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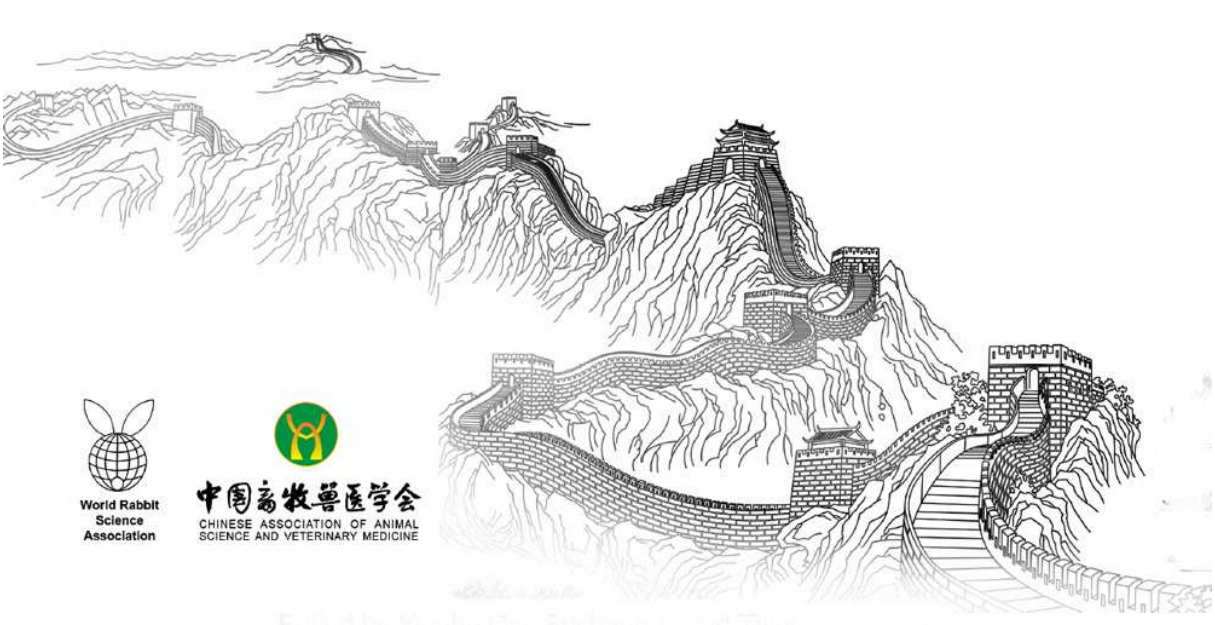

THE RABBIT IN THE GENOMICS ERA: APPLICATIONS AND PERSPECTIVES IN RABBIT BIOLOGY AND BREEDING

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ABSTRACT

The domestic rabbit is a unique species due to its multiple applications. It includes many different breeds, lines and populations with unique phenotypic variants and extremely different performances and production traits. The sequencing of the rabbit genome and the development of new genomic tools have been creating new opportunities in rabbit breeding, biotechnology, study of animal models, conservation genetics and management of animal genetic resources. A quite large number of investigations have used a candidate gene approach to identify DNA markers associated with economic relevant traits (meat quality and carcass traits, reproduction traits and disease resistance)in meat lines. Several coat colour and hair morphology loci have been already characterized at the molecular level and causative mutations have been identified. The needed basic elements/tools to apply genomic selection approaches in rabbits have been developed or could be available from what have been prepared for other species. The refinement of the assembly of the currently available version of the rabbit genome is a prerequisite for more advanced investigations that might include detailed functional annotations to address gene editing.

Key words: Breeding, Genetics, Candidate gene, Coat colour locus, Genomic selection

INTRODUCTION

The European rabbit or domestic rabbit (*Oryctolagus cuniculus*) is a unique species as it is at the crossroad of several uses and applications with similar importance and (direct or indirect) economic values that may depend by countries or interests: i) it is a livestock species raised mainly for meat production but also for fur production, with different specialized lines; ii) it is a fancy animal with a broad spectrum of different and unique phenotypes that are usually recognizedas different breeds; iii) it is an animal model used to investigate and answer many biological questions; iv) it is a biotech tool mainly used to produce antibodies but also other therapeutic agents; v) it is a wild resource, mainly in its native regions where it is controlled by natural enemies; and vi) it is a pest mainly in its non-native regions where it is not controlled by natural enemies. Despite these different and very relevant uses or functions, a relatively low number of studies, compared to other livestock or animal models, have been addressed on this species to understand the genetic factors affecting traits that are important in their numerous applied fields.

Only recently, with the advent of genomics, investigators and practitionershave started to look at the rabbit from another perspective (Miller et al., 2014).Genomics, in some way, unifies all aspects of this lagomorph and provides tools, methodologies and resources that are useful to identify and analyse markers and causative mutations in this species for a large variety of applications.

Genomics relies of new technologies that have been recently developed and that made it possible to increase throughputs mainly in genotyping, sequencing and data analysis. In particular, among the most important advances in this field we can mention next generation sequencing (NGS) technologies. NGS has revolutionized the way in which genomic information is produced in all living organisms. The same is true for the rabbit in which several applications of NGS technologies and approaches have been largely contributing to study variability in the rabbit genome and to characterize its transcriptome for functional annotations. For example, a quick survey in the Sequence Read Archive (SRA) database (http://www.ncbi.nlm.nih.gov/sra) showed that 103 accessions included NGS data obtained by sequencing rabbit genomic regions (whole genome sequencing or targeted sequencing) and that 179 accessions were from RNA-seq data generated from the rabbit for a total of a few terabytes of sequence data(update: 20th of April 2016). Sequence data generated from the rabbit are expected to increase exponentially in

the near future. However, the most important resources generated by genomics in the rabbit during the last years is the sequence of its genome (Carneiro et al., 2014). This fundamental resource has opened new opportunities to understand this multi-purpose species for its different applications and will contribute to sustain future applications.

THE RABBIT GENOME – A FUNDAMENTAL TOOL FOR SUBSEQUENT APPLICATIONS

The karyotype of the European rabbit is made by 21 autosomes plus the sexual chromosomes (2n = 44). These chromosomes have been sequenced and assembled starting from low coverage, producing a first draft of an assembled genome (OryCun1.0), generated within the Mammalian Genome Project by the Broad Institute (Lindblad-Toh et al., 2011). Subsequently this preliminary version, that was used for an evolutionary analysis across mammals, has been refined and a second version has been obtained (OryCun2.0; Carneiro et al., 2014). OryCun2.0 was sequenced to a 7X and made available in Ensembl database (http://www.ensembl.org/Oryctolagus_cuniculus/Info). This genome version includes about 2.74 Gbp, 82% has been anchored to chromosomes. The remaining unanchored contigs have been assembled into a virtual chromosome indicated as "Un". To obtain an approximate evaluation of the precision and completeness of the assembling of a genome, the used parameter is the N50 size that is a statistic that defines assembly quality. N50 is the length such that 50% of the assembled genome lies in blocks of the N50 size or longer. The OryCun2.0 N50 length for supercontigs is 35348.54 kb. The N50 size for contigs is 64.65 kb. To have a first evaluation of the quality of this assembly we could compare it to the N50 of the cattle genome (UMD3.1 genome version) that is 103.78 kb for contigs,one of the best among all livestock species. Thus far, the quality of the assembled cattle genome is much better than that of the rabbit genome. Therefore, we could indirectly deduce that the assembly work for the rabbit genome has not been completed yet. In a near future the advent of long read sequencing technologies (e.g. PacBio, Nanopore, etc.) is expected to change the way in which genomes are assembled (Gordon et al., 2016) and further improvements might be also applied for the rabbit genome.

The total numbers of nucleotides in supercontigs and contigs in OryCun2.0 are 2.66 Gbp and 2.60 Gbp, respectively (http://www.ensembl.org/Oryctolagus_cuniculus/Info/Annotation). The annotation process of the OryCun2.0 genome version identified 19,203 coding genes, 3,375 non-coding genes, 1001 pseudogenes and a total of 24,964 gene transcripts.

At present, the rabbit genome version available in Ensembl database (OryCun2.0; Ensembl Release 84, March 2016)does not report any information on polymorphisms even if extensive studies have been carried out on this species at the genome wide level. The first genome wide identification of single nucleotide polymorphisms (SNPs) in the rabbit genome has been obtained using the Ion Torrent Personal Genome Machine that sequenced reduced representation libraries in a DNA pool-seq approach (Bertolini et al., 2014). This study identified about 62.5 k SNPs (479 of which were missense mutations, and 16 were stop-gained mutations)by sequencing sampled fractions of the rabbit genome that covered about 0.1 Gbp with a detection rate of one SNP per about 1.7 kb of sampled genome. Then, the work of Carneiro et al. (2014) that described the sequencing and assembly of OryCun2.0 reported the discovery of about 50 million highquality SNPs and 5.6 million insertion/deletion polymorphisms by whole genome sequencing of several DNA-pools from different breeds.A second level of variability in the rabbit genome, that has been investigated by just one study so far, is constituted by copy number variation (CNV; Fontanesi et al., 2012b). It is well known now that CNVs (defined as interspecific gains or losses of ≥1 kb of genomic DNA) are very frequent in all mammalian genomes in which they represent the most important source of variability in terms of affected nucleotides with potential relevant impacts on gene expression (covering on the whole ~0.4-25% of a genome; Redon et al., 2006; Conrad et al., 2010). The study in rabbit involved four individuals of different breeds and was carried out using the array comparative genome hybridization (aCGH) technique based on high density probes spread all over the OryCun2.0 genome. A total of 155 copy number variation regions (CNVRs), identified by overlapping or partially overlapping CNV events, covered about 6.62 Mb (~0.3% of the rabbit genome). These 155 CNVRs included 95 gains, 59 losses and one with both gain and loss, localized on all chromosomes except on chromosome 20. At present, CNVs are not annotated in the OryCun2.0 genome version.

Analyses of variability in the rabbit genome have been used in different studies for different purposes and applying different approaches. In particular, considering the rabbit as a meat species, studies have been carried out to identify polymorphisms associated with performance and production traits in population based association studies

and in family based analyses for QTL identification. Other studies have been carried out to identify mutations affecting relevant phenotypic traits that identify breeds or strains and that might be important to establish new animal models based on natural variants available among fancy breeds. The complete sequence of the rabbit genome has also opened the possibility to propose genomic selection in this species even if several limits should be considered for practical applications. Moreover, basic information and annotations of the rabbit genome might open new perspectives in using gene editing approaches for novel and even unexpected potential applications.

CANDIDATE GENE ANALYSES FOR PRODUCTION TRAITS

A candidate gene approach has been already successfully used in many livestock species to identify polymorphisms associated with many different economic traits. This approach is based on simple assumptions that directly link the functions of genes with production traits: variability within genes coding for protein products involved in key physiological functionsor roles directly or indirectly involved in determining an economic trait (e.g. average daily gain, muscle mass deposition, feed conversion rate, reproduction efficiency, disease resistance, etc.) could probably explain a fraction of the genetic variability for the production trait for which the gene has been selected. Therefore, the first step is the selection of the most plausible candidate genes based on previous knowledge that could derive from what is also known in other species. Then, the second step is the identification of polymorphisms in the selected candidate genes. The third step is based on the design of association studies according to the available populations and phenotypes in the investigated animals. All animals with phenotypic traits are genotyped and appropriate statistical tests are used to establish associations between gene markers and production traits. This approach is a shortcut to reach as soon as possible and with a relatively low effort the final goal that is the identification of DNA markers associated with economic traits. The candidate gene approach is, from one hand, a smart approach if we have enough information to pick up the most important genes affecting the targeted trait but, on the other hand, is weak as we usually do not know at priori if the selected candidate is the most important gene (among all potential candidates) affecting the trait in the investigated species and if variability for that gene segregates in the analysed population.

Several studies in rabbits have been based on candidate gene analysis to identify DNA markers associated with economic relevant traits. Table 1 shows a list of genes investigated using this approach. Three groups of studies can be identified based on three main groups of investigated traits that, in turn, define the choice of the candidate genes: association studies for 1) growth and meat production traits (carcass and meat quality traits), 2) reproduction traits in does and 3) disease/disorder resistance traits.

A relatively large number of studies have been carried out to investigate growth rate and meat production traits (carcass and quality traits). In these studies, growth rate has been mainly measured indirectly by weighting the animals at different ages that in many cases reflect different growth stages or different final market weights. In particular, Fontanesi et al. (2011, 2012a, 2012c, 2014b, 2016) used just one important phenotype defined as one of the main selection objectives in a commercial meat rabbit line, i.e. live weight at 70 days, taking advantage from the routine collection of this phenotype in this parental line. Other authors (Peng et al., 2013; Yang et al., 2013; Zhang et al., 2013, 2014; Liu et al., 2014; Wang et al., 2015) investigated several growth, carcass and meat quality traits measured in rabbits of a few breeds/lines (some of them with a limited number of animals) and usually carried out association studies by combining data from more than one breed/line. Sternstein et al. (2014) carried out an association study in an F2 reference population obtained by crossing parental animals of two different breeds (Giant Grey and New Zealand white) and used for a QTL study (Sternstein et al., 2015). In this investigation, about 400 F2 rabbits were phenotyped for a large number of carcass and meat production traits. In this first group of studies, the choice of candidate genes was mainly based on their functions and considering that studies in other species already showed that variants in these genes explains a quite large fraction of the genetic variability for several production traits. In particular, the choice of the myostatin (*MSTN*) gene as candidate in three different studies in rabbits is related to the well-known effects that disruptive mutations in this gene have on muscle mass development, as already described in other animal species, e.g. mouse (McPherron et al., 1997), cattle (Grobet et al., 1997; Kambadur et al., 1997; McPherron and Lee, 1997) and sheep (Clop et al., 2006). Unfortunately, it seems that no disrupting mutations in this gene (that might have a very relevant phenotypic effect like what is observed in beef cattle or meat sheep breeds) segregate in several investigated rabbit breeds or lines (Fontanesi et al., 2011; Peng et al., 2013; Sternstein et al., 2014). However, putative regulatory mutations in this gene might be associated with carcass traits, according to what wasshown in an F2 reference population (Sternstein et al., 2014). The effect

of natural *MSTN* polymorphisms on growth rate (i.e. finishing weight) seems very mild (Peng et al., 2013) or not important (Fontanesi et al., 2011).

Other candidate genes were selected following what was already published in other species. For example, growth hormone (*GH1*), growth hormone receptor (*GHR*), and insulin-like growth factor 2 (*IGF2*) encodes for important components of the somatotropic axis and variability in the genes have been already shown to have relevant effects on growth or production related traits in many different species (e.g. Lagziel et al., 1996; Blott et al., 2003;Van Laere et al., 2003). The same is true for variability in the melanocortin 4 receptor (*MC4R*)gene (involved in the mechanisms controlling energy homeostasis and food intake) for which missense polymorphisms observed in humans and pigs are causative mutations for growth and obesity-related traits (e.g. Kim et al., 2001). Investigating the rabbit *MC4R* gene we identified a novel missense mutation causing an amino acid substitution in a position not yet described to be polymorphic in any other species (p.G34D, located in a conserved position of the extracellular tail of the MC4R protein) that was associated with weight at 70 days in a commercial meat line selected for growth rate for many years (Fontanesi et al., 2013). It was interesting to note that the most favorable allele was also the most frequent one, according to what was expected in this population considering the selection objective that wanted to maximize this trait. This is also the most common situation that we identified for many other polymorphisms in candidate genes for which the positive alleles were usually the most frequent one in a meat rabbit line that has been selected for years for growth performances (e.g. Fontanesi et al., 2012c, 2016).

The second group of candidate genes have been selected to find markers for reproduction traits in does. These studies used a unique animal genetic resource constituted by divergent rabbit lines for uterine capacity.These lines have been developed by at least 10 generations of divergent selection for this trait after having clarified that fetal survival depends mainly on the maternal genotype (Mocé et al., 2004). Polymorphisms in three genes (*OVGP1, PGR* and *TIMP1*) were associated to a few reproduction traits depending by uterine capacity, including embryo implantation and litter size (Estellé et al., 2006; Peiró et al., 2008, 2010; Merchán et al., 2009; Argente et al., 2010; García et al., 2010).

The third group of candidate genes were selected to identify markers associated with resistance to diseases or digestive disorders based on two different experimental designs, respectively. The first experimental design was based on a classical association study between several immunological traits (i.e. the level of several parameters or immunological related molecules) and a candidate gene but no direct association with any pathogen or any specific diseases was carried out (Wan et al., 2014). The limited number of animals and the heterogeneity of the investigated rabbits might need to verify the results in other populations. The second experimental design was based on a case and control design, i.e. between rabbits that showed nonspecific digestive disorders versus rabbits that did not show any digestive disorder. Association was declared when allele frequencies at the selected candidate genes differed significantly between the two groups (Zhang G.W. et al., 2011, 2013; Chen et al., 2013; Liu et al., 2013; Zhang W.X. et al., 2013; Fu et al., 2014)

Based on all these candidate gene studies, it is possible to evidence that the structures of the experimental designs are fundamental to identify meaningful associations. The number of investigated animals is always a crucial factor to identify associations with complex traits in all experiments and this applies also to a candidate gene approach. The number of animals needed might depend by the heritability of the investigated traits and by the possibility to control environmental effects in the specific experiments among several other factors. The other critical question is derived by the available phenotypes that might lead to the selection of the most plausible candidates.These issues open a window on the step forward that will take advantage from the analysis of not only one or few candidate genes but hundreds or even thousands of polymorphisms at the same time, changing the pace by which markers associated with production traits are identified.

Table 1: List of candidate genes investigated in association studies for several economic relevant traits in different rabbit populations.

