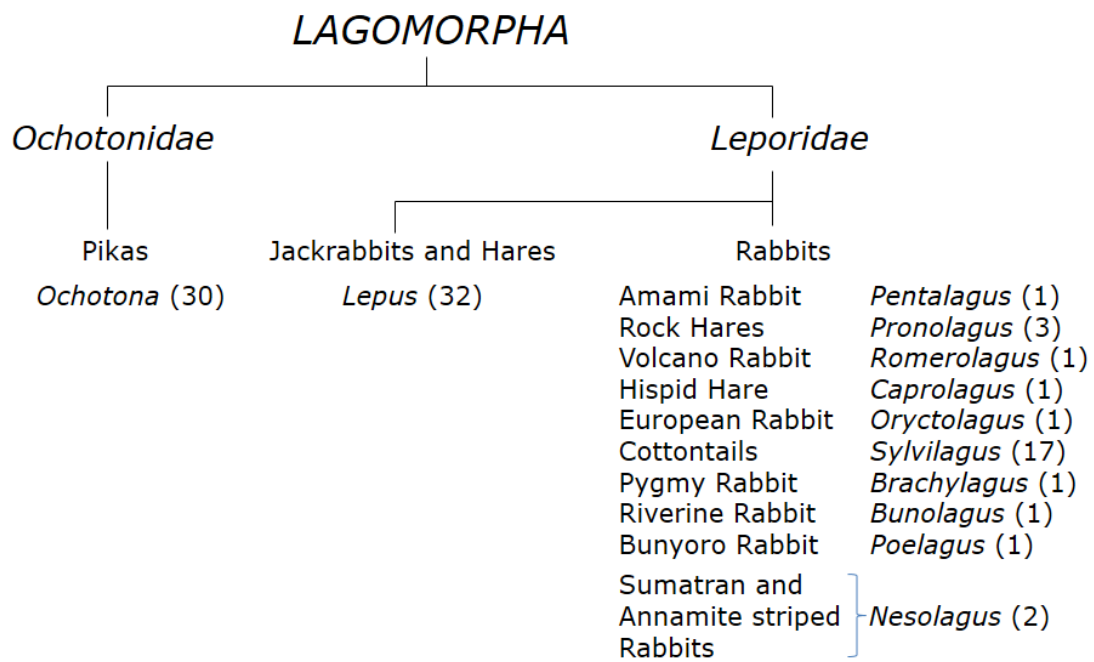


Figure 1. Overview of systematics of the order Lagomorpha (number in parenthesis indicates the number of species within the genera; Hoffmann and Smith 2005; Alves and Hacklander 2008).



Figure 2. Official logo of the Lagomorph Genomics (LaGomiCs) Consortium.

Table 1. Priority list for sequencing lagomorph species. This is an updated list based on the documents produced during the First LaGomiCs meeting held in Bologna (Italy) on the 18-19 February 2013.

Species	Sample providers	Contacts/proposers	Estimated availability (year)
<i>Lepus timidus</i>	Paulo C Alves, Ettore Randi, Cristiano Vernesi, Carl-Gustaf Thulin, Neil Reid	Paulo C Alves, J Melo-Ferreira, Ettore Randi, Cristiano Vernesi, Luca Fontanesi	2016
<i>Lepus europaeus</i>	Paulo C Alves, Ettore Randi, Cristiano Vernesi, Carl-Gustaf Thulin, Zissis Mamuris, Mihajla Djan	Paulo C Alves, José Melo-Ferreira Ettore Randi, Cristiano Vernesi, Luca Fontanesi	2016
<i>Lepus corsicanus</i>	Ettore Randi, Cristiano Vernesi, Luca Fontanesi	Ettore Randi, Cristiano Vernesi, Luca Fontanesi. José Melo-Ferreira	2016
<i>Lepus castroviejoii</i>	Paulo C. Alves	José Melo-Ferreira	-
<i>Lepus capensis</i>	Paulo C. Alves	-	-
<i>Lepus saxatilis</i>	Paulo C. Alves	-	-
<i>Lepus granatensis</i>	Paulo C. Alves	Paulo C. Alves, J Melo-Ferreira	-
<i>Lepus tolai</i>	-	-	-
<i>Lepus nigricolis</i>	-	-	-
<i>Lepus coreanus</i>	Hung Sun Koh	-	-
<i>Lepus callotis</i>	-	-	-
<i>Lepus flavigularis</i>	-	-	-
<i>Lepus insularis</i>	-	-	-
<i>Lepus californicus</i>	-	-	-
<i>Lepus townsendii</i>	Paulo C. Alves	Paulo C. Alves, J Melo-Ferreira	-
<i>Lepus americanus</i>	Paulo C. Alves	Paulo C. Alves, J Melo-Ferreira	-
<i>Lepus othus</i>	-	-	-
<i>Lepus arcticus</i>	-	-	-
<i>Sylvilagus floridanus</i>	-	Thomas McGreevy Jr. Adrienne Kovach, Anthony Tur, Thomas Husband, Tim King	-
<i>Sylvilagus obscurus</i>	-	Thomas McGreevy Jr., Adrienne Kovach,	-