Gene symbol	Gene name	Polymorphisms	Populations	Associated traits	References
Growth and meat production traits (carcass and meat and fat quality traits)					
FTO	Fat mass and obesity associated	3 SNPs in exon 3 (2 missense mutations)	New Zealand, Ira and Champagne rabbits	Body weight at 35, 70, and 84 d; intramuscular fat	Zhang G.W. et al. (2013a)
GH1	Growth hormone	SNP in a putative regulatory region	Commercial meat rabbit line	Finishing weight	Fontanesi et al. (2012a)
GHR	Growth hormone receptor	Missense mutation (SNP)	Commercial meat rabbit line	Finishing weight	Fontanesi et al. (2016)
GHR	Growth hormone receptor	Missense mutation (SNP)	New Zealand, Ira and Champagne rabbits	Eviscerated weight, semi-eviscerated weight, eviscerated slaughter rate, and semi-eviscerated slaughter rate, pH24, weight at 84 d	Zhang et al. (2012)
IGF2	Insulin-like growth factor 2	Indel in a putative regulatory region	Commercial meat rabbit line	Finishing weight	Fontanesi et al. (2012c)
IRS1	Insulin receptor substrate 1	2 synonymous SNPs	New Zealand rabbits	Body weight at 35, 70, and 84 d	Zhang et al. (2014)
MC4R	Melanocortin 4 receptor	Missense mutation (SNP)	Commercial meat rabbit line	Finishing weight	Fontanesi et al. (2013)
MSTN	Myostatin	Missense mutations	Commercial meat rabbit line	None (analysed only finishing weight)	Fontanesi et al. (2011)
MSTN	Myostatin	1 SNP in 5'-flanking region	Ira, Champagne, and Tianfu Black rabbit breeds	Body weight at 84 d	Peng et al. (2013)
MSTN	Myostatin	1 SNP in intron 1	Giant Grey x New Zealand F2 population	Several carcass traits[1]	Sternstein et al. (2014)
NPY	NeuropeptideY	1 SNP in intron 1	Ira, Champagne, and Tianfu Black rabbit breeds	Eviscerated slaughter percentage, semi-eviscerated slaughter percentage	Liu et al. (2014)
PGAM2	Phosphoglycerate mutase	1 synonymous SNP on exon 1	Ira, Champagne, and Tianfu Black rabbit breeds	Body weight at 84 d, average daily gain	Wu et al. (2015)
POMC	proopiomelanocortin	1 SNP in intron 1	Ira, Champagne, and Tianfu Black rabbit breeds	84 d body weight, eviscerated weight, semi-eviscerated weight, ripe meat ratio	Liu et al. (2014)
POU1F1	POU class 1	1 SNP in intron 5	Hyla, Champagne,	pH1, cooking	Wang et al.

	homeobox 1		and Tianfu Black rabbit breeds	loss, intramuscular fat	(2015)
TBC1D1	TBC1 domain family member 1	1 missense mutation in exon 1	European White and New Zealand white rabbits	Body weight at 35 days	Yang et al. (2013)
Reproduction traits in does					
OVGP1	Oviductal glycoprotein 1	1 missense SNP in exon 11 and a microsatellite	F2 cross of two lines divergently selected for uterine capacity	Total number of kits born, number born alive, number of implanted embryos, foetal prenatal embryo survival and development	Merchán et al. (2009); García et al. (2010)
PGR	Progesterone receptor	5 SNPs in two haplotypes	F2 cross of two lines divergently selected for uterine capacity	Embryo implantation and litter size, expression of progesterone receptor isoforms	Peiró et al. (2008); Peiró et al. (2010)
TIMP1	TIMP metallopeptidase inhibitor 1	1 SNP in the promoter region	F2 cross of two lines divergently selected for uterine capacity	Embryo implantation	Estellé et al. (2006); Argente et al. (2010)
Disease/disorder resistance traits					
DECTIN1 (CLE7A)	C-type lectin domain family 7 member A	ss707197675A>G	New Zealand white (case and control study)	Nonspecific digestive disorder	Zhang G.W. et al. (2013a)
IL10	Interleukin 10	Synonymous SNPs in exon 3	New Zealand white, Fujian yellow and their reciprocal crosses	Immune parameters[2]	Wan et al. (2014)
JAK3	Janus kinase 1	1 missense mutation (exon 9) and 1 synonymous SNP (exon 21)	New Zealand white (case and control study)	Nonspecific digestive disorder	Fu et al. (2014)
MYD88	myeloid differentiation primary response 88	Synonymous SNP in exon 4	Yaan and Chengdu populations (case and control study)	Nonspecific digestive disorder	Chen et al. (2013)
NLRP12	NLR family, pyrin domain containing 12	1 missense mutation in exon 3	New Zealand white (case and control study)	Nonspecific digestive disorder	Liu et al. (2013)
NOD2	Nucleotide-binding oligomerization domain containing 2	1 synonymous SNP in exon 10	New Zealand white (case and control study)	Nonspecific digestive disorder	Zhang W.X. et al. (2013)
STAT3	signal transducer and activator of transcription 3	2 synonymous SNPs (exons 4 and 8)	New Zealand white (case and control study)	Nonspecific digestive disorder	Fu et al. (2014)
TLR4	Toll-like receptor 4	5 SNPs (2 synonymous and 3 non-synonymous): 2 haplotypes	New Zealand white (case and control study)	Nonspecific digestive disorder	Zhang et al. (2011)

TYK2	Tyrosine kinase 2	2 haplotypes	New Zealand white (case and control study)	Nonspecific digestive disorder	Fu et al. (2015)

[1]Hot carcass weight; dressing out percentage; reference carcass weight; fore part weight; intermediate part weight; hind part weight; meat weight fore part; meat weight intermediate part; bone weight intermediate part.
[2]IgG level; IL-10 level;, IFN-γ level; White Blood Cell (WBC) count.

QTL ANALYSES FOR MEAT PRODUCTION TRAITS

During the last years, one of the most common objective in livestock genetics (in the most studied species) has been towards the identification of QTL for many different traits by constructing reference populations or by using family-structured populations already available in the field (i.e. in dairy cattle). This was not true for the rabbit as, at present, just one work has been published on the identification of QTL for meat and carcass traits (Sternstein et al., (2015).This study was based on an F2 population constituted by about 360 rabbits obtained by crossing parental animals of two divergent breeds (Giant Grey and New Zealand White) and then again by crossing F1 rabbits. All animals were genotyped with 189 microsatellite markers covering the whole genome. A large number of carcass and meat quality and production traits were analysed on these animals. The most significant QTL were identified on chromosome 7 (for different carcass weights), on chromosome 9 (for bone mass) and chromosome 12 (drip loss) and many other suggestive QTL were reported on almost all chromosomes (Sternstein et al., 2015). These results might be useful to dissect the genetic factors affecting carcass and meat production traits for potential practical applications. However, due to the large linkage disequilibrium created in F2 families it will be difficult to apply fine mapping strategies to better refine the list of potential candidate genes that might be annotated in the genome regions spanning the reported QTL.

It is clear that, based on genomic tools that have been developed or that will be developed in rabbits using genomic information (i.e. the complete sequence of the rabbit genome, the discovery of millions of SNPs, the availability of high throughput genotyping technologies), association and QTL studies will change, following the developments and improvements already observed in other livestock species.

IDENTIFICATION OF MUTATIONS AFFECTING BREED OR LINE-SPECIFIC TRAITS

Many rabbit breeds or lines are characterized by specific coat colours or other phenotypic traits that are usually fixed in these populations. Actually, the name of many rabbit breeds or lines derives by their characteristic phenotypes. These breeds/lines are unique resources that are important for multiple applications (Leroy et al., 2016).

Causative mutations for several loci have been identified by sequencing and then by genotyping candidate genes in different rabbit breeds or lines (Table 2). These variants can constitute interesting genetic models to understand the basic biological mechanisms involved in pigmentations or determining other phenotypes. On the other hand, the identified mutations can be used to identify the breed or line of origin of meat or to define breeding plans in fancy breeds or for fur production.At present, six coat colour loci and two hair morphology loci have been characterized at the molecular level. Two additional loci affecting other traits that could be relevant for meat production or to consider the rabbit as animal model have been analysed at the DNA level (Table 2). That means that many other loci already descibed by classical genetic studies during the last century remain to be investigated.

Pigmentation in mammals is determined by the synthesis of two types of melanins (eumelanins: black/brown pigments; and pheomelanins: yellow/red pigments) that occurs in specialized cells, the melanocytes. The final phenotypic effects in mammals (i.e. coat colour) is determined by the presence, distribution and biochemical activity of the melanocytes and by the relative amount of eumelanins and pheomelanins and by their distribution in melanosomes (the cellular organelles that are the site for synthesis, storage and transport of melanins). More than 300 loci have been shown to affect coat colour in mice regulating or altering melanocyte development and migration during embryogenesis, melanocyte morphology and functions, its components and its enzymatic machinery (e.g. Bennett and Lamoreux, 2003). In rabbits, only the main loci have been described so far (Robinson, 1958).

Extension and *agouti* are the main loci that affect the production and relative amount of eumelanin *vs* pheomelanin in the melanocytes (Searle, 1968). These loci show epistatic interactions: wild type *extension*alleles are required for expression of*agouti*alleles. Dominant alleles at the *extension* locus produce black pigmentation, whereas recessive alleles extend the production of pheomelanins, causing yellow/red/pale pigmentation. On the contrary, dominant *agouti* alleles determine pheomelanic phenotypes whereas recessive alleles cause black coat colour with a few exceptions.The *Extension* locus encodes the melanocortin 1 receptor (*MC1R*) (Robbins et al., 1993). This protein belongs to the seven transmembrane G protein coupled receptors that binds the α melanocyte-stimulating hormone (αMSH) inducing eumelanin synthesis. The *agouti* locus encodes the agouti signaling protein (ASIP) that is a small paracrine signalling protein (131-135 amino acids in different mammals) that affects pigmentation blocking the αMSH-MC1R interaction which, in turn, causes a pigment-type switching from eumelanins to phaeomelanins (Bultman et al., 1992).

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Fontanesi et al. (2006, 2010b) sequenced the rabbit*MC1R* gene in several rabbit breeds with different coat colours and characterized at the molecular level the most important alleles at the *extension* locus described by classical genetic studies (Robinson, 1958; Searle, 1968; Table 2). Two putative variants of the wild type allele (E^+) were identified. Three different in-frame deletions (two of 6 bp and one of 30 bp) characterize the E^D (dominant black; that might be the same as the E^S allele described by the classical genetic literature), the e^J (Japanese brindling) and the *e*(recessive red, non-extension of black), respectively. Figure 1 shows the 2D structure of the deduced MC1R protein with evidenced the deletions of the corresponding amino acids based on the mutated alleles.

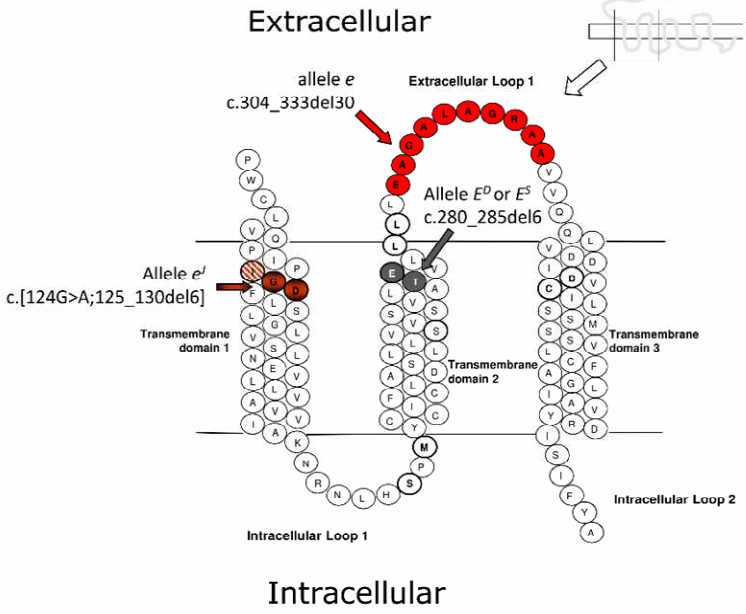

Figure 1: Details of the inferred 2D structure of the deduced rabbit MC1R protein with indicated the mutations causing different alleles.

Two mutated alleles at the *agouti* locus were characterized at the DNA level by sequencing the *ASIP* gene in different breeds (Fontanesi et al., 2010a; Table 2). The coding sequence of the a^t (black and tan) allele differed by the wild type allele (*A*) by two missense mutations. The recessive *a* (black nonagouti) allele is determined by a frameshift insertion in the first coding exon of the *ASIP* gene.

Several alleles at the rabbit *C* locus (a*albino* locus) were characterized by sequencing the tyrosinase (*TYR*) gene that encodes for a key enzyme in the melanin synthesis (Aigner et al., 2000; Table 2). The *Chinchilla* allele (c^{Ch}) is due to two missense mutations, the *Himalayan* allele (c^H) carry only one of the two missense mutations of the

Chinchilla allele and the *albino* allele (*c*) is derived by another missense mutation (p.T373K). Another missense mutation in the *TYR* gene has been identified in wild rabbits (Utzeri, Ribani and Fontanesi, unpublished results).

The dilution of both eumelanic and pheomelanic pigmentations is caused by the *dilute* locus in rabbit (Castle, 1930; Robinson, 1958; Searle, 1968). As a result of the recessive mutated allele (*d*), the black is diluted to grey (termed blue by fancy breeders), that characterizes a few rabbit breeds, like Blue Vienna (Castle 1930; Robinson 1958). In mice, similar phenotypes are determined by mutations in the *myosin Va* (*Myo5a*; *dilute* locus), *Rab27a* (*ashen* locus) and *melanophilin* (*Mlph*; *leaden* locus) genes (Mercer et al., 1991; Wilson et al., 2000; Matesic et al., 2001) that encode proteins that constitute the melanosome transport complex (Barral and Seabra 2004). Fontanesi et al. (2012d) excluded as the determinant of the rabbit *dilute* locus variability in the rabbit *MYO5A* homologous gene. Then, in a subsequent study, Fontanesi et al. (2014a), by sequencing the rabbit*MLPH*gene in different breeds including animals with the blue coat colour phenotype segregating in a family, identified a causative mutation determined by a frameshift mutation (g.549853delG). Lehner et al. (2013) identified another mutation determining the recessive *d* allele at this locus, causing the skipping of two exons of the rabbit*MLPH* gene.

Classical genetic studies suggested the presence of two alleles at the rabbit *brown* coat colour locus (Catlle, 1930; Robinson, 1958; Searle, 1968): a wild type *B* allele that gives dense black pigment throughout the coat and a recessive *b* allele that in homozygous condition (*b*/*b* genotype) produces brown rabbits that are unable to develop black pigmentation. In several other species this locus is determined by mutations in the *tyrosinase-related protein 1* (*TYRP1*) gene, encoding a melanocyte enzyme needed for the production of dark eumelanin. Utzeri et al. (2014) sequenced the rabbit *TYRP1* gene and showed that the b allele at this locus is determined by a single nucleotide polymorphism in exon 2 that leads to a premature stop codon at position 190 of the deduced protein sequence (p.W190ter). This mutation was identified only in the brown Havana rabbits that have a brown coat colour.

The *English spotting* coat colour locus in rabbits, also known as *Dominant white spotting* locus, is determined by an incompletely dominant allele (*En*). Rabbits homozygous for the recessive wild-type allele (*en*/*en*) are self-colored, heterozygous *En/en* rabbits are normally spotted (as requested by the standard of several spotted breeds, like Checkered Giant and English Spotting), and homozygous *En/En* animals are almost completely white. Compared to vital *en*/*en* and *En/en* rabbits, *En/En* animals are subvital because of a dilated ('mega') cecum and ascending colon (Böderek et al., 1995; Wieberneit and Wegner, 1995; Fontanesi et al., 2014b). We first excluded the endothelin receptor B (*EDNRB*) gene as a potential candidate gene for this locus (Fontanesi et al., 2010c). Then, Fontanesi et al. (2014b) showed that an SNP (g.93948587T>C) in the v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (*KIT*) gene cosegregated with the coat colour phenotype in a large Checkered Giant family, indicating that this gene, already shown to affect spotted phenotypes in other livestock species, is the causative gene of the *English spotting* locus in rabbit. The *En/En* rabbit model showed neuro-Interstitial Cells of Cajal (ICC) changes reminiscent of the human non-aganglionic megacolon. This rabbit model may provide a better understanding of the molecular abnormalities underlying conditions associated with non-aganglionic megacolon.

Common rabbit fur is usually constituted by 3 types of hair differing in length and diameter (guard hair: 3–4 cm long for a diameter of 50–60 µm; awn hair: 3–3.5 cm/25–30 µm; down hair: 2.5–3 cm/15 µm) while that of rex rabbits is essentially made up of soft and short down-hair (Diribarne et al., 2011). Rex short hair coat phenotypes in rabbits were shown to be controlled by three distinct loci: *Rex 1* (with the recessive causative allele indicated as r^1), *Rex 2* (r^2) and *Rex 3* (r^3; Robinson, 1958). Diribarne et al. (2011) identified the causative mutation (r^1 allele) of the *Rex 1* locus through a positional candidate gene approach. This mutation is due to a frameshift polymorphism determined by one bp deletion in exon 9 of the lipase member H (*LIPH*) gene mapped on rabbit chromosome 14. Polymorphisms in this gene are also associated with alopecia and hair loss phenotypes in humans.

Excessive long hair phenotypes occuring in several species, including the rabbit (*angora* locus) is caused by recessive alleles. Mutations in the fibroblast growth factor 5 (*FGF5*) gene were shown to affect this phenotype in mice and other species (e.g. Hebért et al., 1994). Using a candidate gene approach this gene was also investigated in angora and non-angora rabbitsshowing that one in-frame insertion was in almost complete linkage disequilibrium with the putative *angora* allele (Mulsant et al., 2004). However, it could be also possible that different mutations in this gene cause the angora phenotype (Mulsant et al., 1994). These results were indirectly confirmed in an F2 rabbit population in which the *angora* locus was mapped on chromosome 15 in a region encompassing the rabbit*FGF5* gene (Chantry-Darmon et al., 2006).

A locus that could be interesting for meat production is the *Yellow fat* (Robinson, 1958). Using a candidate gene approach, Strychalski et al. (2015) analysed the beta-carotene oxygenase 2 (*BCO2*) gene and identified a 3-bp deletion that might dermine the fat colour in rabbits. This gene encodes for an enzyme involved in the carotenoid metabolism. *BCO2* mutations in cattle and sheep causes the yellow-fat phenotype (Tian et al., 2010; Våge and Boman, 2012).

One of the first animal model for a very important trait has been described in rabbit as a monogenic trait. Watanabe heritable hyperlipidemic (WHHL) rabbit is an important animal model for familial hypercholesterolemia. This model is derived by a natural deletion of 4 amino acids in the low density lipoprotein receptor (*LDLR*) gene that affect the possibility for this receptor to be transported to the cell surface causing hypercholesterolemia (Yamamoto et al., 1988).

This list of monogenic traits affecting different traits that have been already characterized at the molecular level with the identification of causative genes and in most cases with the identification of the causative mutations will probably increase in the future. The combination of genome wide association studies and next generation sequencing will make it possible to quickly map and then identify relevant mutations of loci already described in the past or newly occurred mutations in rabbit populations used for many different purposes.

Table 2: Genes affecting monogenic phenotypes

Locus	Gene symbol	Gene name	Alleles	Mutations	References
Coat colour loci					
Extension	*MC1R*	melanocortin 1 receptor	E^+(wild type)	Two wild type alleles differing by two SNPs: c.[333A>G;555T>C]	Fontanesi et al. (2006, 2010b)
			E^D or E^S (dominant black or steel)	6 bp-in-frame deletion: c.280_285del6	
			e (red, non-extension of black)	30 bp-in frame deletion: c.304_333del30	
			e^J (Japanese brindling)	6 bp-in frame deletion flanked by a G>A transition in 5': c.[124G>A;125_130del6]	
Agouti	*ASIP*	agouti-signalling protein	*A* (light-bellied agouti; wild type)	Wild type allele	Fontanesi et al. (2010a)
			a (recessive black nonagouti)	c.5_6insA	
			a^t (black and tan)	p.L55M and p.L89P	
C(*albino*)	*TYR*	tyrosinase	*C* (fully coloured)	Wild type allele	Aigner et al. (2000)
			c^{Ch} (Chinchilla)	p.E294G and p.T358I	
			c^H (Himalayan albinism)	p.E294G	
			c (albino, total lack of pigments)	p.T373K	
Dilute	*MLPH*	melanophilin	*D* (wild type, intense black and red)	Several wild type alleles	Fontanesi et al. (2014a)
			d (dilution of blck to blue and red to yellow)	g.549853delG	
			d (dilution of blck to blue and red to	Two exon skippin mutation	Lehner et al. (2013)

			yellow)		
Brown	*TYRP1*	tyrosinase-related protein 1	*B* (wild type)	Several wild type alleles	Utzeri et al. (2014)
			b (brown)	p.Trp190ter	
English spotting	*KIT*	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	*en*(solid coloured, wild type, recessive)	Wild type sequences	Fontanesi et al. (2014b)
			En (English spotted; partially dominant)	g.93948587T>C (in complete linkage disequilibrium with the segregating alleles)	
Hair and coat structure loci					
Rex 1	*LIPH*	lipase member H	R^1(wild type allele)	Wild type sequence	Diribarne et al. (2011)
			r^1 (mutated allele)	1362delA (deletion in exon 9)	
Angora	*FGF5*	fibroblast growth factor 5	*L* (wild type allele)	Wild type sequence	Mulsant et al. (2004); Chantry-Darmon et al. (2006)
			l (mutated allele(s))	In frame insertion of 3 bp (exon 3); T>C SNP	
Other loci					
Yellow fat	*BCO2*	beta-carotene oxygenase 2	*Y* (white fat)	Wild type sequences	Strychalski et al. (2015)
			y (yellow fat)	A three-bp deletion in exon 6	
Watanabe heritable hyperlipidemia	*LDLR*	low density lipoprotein receptor	Two alleles in the Watanabe population	In-frame deletion of 12 bp (mutated allele)	Yamamoto et al. (1986)

GENOMIC SELECTION IN RABBITS?

Breeding and crossbreeding strategies based on quantitative genetics approaches have largely driven genetic progress in meat rabbit lines during the last decades. Even if the application of BLUP Animal Models has not been fully implemented for the evaluation of bucks and does in selected nuclei in all lines, it is clear that the new developments derived by the implementation of genomic selection, that is becoming a routine in other species, are attracting rabbit breeders.

Genomic selection can be considered an enhanced version of marker or gene assisted selection (Dekkers and Hospital, 2002). In rabbits, as far as I know, marker assisted selection has not been implemented in its classical version due to the paucity of studies that identified useful markers for this purpose and the practical difficulties and limits of this approach. Genomic selection was proposed to predict the genetic value of the animals based on the genotype at thousands of single nucleotide polymorphisms (SNPs) covering the whole genome, overcoming the limits of marker assisted selection plans (Meuwissen et al., 2001). When the concept of genomic selection was first defined, technologies and information needed to develop this idea were not available yet. Three main subsequent advances have made it possible to implement genomic selection in the most relevant livestock species, starting from dairy cattle: i) the sequencing of their genome and the identification of thousands or even millions of polymorphisms (mainly SNPs); ii) the development of high throughput genotyping technologies that can genotype

thousands of SNPs spread all over the genome in a cost-effective manner; iii) the development of statistical methods to estimate the allelic effects of thousands of markers in a data sets of limited number of animals (Samorè and Fontanesi, 2016).

What is the situation in rabbit about these issues needed to start thinking about any application of genomic selection in this species?
i) The rabbit genome has been sequenced and millions of polymorphisms have been already identified (e.g. Bertolini et al., 2014; Carneiro et al., 2014); ii) the international rabbit genomic research community, under the umbrella of the European funded COST Action TD1101 "A Collaborative European Network on Rabbit Genome Biology – RGB-Net" has just developed a commercial SNP genotyping panel in collaboration with Affymetrix; iii) statistical methods can be derived from what has been developed in other species and, in particular, all strategies that are developed in pigs could be adapted also in rabbit, considering similar selection problems and strategies between the two species.

Genomic selection is based on the prediction of the breeding value (the genomic breeding value or GEBV) of each individual by summing up all SNP allele effects over the whole genome. Marker effects are estimated as a regression of the phenotype on the genotype in training data sets, i.e. the animals in the population with both phenotypic and genotypic (or genomic) information, and these estimates are used to predict GEBV for all individuals with genomic data without any phenotypic information (prediction population). Therefore, these animals are selected based on their genotype at thousands of SNPs, covering the whole genome, without the need of recording phenotype information on all animals under evaluation (Samorè and Fontanesi, 2016). Depending on prior distributions considered in SNP effects estimation, different procedures based on this strategy (i.e. training and prediction populations) were proposed by several authors (Meuwissen et al., 2001; VanRaden, 2008; Yi and Yu, 2008; Gianola et al., 2009; Calus, 2009; Habier et al., 2011; reviewed in Samorè and Fontanesi, 2016). A modified approach, known as single step method, incorporates marker information into the traditional pedigree models accounting also for all phenotypic and pedigree information available, including pedigree and performance records collected from non-genotyped individuals (Legarra et al., 2009; Mistzal et al., 2009; Aguilar et al., 2010).

The introduction of genomic selection is expected to increase the genetic progress (ΔG), according to the classical concepts of quantitative genetics (Falconer, 1989), following the general formula:
$\Delta G = (i * r * \sigma_g) / L$
where i is the selection intensity, r is the accuracy, σ_g is the genetic variability and L is the generation interval.The two terms that would be directly affected by the introduction of genomic selection are the generation interval (L) and the accuracy (r) of the predictions. In rabbits, it seems that the benefits might come only from an increased accuracy of genetic predictions and for the possibility to predict maternal traits in bucks as also already proposed in pigs (Samorè and Fontanesi, 2016). However, these advantages should be balanced by intrinsic limits of the rabbit breeding systems derived by i) the high cost of genotyping, compared to the individual animal value, ii) the peculiarities of rabbit selection schemes, based on pyramidal population structures with selection mainly on pure lines, but the final performances are expressed on crossbred animals, iii) the short time available for the genetic evaluation, and iv) the overall implementation of the logistics aspects, including storage of DNA or other biological materials from the animals, computation power, storage and handling data and personnel training (Samorè and Fontanesi, 2016). On the other hand, it could be possible to use genomic selection approaches in combination with high phenotyping strategies in nuclei in which important parameters or predictors of new phenotypes (i.e. disease resistance) might be included. Therefore, specific application of genomic selection programs in rabbit breeding can be envisaged in particular situations when it is possible to manage these limits and when the economic balance is positive, considering the possibility to select for "difficult" traits.

CONCLUSIONS

What we have presented here is a very promising and still (in large parts) unexplored scenario in which genomics is changing the way the rabbit is studies to take advantage from the discovery and then from the use of natural and valuable variability that is present within and between many rabbit breeds, lines or populations. The refinement of the complete sequence of the rabbit genome is a prerequisite for more advanced investigations that might include detailed functional annotations. The nascent international effort of the Functional Annotation of Animal Genomes project (FAANG; Andersson et al., 2015) could help to improve the annotation of the rabbit genome for subsequent

more detailed and precise applications that might include gene editing of important defined genes to create new animal models or new lines for other purposes. However, the production of many genomic information not only in rabbit but also in all other livestock species should be combined with a parallel improvement in the strategy of phenotyping to overcome the phenotype gap that is one of the main bottle-neck in the genomic era to make sense from nucleotide data.

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The rabbit in the genomics era: applications and perspectives in rabbit biology and breeding

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The University of Bologna's Partnerships around the world

CHINA

The University of Bologna hosts one of Italy's most active branches of the Confucius Institute, and was recognised as the best of 2012.
Local relations of the more than 800 Chinese students at Bologna are supported by the "Collegio di Cina" Association.

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Avvisi

Bando assegno di ricerca prot. 389 - scad. presentazione domande 23/03/2015 ore 12:00 a Bologna- tutor Prof. Luca Fontanesi
Pubblicato il 10 marzo 2015

Bando assegno di ricerca prot. 326 - scad. presentazione domande 16/03/2015 ore 12:00- tutor Prof. Marco Dalla Rosa
Pubblicato il 26 febbraio 2015

Proposta di scambio contestuale di docenti tra due sedi Universitarie
Pubblicato il 2 dicembre 2014

Vedi tutto

Eventi

20 aprile 2015
Climate Change and Coastal adaptation day

venerdì 20 marzo 20

The rabbit in the genomics era: applications and perspectives in rabbit biology and breeding

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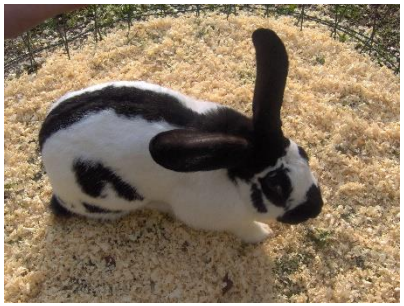
Rabbit is a key species

- Livestock resource
  - Meat, fur, pet, fancy breeds
  - European meat market: 1.6 billion €



- Animal model and bioreactor
  - Model of prolific livestock species (pig)
  - Basic biology
  - Human diseases
  - Biotechnology applications
  - World antibodies production: 3-5 billion €

- Wild resource
  - Ecology, game species, pest
  - Related species (wild lagomorphs)

What is genomics?

Study of genomes

In 1986 mouse geneticist Thomas Roderick used Genomics for “mapping, sequencing and characterizing genomes”

What is a genome?

Entire genetic content / information of an organism

…ACGTGTGCGTGAAAGGG…

CTCGCGTCTGGGCGGGGGTCGGAAGGGGCAATTCTTTCTGGCTTTTCTACCTTGCTTCTTGTCCCCCCTC
TCCTTTCCAATTGTATGCGGGCGAGTGTGAGAGCCATGGAGCGAAGAGCCTGGACTCTGCAGTGTACTGC
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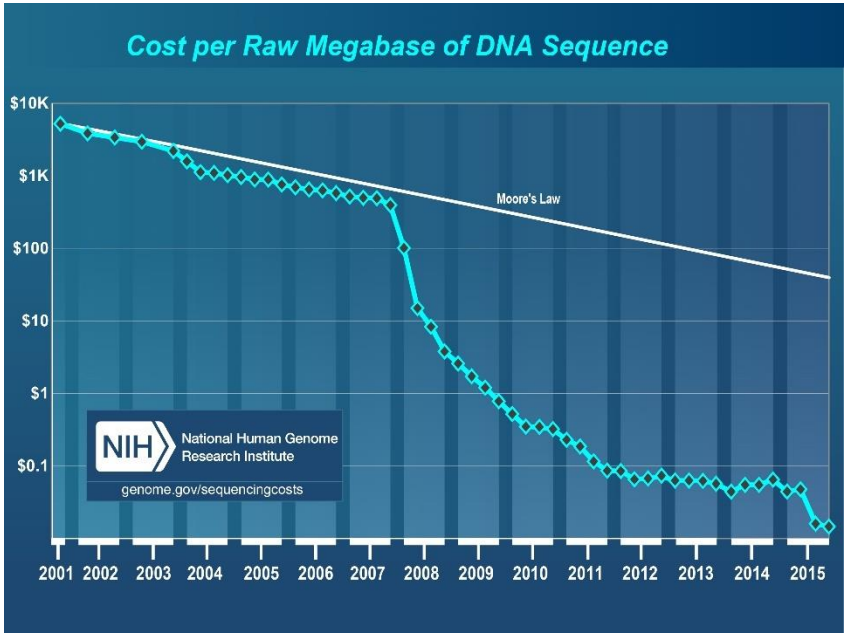
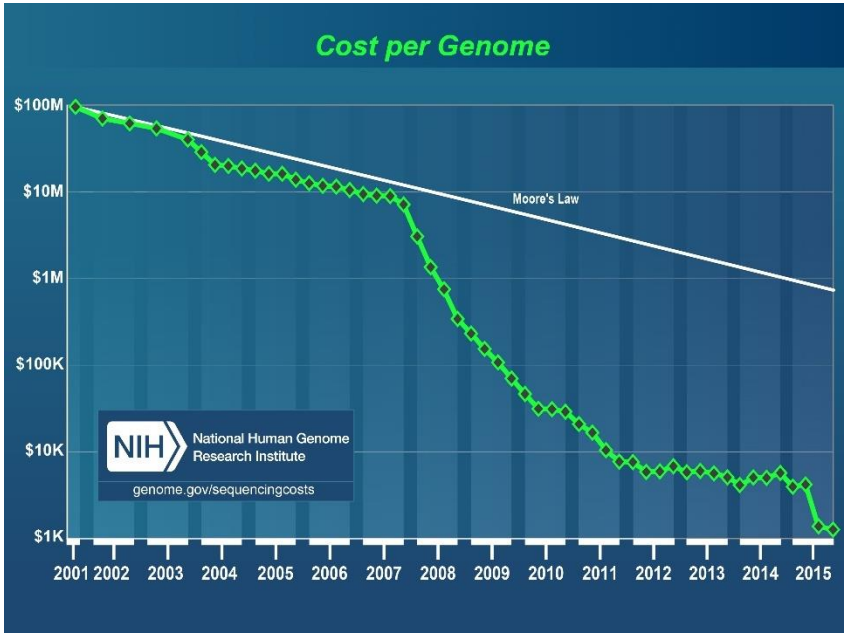
~3 billions





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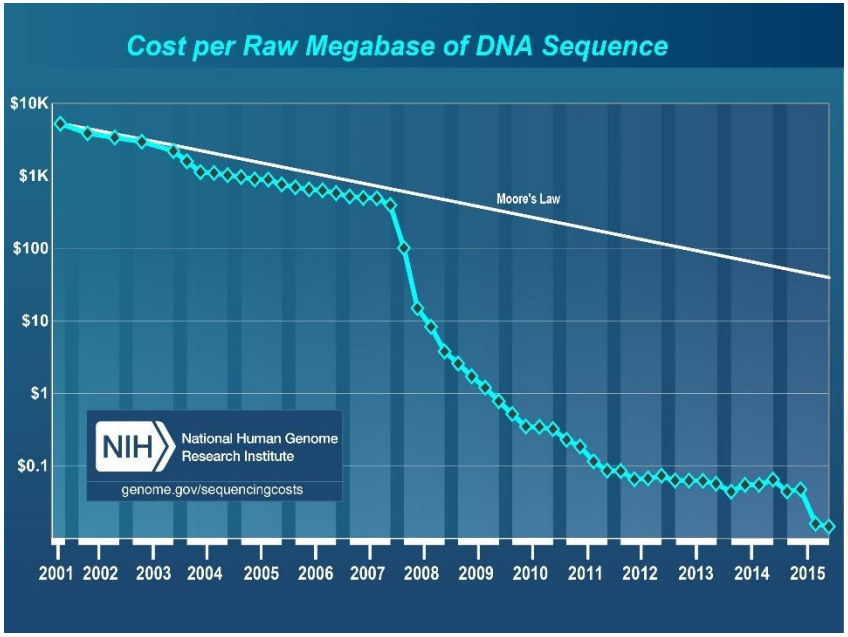

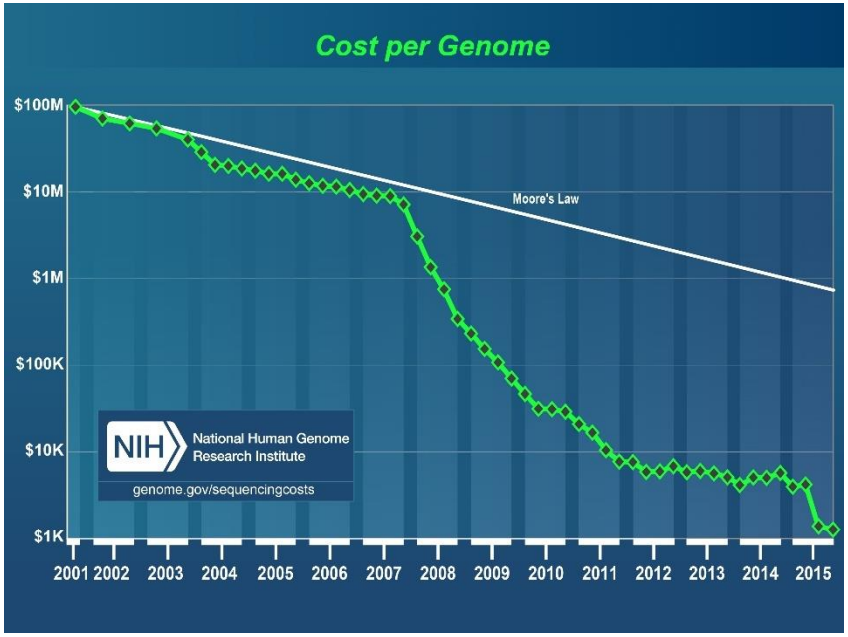

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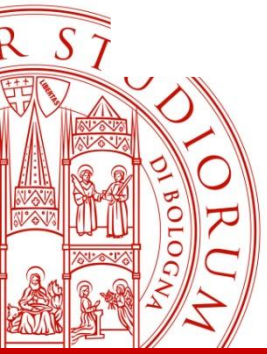

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PERSPECTIVE

Big Data: Astronomical or Genomical?