		Anthony Tur, Thomas Husband, Tim King	
<i>Sylvilagus transitionalis</i>	-	Thomas McGreevy Jr., Adrienne Kovach, Anthony Tur, Thomas Husband, Tim King	-
<i>Sylvilagus audubonii</i>	-	-	-
<i>Sylvilagus cunicularius</i>	-	-	-
<i>Sylvilagus brasiliensis</i>	-	-	-
<i>Sylvilagus mansuetus</i>	-	-	-
	-	-	-
<i>Sylvilagus nuttallii</i>	-	-	-
<i>Ochotona curzoniae</i>	-	-	-
<i>Ochotona macrotis</i>	Katherine Solari	-	-
<i>Ochotona princeps</i> (>7x)	-	-	-
<i>Ochotona thibetana</i>	-	-	-
<i>Prolagus sardus</i> (Ext, bones)	Chiara Angelone	Luca Fontanesi, Cristiano Vernesi	2016
<i>Romerolagus diazi</i>	Fernando A. Cervantes	Luca Fontanesi, Paulo C. Alves	2016-17
<i>Pronolagus rupestris</i>	Terrence J. Robinson	Luca Fontanesi	2016-17
<i>Bunolagus monticularis</i>	-	-	-
<i>Pentalagus furnessi</i>	-	-	-

Table 2. List of ongoing or planned sequencing programs in lagomorph species.

Species	Status/comments	NGS/Sequencing strategy/Depth	Biological questions/projects	Principal investigators/contacts	Partners
<i>Ochotona macrotis</i>	ongoing	Transcriptome/Illumina	Adaptation/Climate Change	Katie Solari, Liz Hadly, Uma Ramakrishnan	
<i>Ochotona princeps</i>	completed (7X)	Genome/Sanger/Illumina	Mammalian Genome Project	Kerstin Lindblad-Toh, Federica Di Palma	-
<i>Ochotona princeps</i>	ongoing	Transcriptome/454	Conservation/Climate change	Michael Russello	-
<i>Ochotona princeps</i>	ongoing	Genome/Illumina	Conservation/Climate change	Michael Russello	-
<i>Lepus americanus</i>	Ongoing (20x)	Genome/RNA-seq/Illumina	Adaptation/Conservation/Climate change	Paulo C. Alves, José Melo-Ferreira,	Jeffrey M. Good, L. Scott Mills
<i>Lepus americanus</i>	ongoing	All exome/Illumina	Adaptation/Conservation/Climate change	Jeffrey M. Good, Paulo C. Alves, José Melo-Ferreira,	L. Scott Mills
<i>Lepus americanus</i>	completed (10X)	Genome/Illumina	Rabbit domestication project	Leif Andersson	CIBIO, Miguel Carneiro, Nuno Ferrand, Paulo C. Alves
<i>Lepus castroviejo</i>	Planned	Genome/Illumina	Reticulate evolution/speciation/adaptation	José Melo-Ferreira, Paulo C. Alves, Pierre Boursot	-
<i>Lepus corsicanus</i>	Planned	Genome/Illumina	Speciation/Conservation	Ettore Randi, Cristiano Vernesi, Luca Fontanesi	-
<i>Lepus corsicanus</i>	Planned	Genome/Illumina	Reticulate evolution/speciation/adaptation	José Melo-Ferreira, Paulo C. Alves, Pierre Boursot	-
<i>Lepus europaeus</i>	Ongoing (15X, 10 specimens)	Genome/Illumina	Reticulate evolution/speciation/adaptation	José Melo-Ferreira, Paulo C. Alves, Pierre Boursot	-
<i>Lepus europaeus</i>	Planned	Genome/Illumina + Ion Proton	Conservation/Climate change	Cristiano Vernesi, Ettore Randi, Luca Fontanesi	-
<i>Lepus europaeus</i>	completed	RNA-seq of heart and liver of six hares (2 from Greece, 2 from Cyprus, 2 from Poland)	-	Zissis Mamuris	-
<i>Lepus granatensis</i>	Ongoing (20x, 10 specimens)	Genome/Illumina	Reticulate evolution/speciation/adaptation	José Melo-Ferreira, Paulo C. Alves, Pierre Boursot	-
<i>Lepus timidus</i>	Planned	Genome/Illumina	Conservation/Climate change	Cristiano Vernesi, Ettore Randi, Luca Fontanesi	-
<i>Lepus timidus</i>	Ongoing 20x, 4 specimens, including a reference genome (60x)	Genome/Illumina	Reticulate evolution/speciation/adaptation	José Melo-Ferreira, Paulo C. Alves, Pierre Boursot,	Jeffrey M. Good, L. Scott Mills
<i>Lepus timidus hibernicus</i>	Planned	Genome/Illumina	Determine levels of interspecific introgression with <i>L. europaeus</i>	Neil Reid	Paulo C. Alves
<i>Lepus townsendii</i>	Planned	Genome/Illumina	Reticulate evolution/speciation/adaptation	José Melo-Ferreira, Paulo C. Alves,	L. Scott Mills
<i>Oryctolagus cuniculus</i>	completed (7X)	Genome/Sanger/Illumina	Mammalian Genome Project/ Rabbit domestication project	Leif Andersson, Kerstin Lindblad-Toh, Federica Di Palma	CIBIO, Miguel Carneiro, Nuno Ferrand
<i>Poelagus marjorita</i>	Planned	Genome/Illumina	Reticulate evolution/speciation/adaptation	José Melo-Ferreira, Paulo C. Alves, N Ferrand	-
<i>Sylvilagus floridanus</i>	Ongoing	Genome/Illumina	Conservation	Thomas McGreevy Jr. Adrienne Kovach, Anthony Tur, Thomas Husband, Tim King	-
<i>Sylvilagus obscurus</i>	Ongoing	Genome/Illumina	Conservation	Thomas McGreevy Jr., Adrienne Kovach,	-

				Anthony Tur, Thomas Husband, Tim King	
<i>Sylvilagus transitionalis</i>	ongoing	Genome/Illumina	Conservation	Thomas McGreevy Jr., Adrienne Kovach, Anthony Tur, Thomas Husband, Tim King	-

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