Zachary D. Stephens[1], Skylar Y. Lee[1], Faraz Faghri[2], Roy H. Campbell[2], Chengxiang Zhai[3], Miles J. Efron[4], Ravishankar Iyer[1], Michael C. Schatz[5]*, Saurabh Sinha[3]*, Gene E. Robinson[6]*

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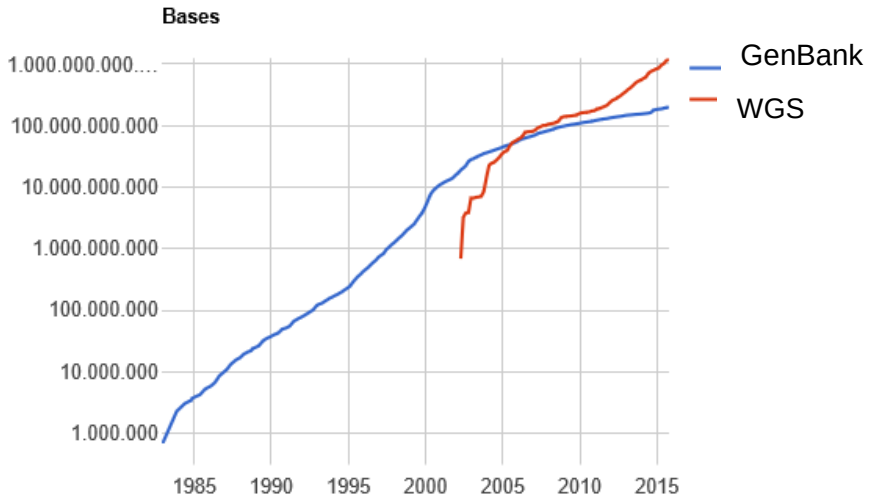
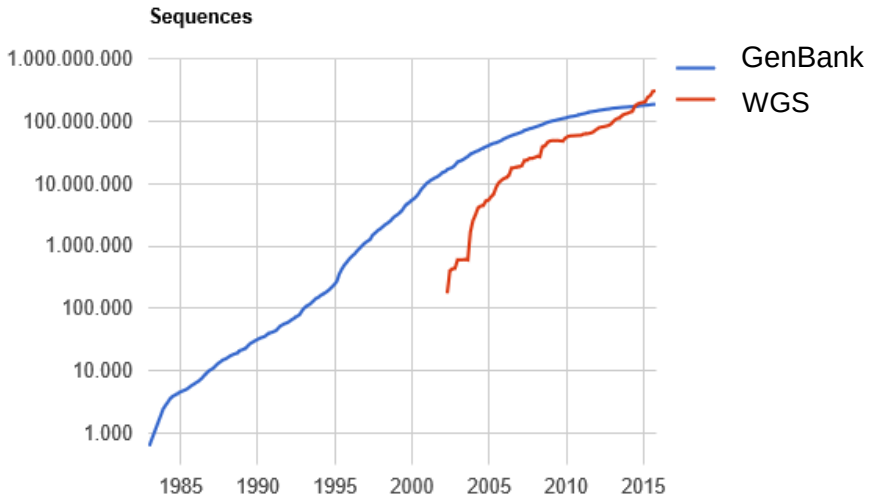
Growth of GenBank and Whole Genome Shotgun (WGS)



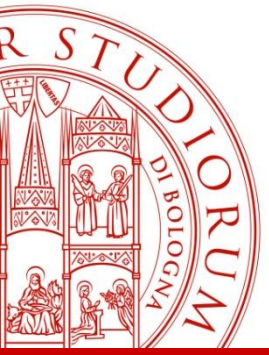


Genomic data

Zachary et al. 2015

Data Phase	Astronomy	Twitter	YouTube	Genomics
Acquisition	25 zetta-bytes/year	0.5–15 billion tweets/year	500–900 million hours/year	1 zetta-bases/year
Storage	1 EB/year	1–17 PB/year	1–2 EB/year	2–40 EB/year
Analysis	In situ data reduction	Topic and sentiment mining	Limited requirements	Heterogeneous data and analysis
	Real-time processing	Metadata analysis		Variant calling, ~2 trillion central processing unit (CPU) hours
	Massive volumes			All-pairs genome alignments, ~10,000 trillion CPU hours
Distribution	Dedicated lines from antennae to server (600 TB/s)	Small units of distribution	Major component of modern user's bandwidth (10 MB/s)	Many small (10 MB/s) and fewer massive (10 TB/s) data movement

doi:10.1371/journal.pbio.1002195.t001



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doi:10.1371/journal.pbio.1002195.t001

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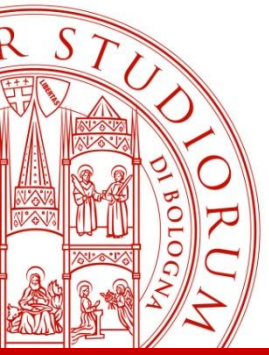
Exabyte (1 000 000 000 000 000 000 bytes)
Zettabyte (1 000 000 000 000 000 000 000 bytes)

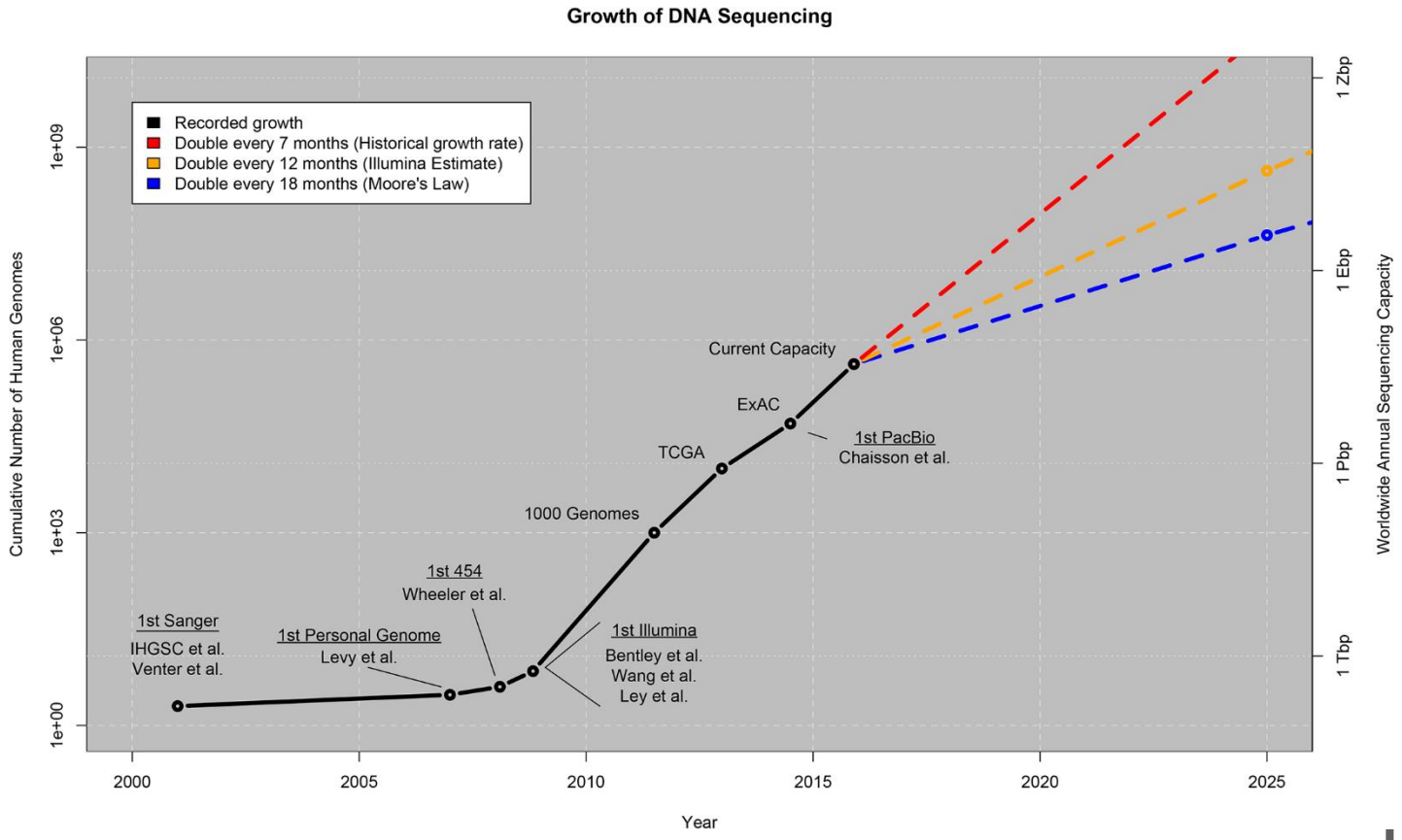


Genomic data

Zachary et al. 2015

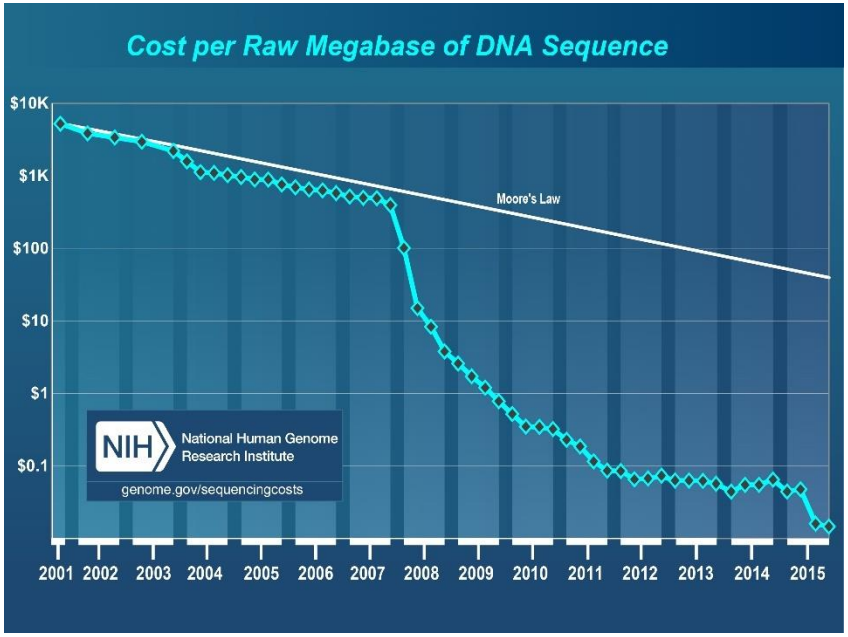
Data Phase	Astronomy	Twitter	YouTube	Genomics
Acquisition	25 zetta-bytes/year	0.5–15 billion tweets/year	500–900 million hours/year	1 zetta-bases/year
Storage	1 EB/year	1–17 PB/year	1–2 EB/year	2–40 EB/year
Analysis	In situ data reduction	Topic and sentiment mining	Limited requirements	Heterogeneous data and analysis
	Real-time processing	Metadata analysis		Variant calling, ~2 trillion central processing unit (CPU) hours
	Massive volumes			All-pairs genome alignments, ~10,000 trillion CPU hours
Distribution	Dedicated lines from antennae to server (600 TB/s)	Small units of distribution	Major component of modern user's bandwidth (10 MB/s)	Many small (10 MB/s) and fewer massive (10 TB/s) data movement

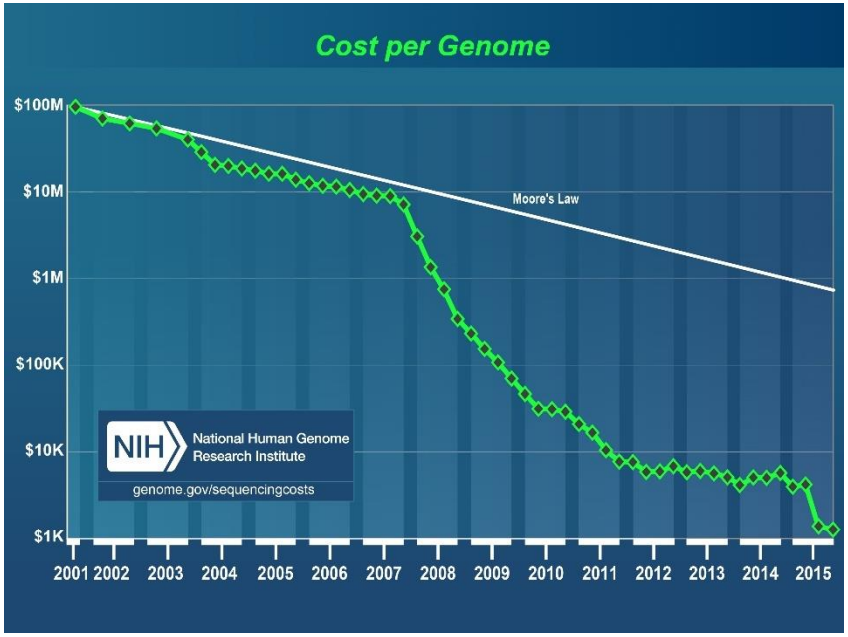
doi:10.1371/journal.pbio.1002195.t001



It is clear that livestock species are contributing to this explosion of data

…. but the rabbit will probably arrive later





Roche 454

Illumina

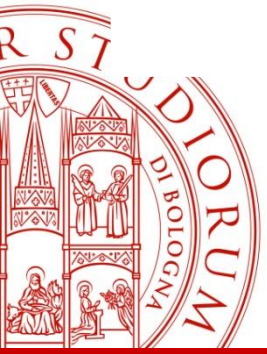
Solid

Ion Torrent

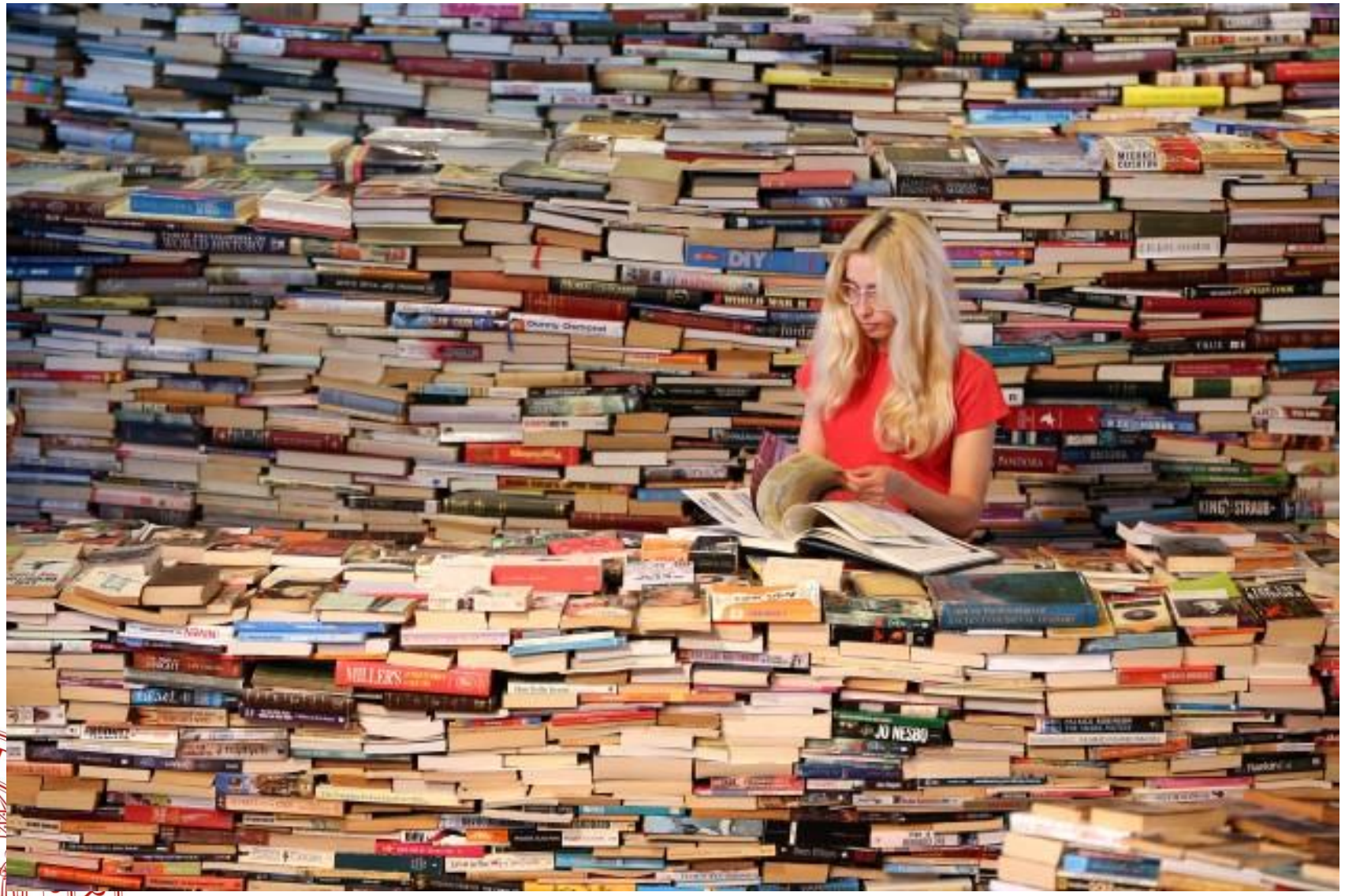
Ion Proton

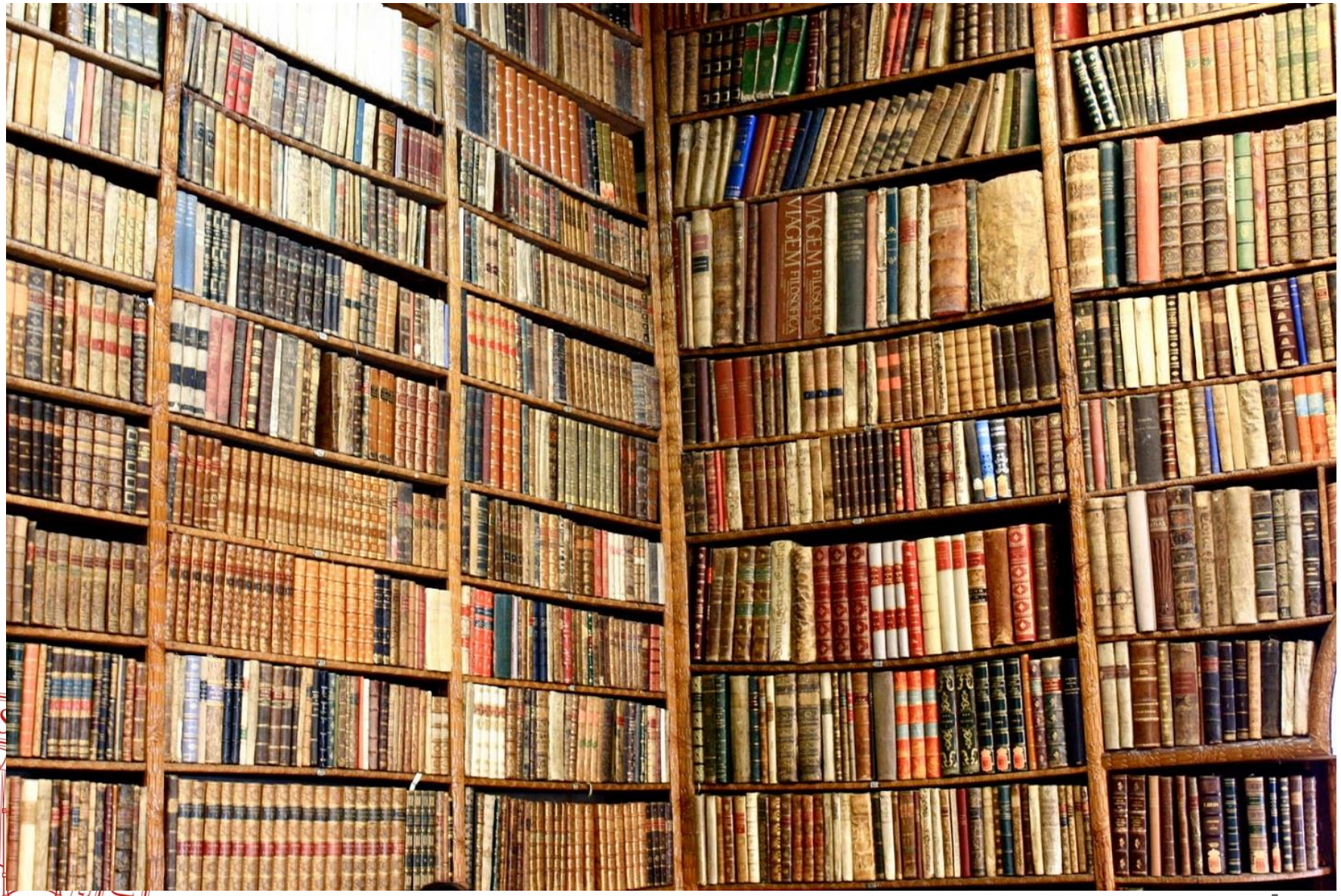
PacBio

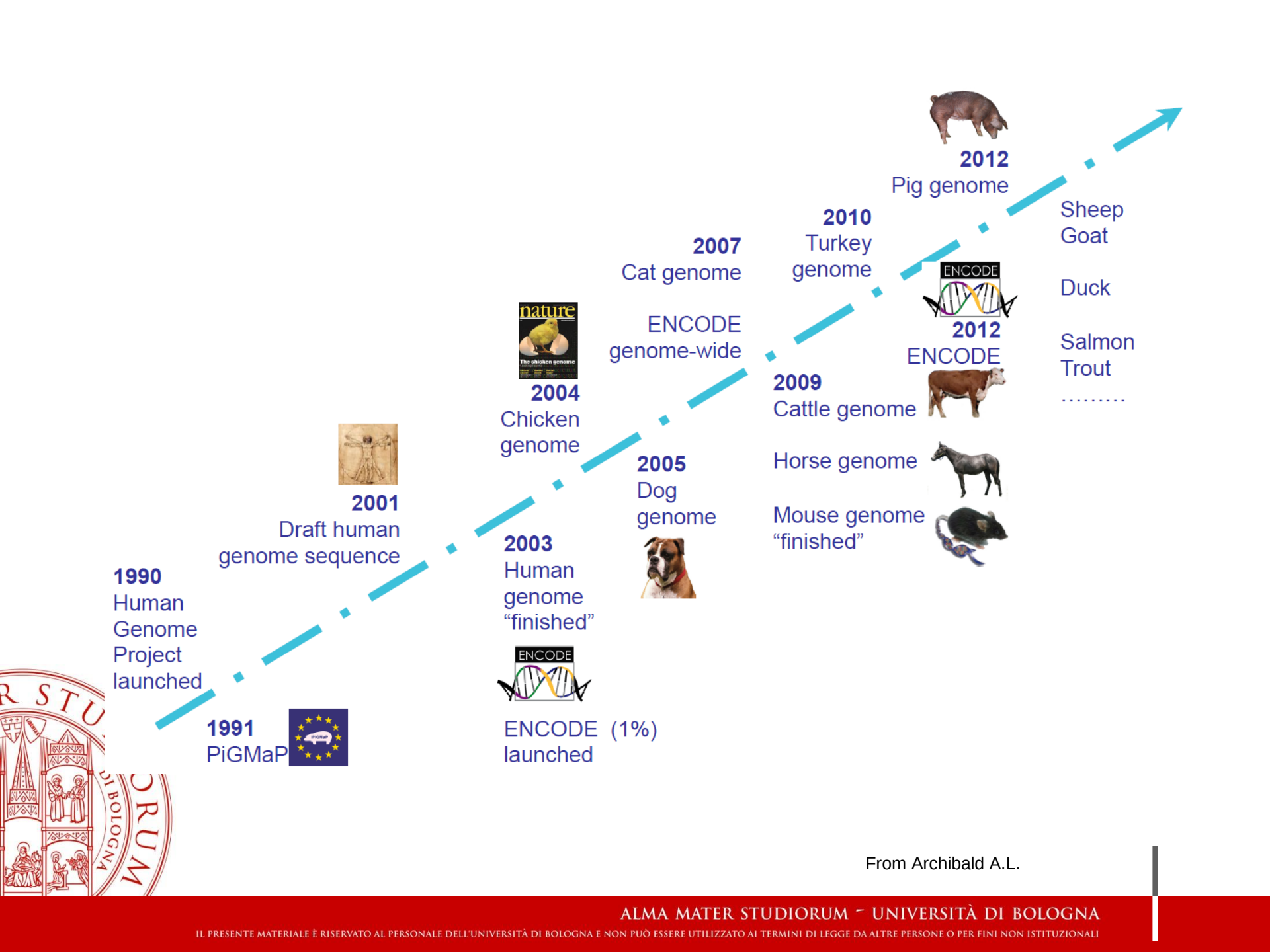
Nanopore MinIon



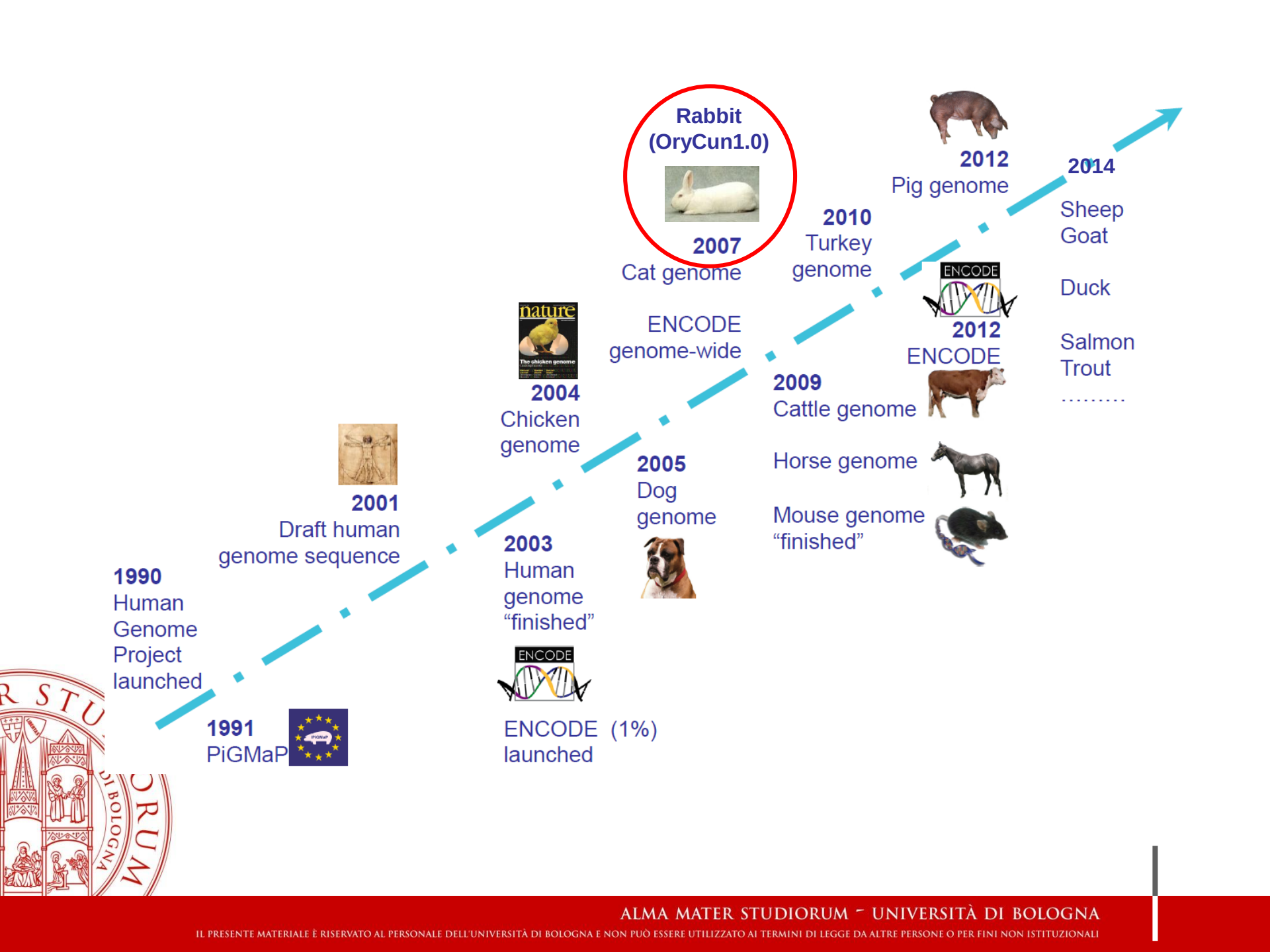
Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP) Available at: www.genome.gov/sequencingcostsdata. Accessed [1st of June 2016].







From Archibald A.L.



1990
Human Genome Project launched

1991
PiGMaP

2001
Draft human genome sequence

2003
Human genome "finished"

2004
Chicken genome

ENCODE (1%) launched

2005
Dog genome

2007
Cat genome

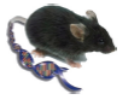
ENCODE genome-wide

Rabbit (OryCun1.0)

2009
Cattle genome

Horse genome

Mouse genome "finished"



2010
Turkey genome

2012
Pig genome

2012
ENCODE

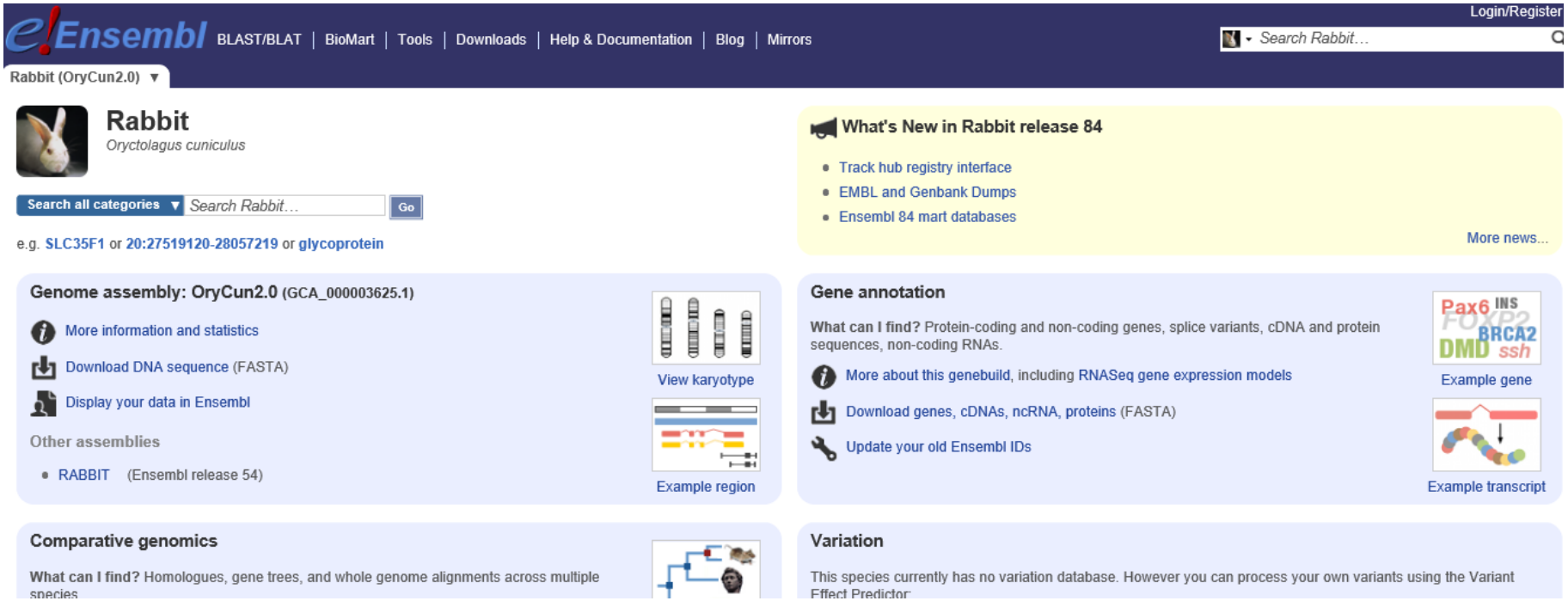
Rabbit (OryCun2.0)

2014

Sheep
Goat

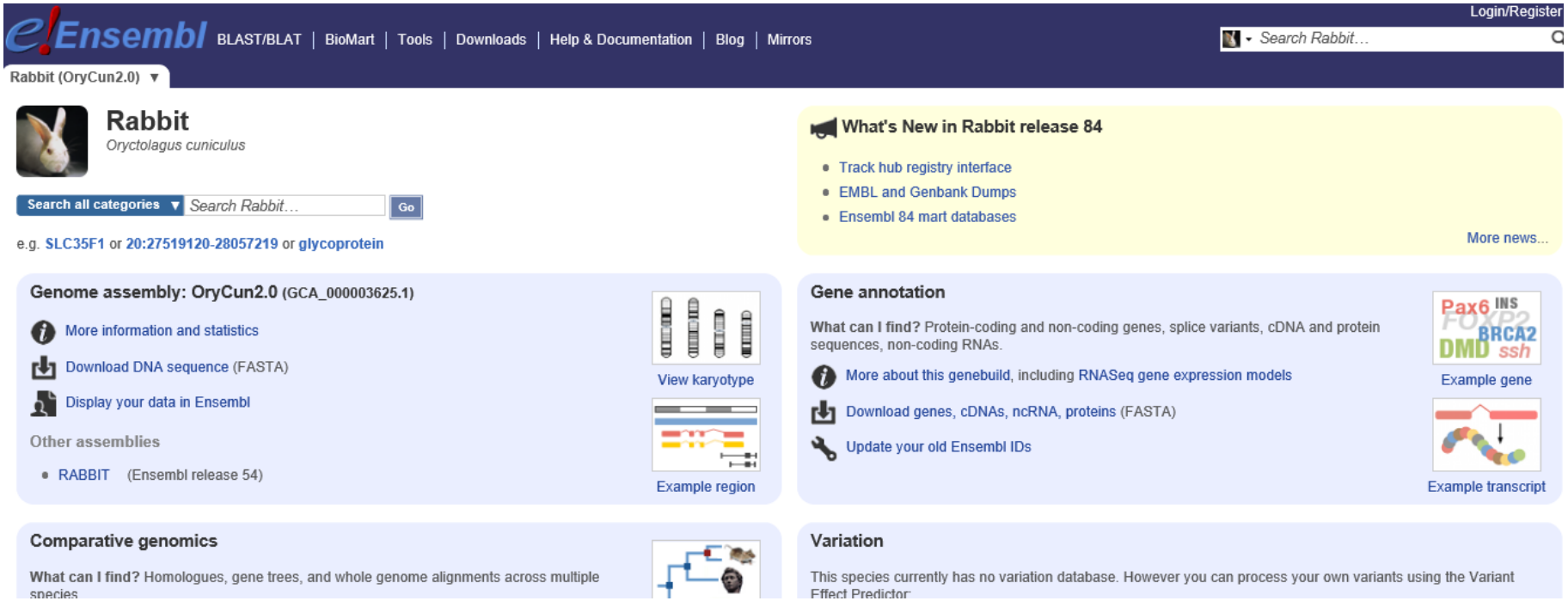
Duck

Salmon
Trout
.....

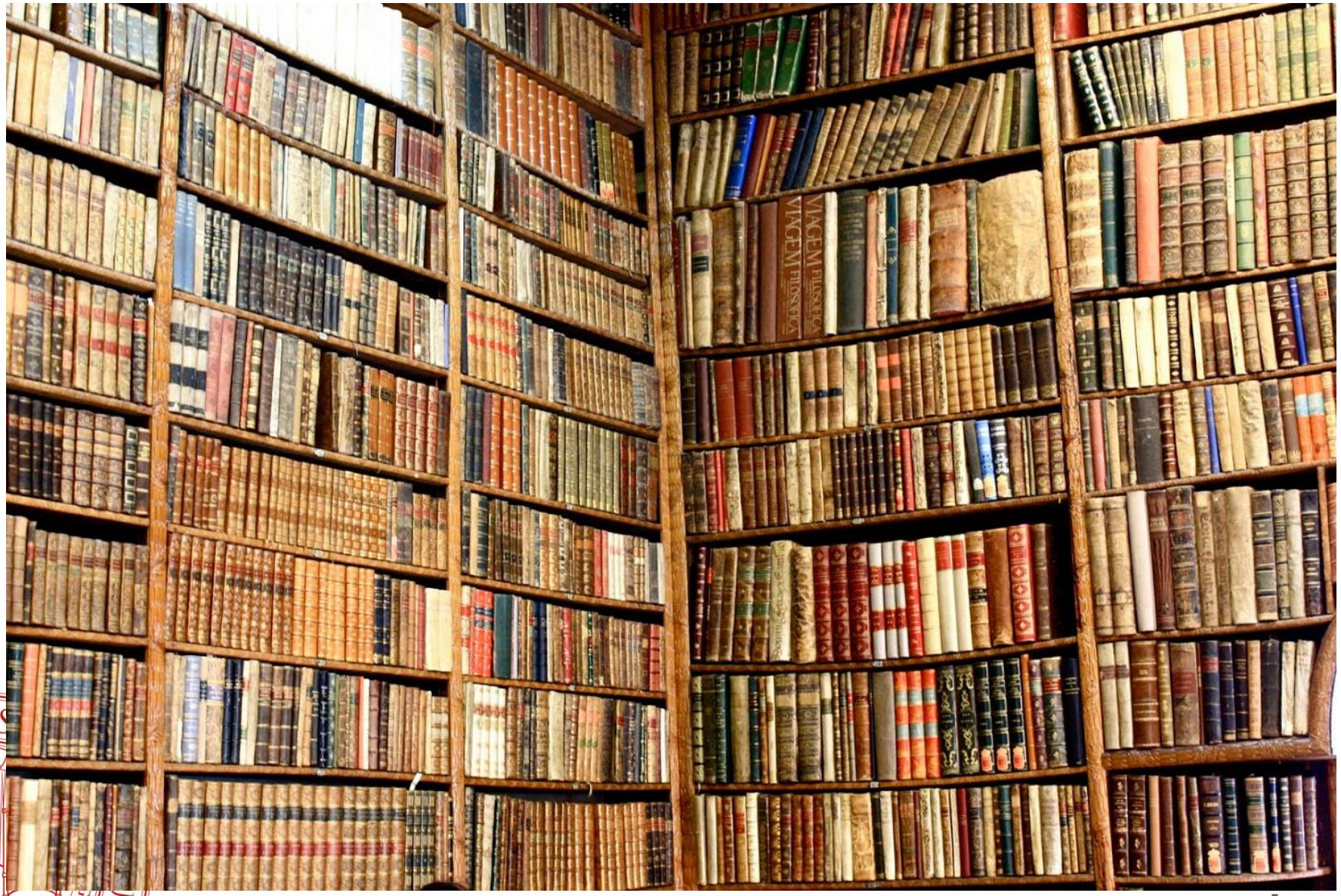


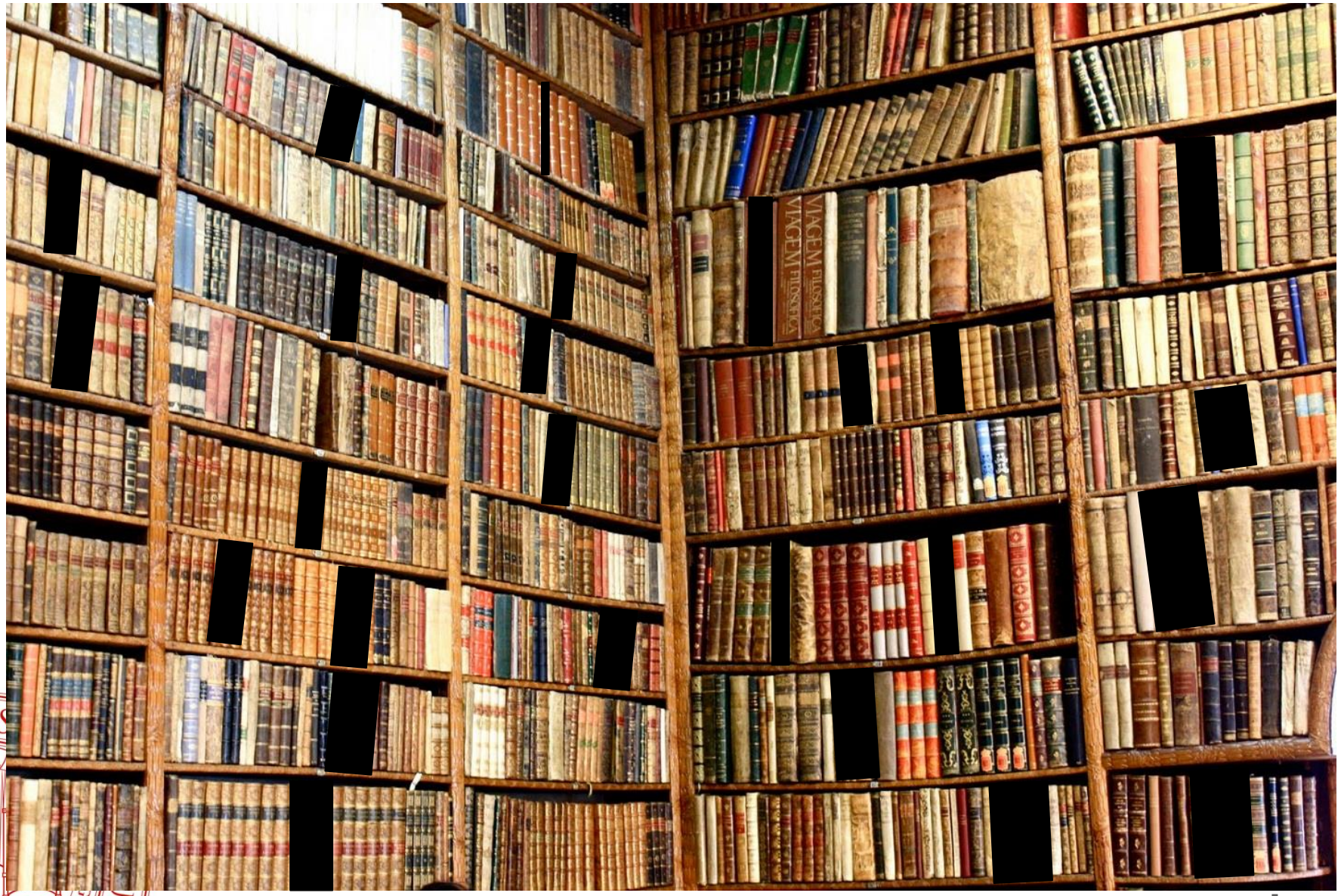
The total numbers of nucleotides in supercontigs and contigs in OryCun2.0 are 2.66 Gbp and 2.60 Gbp, respectively

The annotation process of the OryCun2.0 genome version identified 19,203 coding genes, 3,375 non-coding genes, 1001 pseudogenes and a total of 24,964 gene transcripts.

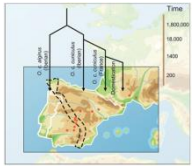


This genome version includes about 2.74 Gbp, 82% has been anchored to chromosomes.
N50 is the length such that 50% of the assembled genome lies in blocks of the N50 size or longer.
The OryCun2.0 N50 length for supercontigs is 35348.54 kb. The **N50** size for contigs is 64.65 kb.





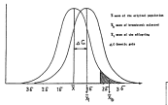
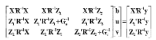
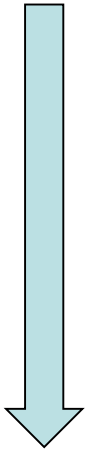
Evolutionary history of the domestic rabbit










Time line

Domestication
VII century

XX century
Modern Fancy breeds

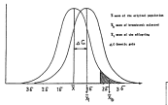
1970
Application of quantitative genetics theory

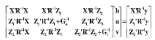
1990
BLUP Animal Model

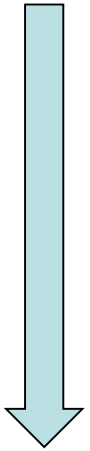
2007
OryCun1.0

2016
Genomic tools

Evolutionary history of the domestic rabbit







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2016

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tools

EVOLUTIONARY GENOMICS

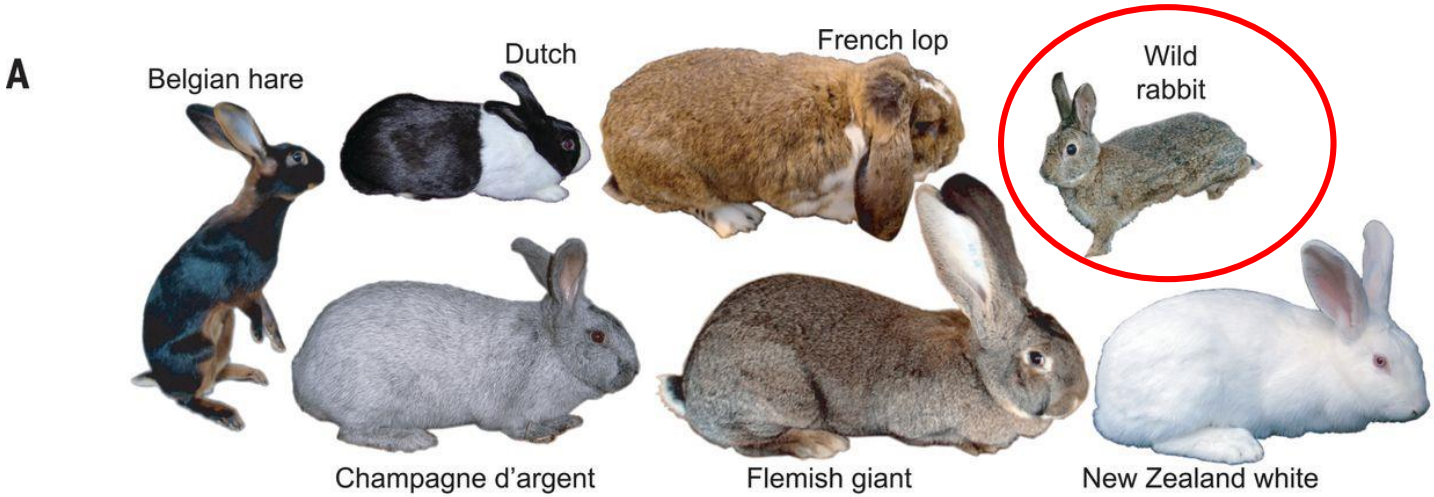
Rabbit genome analysis reveals a polygenic basis for phenotypic change during domestication

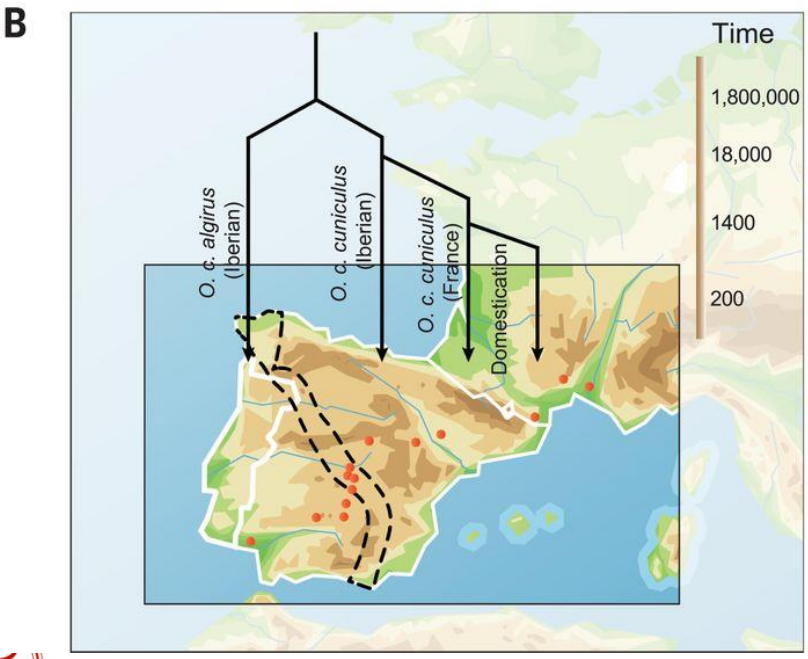
Miguel Carneiro,[1*] Carl-Johan Rubin,[2*] Federica Di Palma,[3,4*] Frank W. Albert,[5†] Jessica Alföldi,[3] Alvaro Martinez Barrio,[2] Gerli Pielberg,[2] Nima Rafati,[2] Shumaila Sayyab,[6] Jason Turner-Maier,[3] Shady Younis,[2,7] Sandra Afonso,[1] Bronwen Aken,[8,9] Joel M. Alves,[1,10] Daniel Barrell,[8,9] Gerard Bolet,[11] Samuel Boucher,[12] Hernán A. Burbano,[5‡] Rita Campos,[1] Jean L. Chang,[3] Veronique Duranthon,[13] Luca Fontanesi,[14] Hervé Garreau,[11] David Heiman,[3] Jeremy Johnson,[3] Rose G. Mage,[15] Ze Peng,[16] Guillaume Queney,[17] Claire Rogel-Gaillard,[18] Magali Ruffier,[8,9] Steve Searle,[8] Rafael Villafuerte,[19] Anqi Xiong,[20] Sarah Young,[3] Karin Forsberg-Nilsson,[20] Jeffrey M. Good,[5,21] Eric S. Lander,[3] Nuno Ferrand,[1,22*] Kerstin Lindblad-Toh,[2,3*§] Leif Andersson[2,6,23*§]

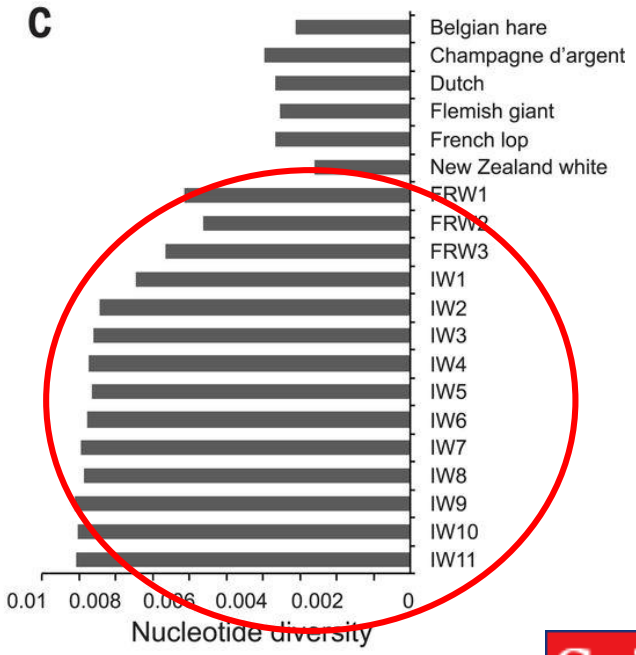
Science
AAAS

Rabbit genome analysis reveals a polygenic basis for phenotypic change during domestication
Miguel Carneiro *et al.*
Science **345**, 1074 (2014);
DOI: 10.1126/science.1253714

GB-Net



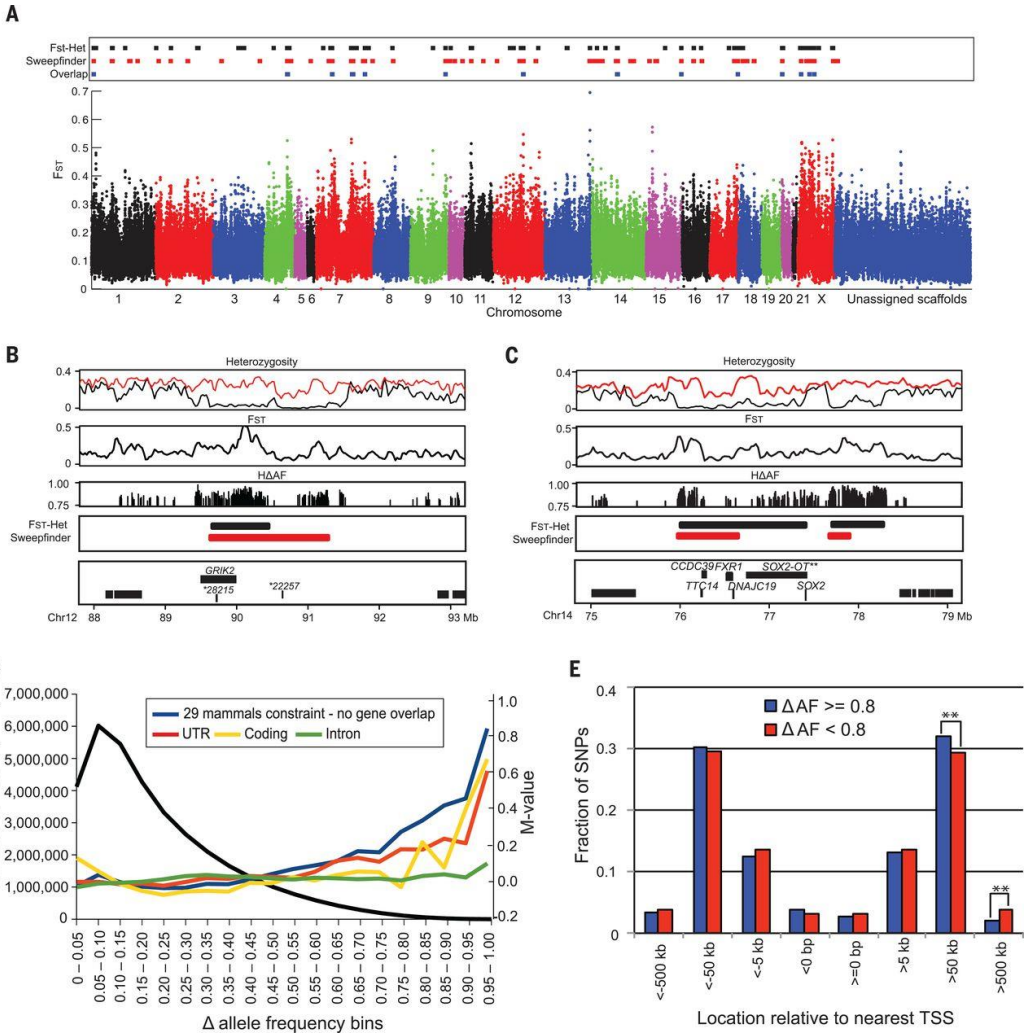




Carneiro et al. Science 2014;345:1074-1079

Science
AAAS

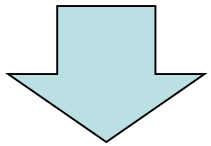
Selective sweep and Δ allele frequency analyses
(A) Plot of FST values between wild and domestic rabbits.



Carneiro et al. Science 2014;345:1074-1079

Take home message

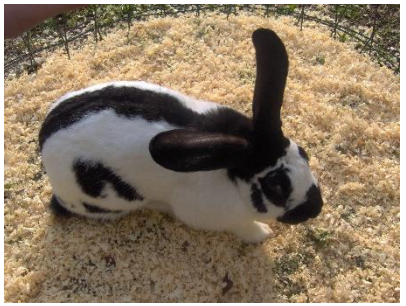
Domestication in rabbit has been a soft domestication process



based on shifts in allele frequencies at many loci affecting behavior

Rabbit is a key species

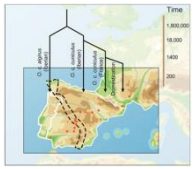
- Livestock resource
  - Meat, fur, pet, fancy breeds
  - European meat market: 1.6 billion €



- Animal model and bioreactor
  - Model of prolific livestock species (pig)
  - Basic biology
  - Human diseases
  - Biotechnology applications
  - World antibodies production: 3-5 billion €

- Wild resource
  - Ecology, game species, pest
  - Related species (wild lagomorphs)

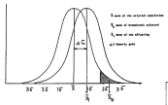
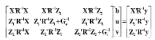
Evolutionary history of the domestic rabbit










Time line

Domestication

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1970

Application of quantitative genetics theory

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BLUP Animal Model

2007

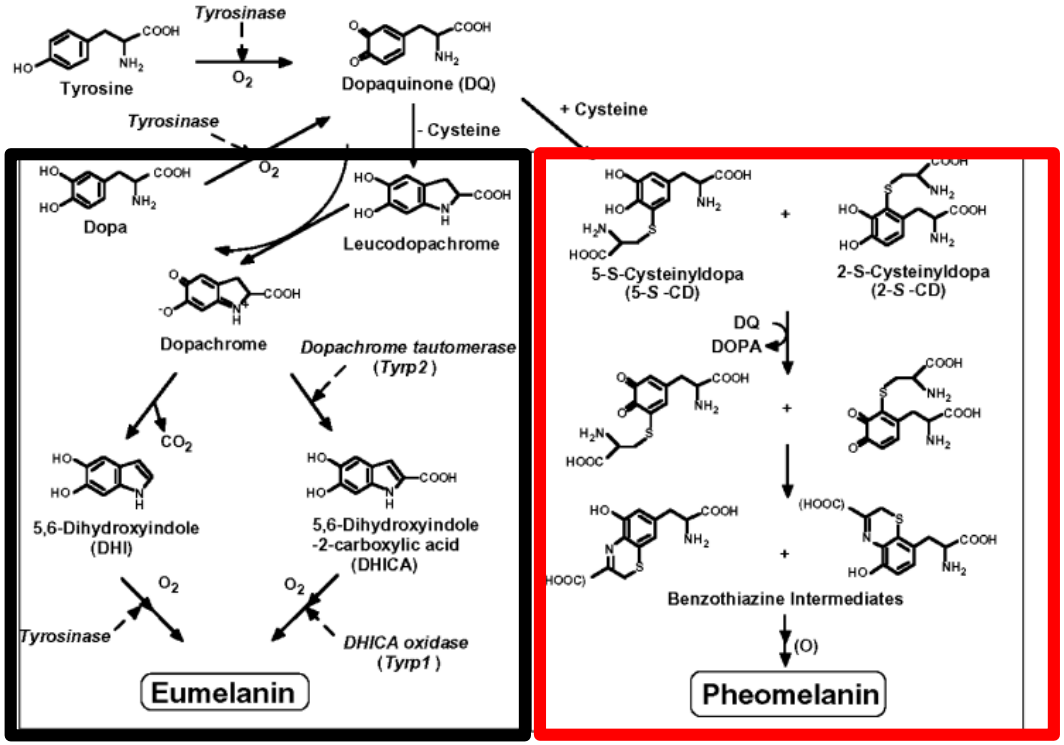
OryCun1.0

2016

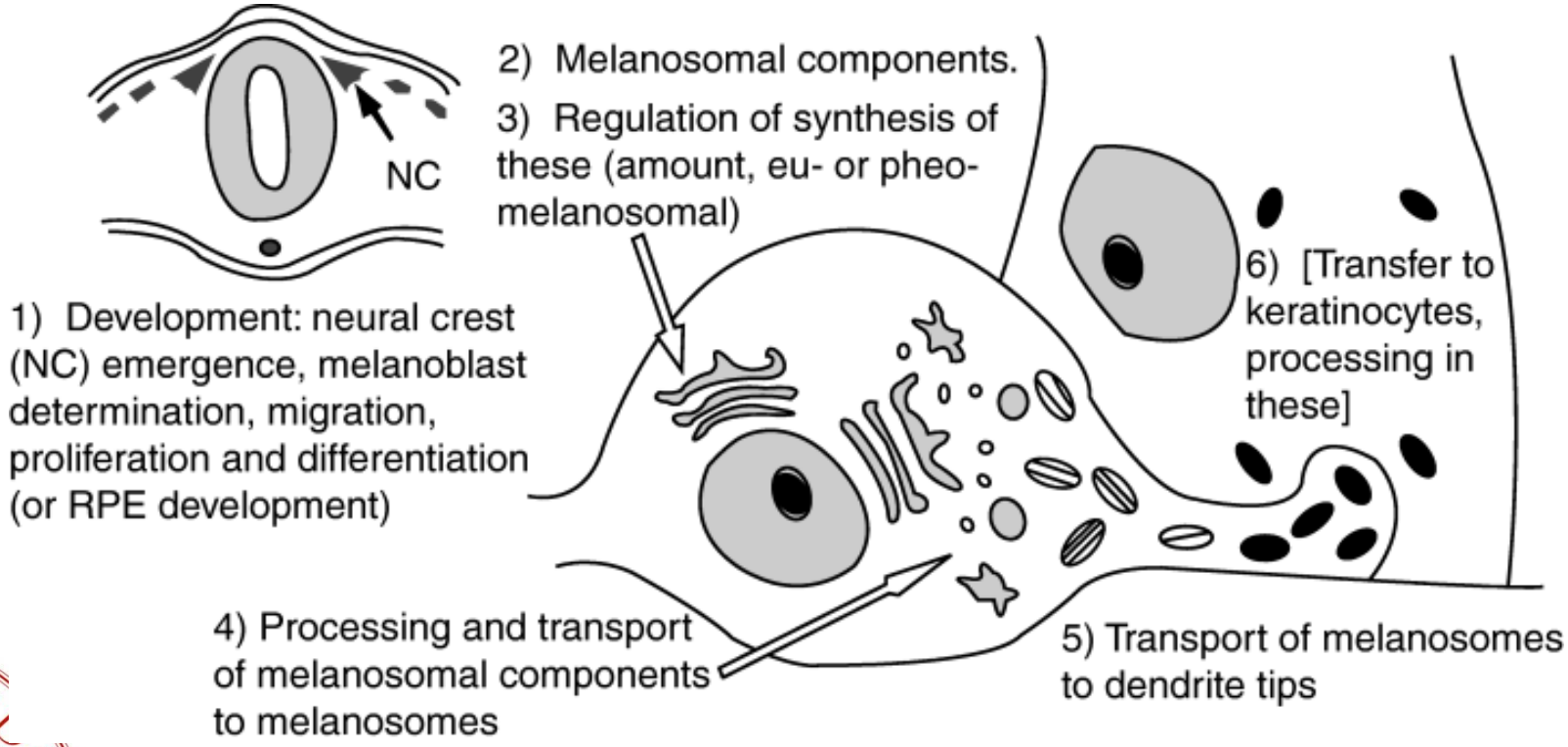
Genomic tools

Pigmentation in mammals is mainly determined by the distribution of distinct melanin pigments:

1) pheomelanin (red/yellow)
2) eumelanin (dark/black)



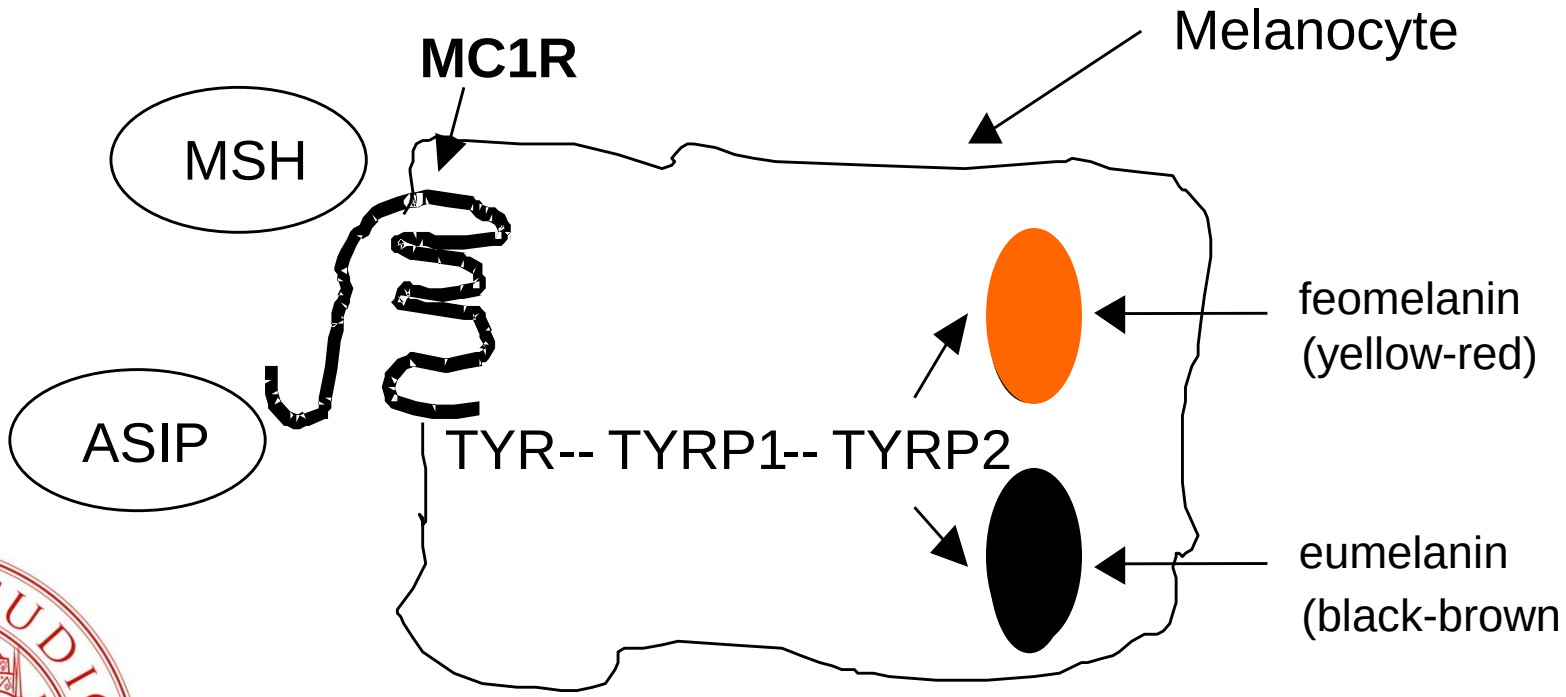
Main processes affected by colour genes



Classical genetic studies carried out just after the rediscovery of Mendel's laws defined several coat colour loci in rabbits

Extension
Agouti
Dilute
Brown
English spotting
…..

The ***Extension*** locus codes for the **Melanocortin receptor 1 (MC1R)**
The ***Agouti*** locus codes for the **Agouti Signaling Protein (ASIP)**



Alleles at the *Extension* locus

Locus	Alleles	
Extension	E^D	(Dominant black)
	E^S	(Steel)
	E	(Normal extension)
	e^J	(Japanese brindling)
	e	(Non-extension of black)

SHORT COMMUNICATION

doi:10.1111/j.1365-2052.2006.01494.x

Mutations in the *melanocortin 1 receptor* (*MC1R*) gene are associated with coat colours in the domestic rabbit (*Oryctolagus cuniculus*)

L. Fontanesi, M. Tazzoli, F. Beretti and V. Russo

DIPROVAL, Sezione di Allevamenti Zootecnici, Faculty of Agriculture, University of Bologna, Via F.lli Rosselli 107, Villa Levi – Coviolo, 42100 Reggio Emilia, Italy

Fontanesi *et al. BMC Genetics* 2010, **11**:59
http://www.biomedcentral.com/1471-2156/11/59

BMC Genetics

RESEARCH ARTICLE Open Access

A composite six bp in-frame deletion in the melanocortin 1 receptor (*MC1R*) gene is associated with the Japanese brindling coat colour in rabbits (*Oryctolagus cuniculus*)

Luca Fontanesi[1*], Emilio Scotti[1], Michela Colombo[1], Francesca Beretti[1], Lionel Forestier[2], Stefania Dall'Olio[1], Séverine Deretz[3], Vincenzo Russo[1], Daniel Allain[4], Ahmad Oulmouden[2]

Rabbit *MC1R* sequence

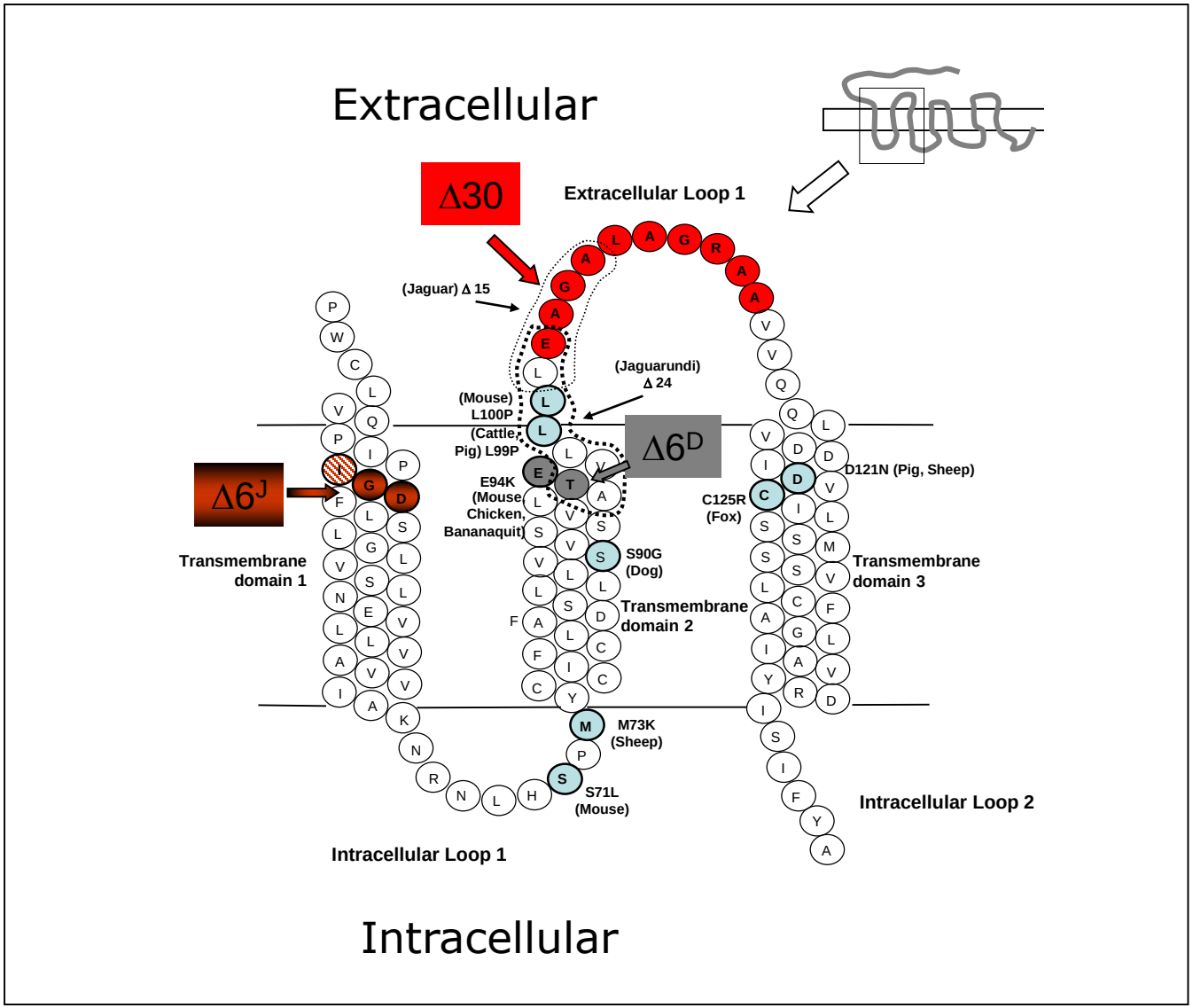
```
  CCCCGGACGGGACT ATG CCC ATG CAG GCG CCC CAG AGC AGG CTG CTG GGC TCC
                    M   P   M   Q   A   P   Q   S   R   L   L   G   S

CTC AAT GCC ACG GCC ACA GCC TCC CCC AGT CCT GGG CTA GCT GCC AAC CAC
 L   N   A   T   A   T   A   S   P   S   P   G   L   A   A   N   H

ACA GGA CCC TGG TGT CTG CAG GTG CCC ATC CCC AAT GGG CTC TTC CTC AGC
 T   G   P   W   C   L   Q   V   P   I   P   D   G   L   F   L   S

CTG GGG CTG GTG AGC CTG GTG GAG AAC CTG CTG GTA GTG GTT GCC ATC GCC
 L   G   L   V   S   L   V   E   N   L   L   V   V   V   A   I   A

AAG AAC CGC AAC CTG CAC TCG CCC ATG TAC TGC TTC ATC TGC TGC CTG GCC
 K   N   R   N   L   H   S   P   M   Y   C   F   I   C   C   L   A

TTG TCC GAC CTG CTG GTG AGC GTG AGC AGC GTG CTG GAG ACG GCC GTC CTG
 L   S   D   L   L   V   S   V   S   S   V   L   E   T   A   V   L

CTG CTG CTG GAG GCG GGC GCC TTG GCC GGC CGG GCC GCA GTG GTG CAG CAG
 L   L   L   E   A   G   A   L   A   G   R   A   A   V   V   Q   Q

CTG GAC GAC GTC ATC GAC GTG CTC ATC TGC AGC TCC ATG GTG TCC AGC CTC
 L   D   D   V   I   D   V   L   I   C   S   S   M   V   S   S   L

TGC TTC CTG GGC GCC ATC GCC GTG GAC CGC TAC ATC TCC ATC TTC TAC GCA
 C   F   L   G   A   I   A   V   D   R   Y   I   S   I   F   Y   A

CTG CGC TAC CAC AGC ATC GTG ACG CTG CCC AGG GCG CGG TGT GTC GTC CTG
 L   R   Y   H   S   I   V   T   L   P   R   A   R   C   V   V   L

GCC GTC TGG GGG GCC AGT GTC ACC TCC AGC TCC CTC TTC GTT GCC TAC TAC
 A   V   W   G   A   S   V   T   S   S   S   L   F   V   A   Y   Y

AAC CAT ACG GCC GTC CTG CTC TGC CTC ATC ATC CTC TTC TTG GCC ATG CTG
 N   H   T   A   V   L   L   C   L   I   I   L   F   L   A   M   L

GCC CTC ATG GCA GTT TTG TAC GTC CGC ATG TTC ACC CGG GCA TGC CAG CAC
 A   L   M   A   V   L   Y   V   R   M   F   T   R   A   C   Q   H

.....
```

Deletion of 6 bp in Japanese and Rhinelander ($\Delta 6^{J}$)

Deletion of 6 bp in Checkered Giant ($\Delta 6^{D}$)

Deletion of 30 bp in Burgundy Fawn ($\Delta 30$)

2D structure of the rabbit MC1R protein



***MC1R* genotypes in different breeds**

Δ30/ Δ30

New Zealand red

Burgundy fawn

Thuringian

Gold Saxony

Lop (Madagascar)

Δ6/ Δ6

Checkered giant

Californian

New Zealand white

E/E

Giant grey

Belgian hare

Vienna blue

Alaska

Japanese

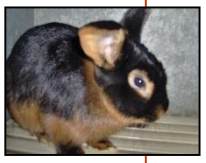
Rhinelander

Δ6J/Δ6J

… there is an unknown epigenetic mechanism that may determine the shift between black/red pigmentation

Alleles at the *Agouti* locus

Locus	Alleles	
Agouti	*A*	(Agouti)
	a^t	(Tan)
	a	(Self, non-agouti)



Genomics 95 (2010) 166–175

Contents lists available at ScienceDirect

Genomics

journal homepage: www.elsevier.com/locate/ygeno

Characterization of the rabbit agouti signaling protein (*ASIP*) gene: Transcripts and phylogenetic analyses and identification of the causative mutation of the nonagouti black coat colour☆

Luca Fontanesi [a,*], Lionel Forestier [b], Daniel Allain [c], Emilio Scotti [a], Francesca Beretti [a], Séverine Deretz-Picoulet [d], Elena Pecchioli [e], Cristiano Vernesi [e], Terence J. Robinson [f], Jason L. Malaney [g], Vincenzo Russo [a], Ahmad Oulmouden [b,*]

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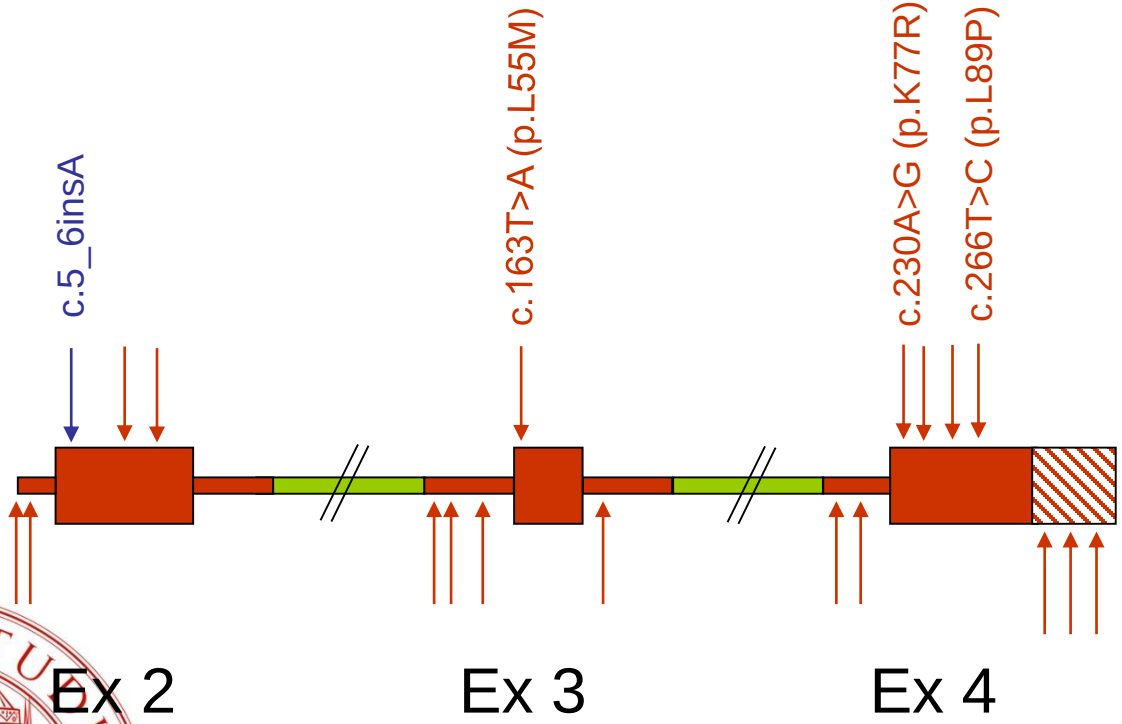
ABSTRACT

The agouti locus encodes the agouti signalling protein (ASIP) which is involved in determining the switch from eumelanin to pheomelanin synthesis in melanocytes. In the domestic rabbit (*Oryctolagus cuniculus*) early studies indicated three alleles at this locus: *A*, light-bellied agouti (wild type); *a*^{t}, black and tan; *a*, black nonagouti. We characterized the rabbit *ASIP* gene and identified the causative mutation (an insertion in exon 2) of the black nonagouti allele whose frequency was evaluated in 31 breeds. Phylogenetic analysis of *ASIP* sequences from *Oryctolagus* and 9 other species of the family *Leporidae* placed *Oryctolagus* as sister species to *Pentalagus* and *Bunolagus*. Transcription analysis in wild type agouti rabbits revealed the presence of two major transcripts with different 5′-untranslated regions having ventral or dorsal skin specific expression. *ASIP* gene transcripts were also detected in all examined rabbit tissues distinguishing the rabbit expression pattern from what was observed in wild type mice.

Agouti locus = *ASIP* gene

Identified 18 SNPs and 1 indel



c.-10-34C>T
c.-10-31C>T
c.5_6insA
c.126G>A
c.147G>A
c.161-223T>A
c.161-192G>A
c.161-70C>T
c.163T>A (p.L55M)
c.225+5A>G
c.226-92G>A
c.226-63G>A
c.230A>G (p.K77R)
c.234G>T
c.252G>A
c.266T>C (p.L89P)
c.*14A>G
c.*23G>C
c.*41C>T

ASIP Exon 2 genotypes (insertion: c.5_6insA) in different breeds

ins/ins (a/a)

wt & ins (A & a)

wt/wt (A/A)

Havana

Vienna blue

Checkered giant

Chinchilla

English spot

Alaska

Californian

Giant grey

Burgundy fawn

Dutch

Champagne d'Argent

Rhinelander

Belgian hare

New Zealand white

Silver

Thuringian

Dilute

ANIMAL GENETICS Immunogenetics, Molecular Genetics and Functional Genomics
doi: 10.1111/age.12104

A frameshift mutation in the *melanophilin* gene causes the dilute coat colour in rabbit (*Oryctolagus cuniculus*) breeds

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Alleles at the *Dilute* locus

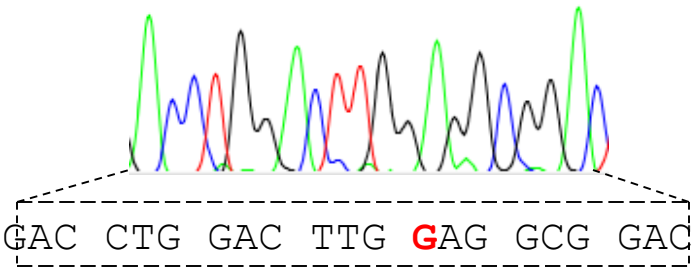
Locus	Alleles	
Dilute	*D*	(normal black)
	d	(blue)

Vienna Blue

Melanophilin gene (*MLPH*)

wild type allele

...ACCTGGACTT**GG**AGGCGGAC...



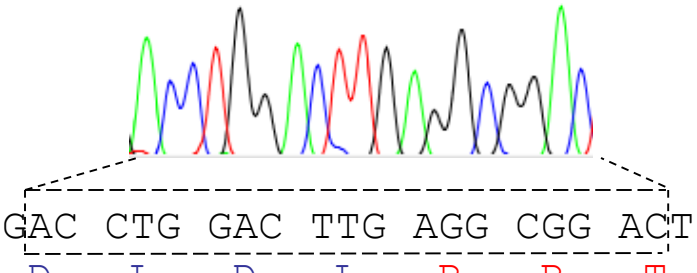
```
AAA AAG CGG CTC CTC TCC ATC CAC GAC CTG GAC TTG GAG GCG GAC
 K   K   R   L   L   S   I   H   D   L   D   L   E   A   D

TCG GAT CAC TCC ACG CGG TCC TGT GGT CAG CTC CTG GAC TTG TCC
 S   D   H   S   T   R   S   C   G   Q   L   L   D   L   S

TCC GAG GCT GAG GCC ACG GGC AGC CTG CAG
 S   E   A   E   A   T   G   S   L   Q
```

dilute allele

...ACCTGGACTT**G**AGGCGGAC...



```
AAA AAG CGG CTC CTC TCC ATC CAC GAC CTG GAC TTG AGG CGG ACT
 K   K   R   L   L   S   I   H   D   L   D   L   R   R   T

CGG ATC ACT CCA CGC GGT CCT GTG GTC AGC TCC TGG ACT TGT CCT
 R   I   T   P   R   G   P   V   V   S   S   W   T   C   P

CGG AGG CTG AGG CCA CGG GCA GCC TGC AG
 P   R   L   R   P   R   A   A   C   X
```

Melanophilin gene (*MLPH*)

= black

= blue

del/G del/del del/G

del/G del/del del/del del/G del/del del/G del/del del/G

del/G del/del del/G del/del del/G del/del del/del del/del

Alleles at the *Brown* locus

Locus	Alleles	
Dilute	*B*	(normal black)
	b	(brown)

ANIMAL GENETICS Immunogenetics, Molecular Genetics and Functional Genomics
SHORT COMMUNICATION
doi: 10.1111/age.12171

A premature stop codon in the *TYRP1* gene is associated with brown coat colour in the European rabbit (*Oryctolagus cuniculus*)

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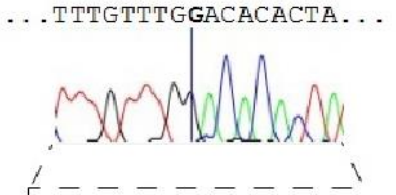
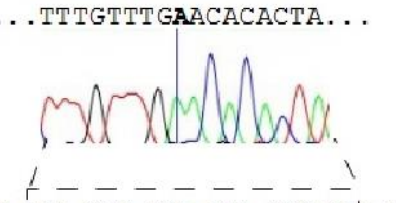
Tyrosinase-related protein 1 (*TYRP1*)

Checkered Giant



Havana



FAGenomicH

Farm Animal Genomics for Humans

Genomics applied to the improvement of farm animal productions

Genomics applied for the characterization of animal models of human genetic diseases

Alleles at the *English spotting* locus

Locus		Alleles
English spotting	*En*	(English spotting)
	en	(normal, non spotted)

English spotting

which necessitated their abandonment. NACHTSHEIM is inclined to this view by analogy to the mouse where dominant white is either lethal or semi-lethal when present in the homozygous condition. Since the degree of white spotted in the English homozygote is less

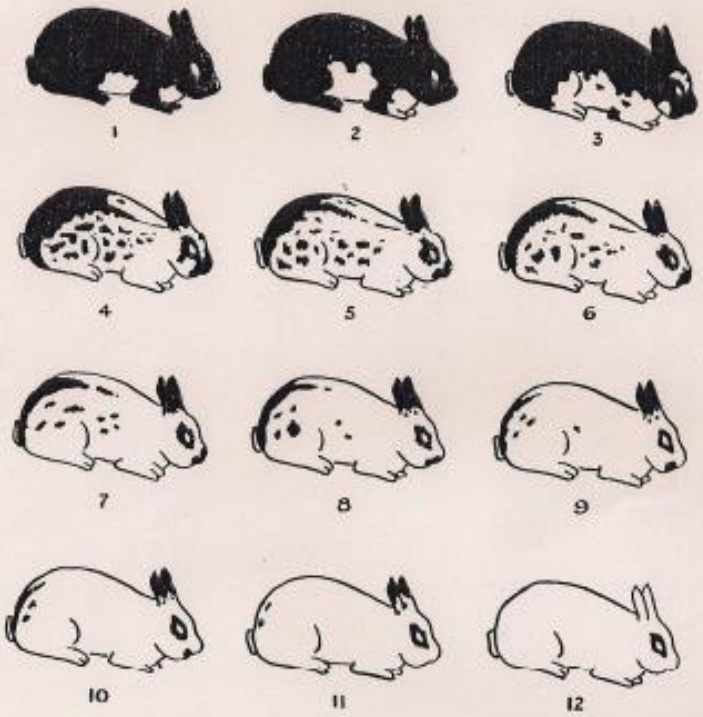


Fig. 2. Variation of expression of English-type white spotting.

than that of the mouse (the mouse homozygote is pure white with dark eyes) it is suggested that the lethalness of the rabbit gene will be correspondingly less severe. The inviability of the English gene may be so slight that a good environment may largely overshadow the effects to be expected.

Essentially the same suggestion is advanced by RIFAAT (1954*b*) who, however, makes the point that the analogy is supported by

Variation of expression
of English-type white spotting

English spotting

WORLD RABBIT SCIENCE 1995, 3 (1), 19-26.

ALBINO RABBITS CAN SUFFER FROM MEGACOLON-SYNDROME WHEN THEY ARE HOMOZYGOUS FOR THE "ENGLISH SPOT" GENE (EnEn)

WIEBERNEIT D., WEGNER W.

Zur Problematik der Scheckenzucht bei Kaninchen. 4. Mitteilung: Morpho- und histometrische Befunde am ZNS und an der Schilddrüse sowie SH-Gehalte im Schlachtblut von Hybridkaninchen, Beurteilung des Heterosiseffektes

Von K. FLEMMING, C. KÜHNEL, D. WIEBERNEIT und W. WEGNER

Aus dem Institut für Tierzucht und Vererbungsforschung der Tierärztlichen Hochschule Hannover

FLEMMING, K., C. KÜHNEL, D. WIEBERNEIT und W. WEGNER (1994): **Zur Problematik der Scheckenzucht bei Kaninchen. 4. Mitteilung: Morpho- und histometrische Befunde am ZNS und an der Schilddrüse sowie SH-Gehalte im Schlachtblut von Hybridkaninchen, Beurteilung des Heterosiseffektes.**
Dtsch. tierärztl. Wschr. **101**, 434–439

J. Vet. Med. A. **42**, 549–559 (1995)

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Institute of Animal Breeding and Genetics, Hannover School of Veterinary Science, Bünteweg 17p, 30559 Hannover, Germany

Pathophysiological and Functional Aspects of the Megacolon-Syndrome of Homozygous Spotted Rabbits

D. BÖDEKER*, O. TÜRCK, E. LOVÉN, D. WIEBERNEIT and W. WEGNER

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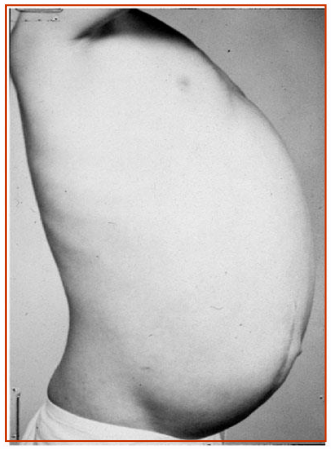
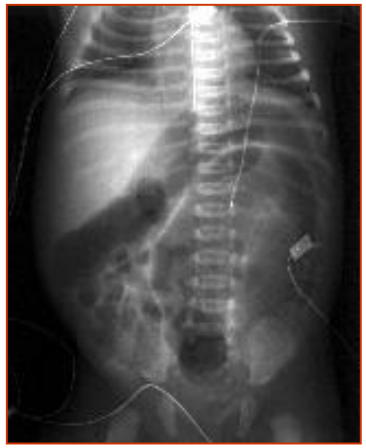
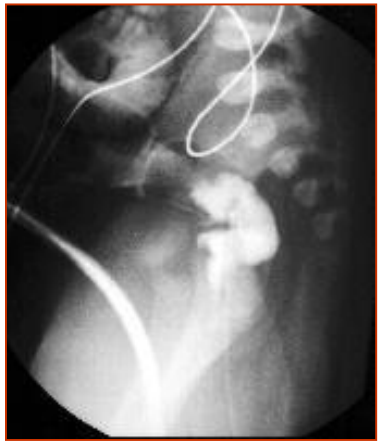
Hirschsprung disease

The disorder described by Hirschsprung (1888) and known as Hirschsprung disease or aganglionic megacolon is characterized by congenital absence of intrinsic ganglion cells in the myenteric (Auerbach) and submucosal (Meissner) plexuses of the gastrointestinal tract (from OMIM).

Incidence of 1/5000 births







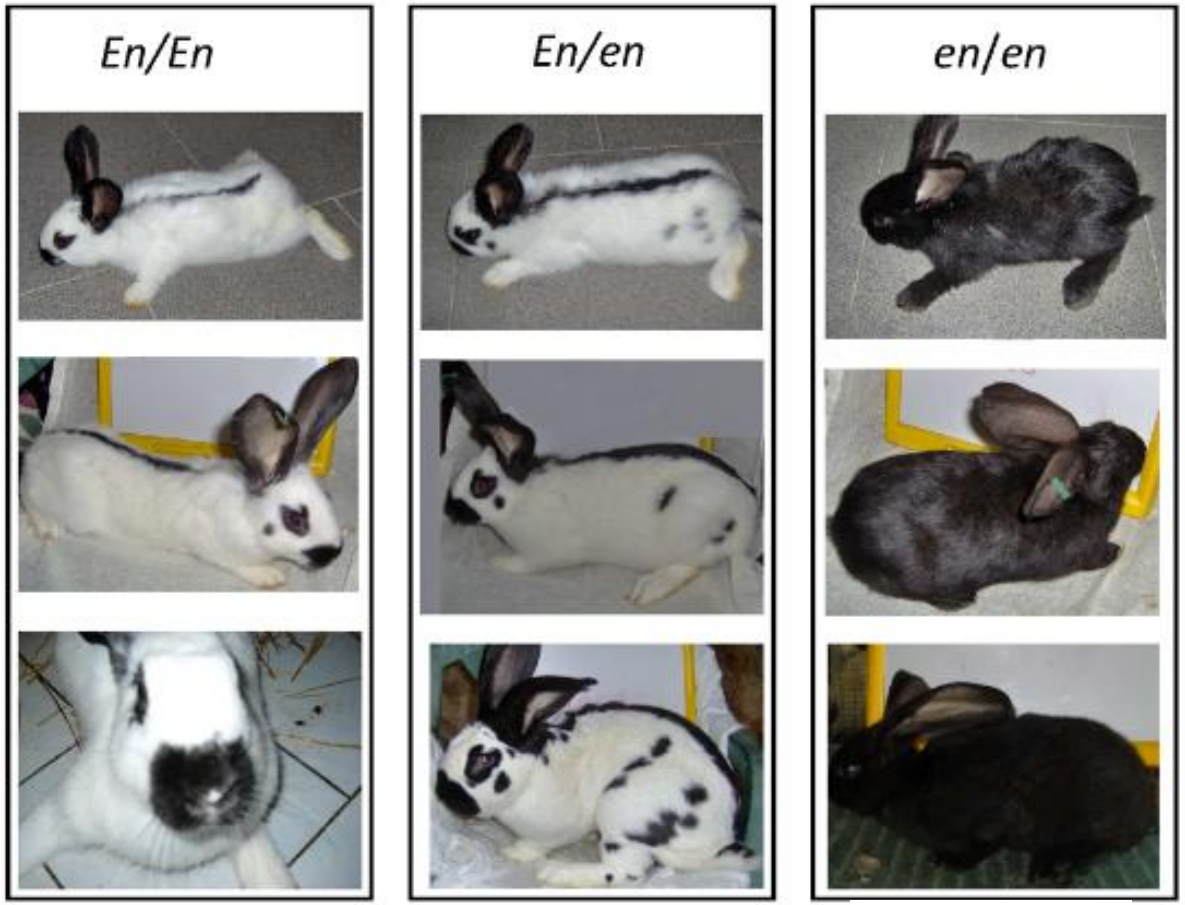
OPEN ACCESS Freely available online

PLOS ONE

The *KIT* Gene Is Associated with the *English Spotting* Coat Color Locus and Congenital Megacolon in Checkered Giant Rabbits (*Oryctolagus cuniculus*)

Luca Fontanesi[1,2]*, Manuela Vargiolu[3], Emilio Scotti[1], Rocc Pellegrini[6], Maurizio Mazzoni[4], Martina Asti[4], Roberto Chi Paolo Clavenzani[4], Roberto De Giorgio[5]*

1 Department of Agricultural and Food Sciences, Division of Animal Sciences, Laboratory of Genome Biology, University of Bologna, Bologna, Italy, **3** Health Sciences and Technologies-I Bologna, Italy, **4** Department of Veterinary Medical Science, University of Bologna, Bologna, It Ricerca Biomedica Applicata (C.R.B.A.), St. Orsola-Malpighi Hospital, University of Bologna, Bolog Anatomy and Histology, University of Florence, Florence, Italy, **7** Department of Medical and University of Bologna, Bologna, Italy



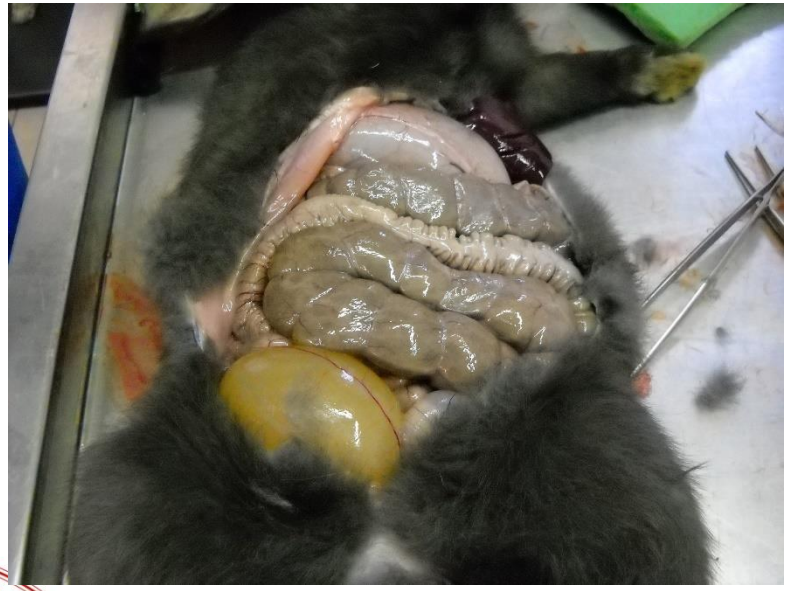
Subvital (discarded)

Normal (selected for show)

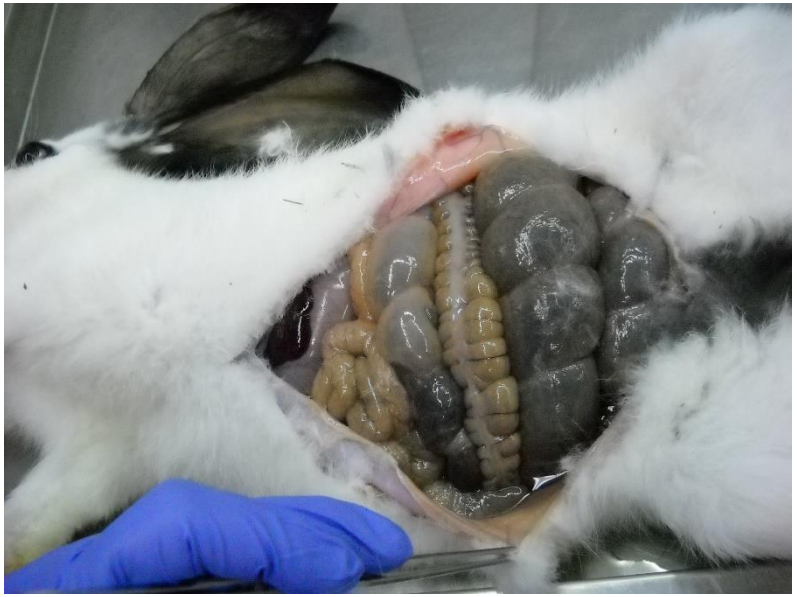
Normal (discarded)

English spotting

en/en



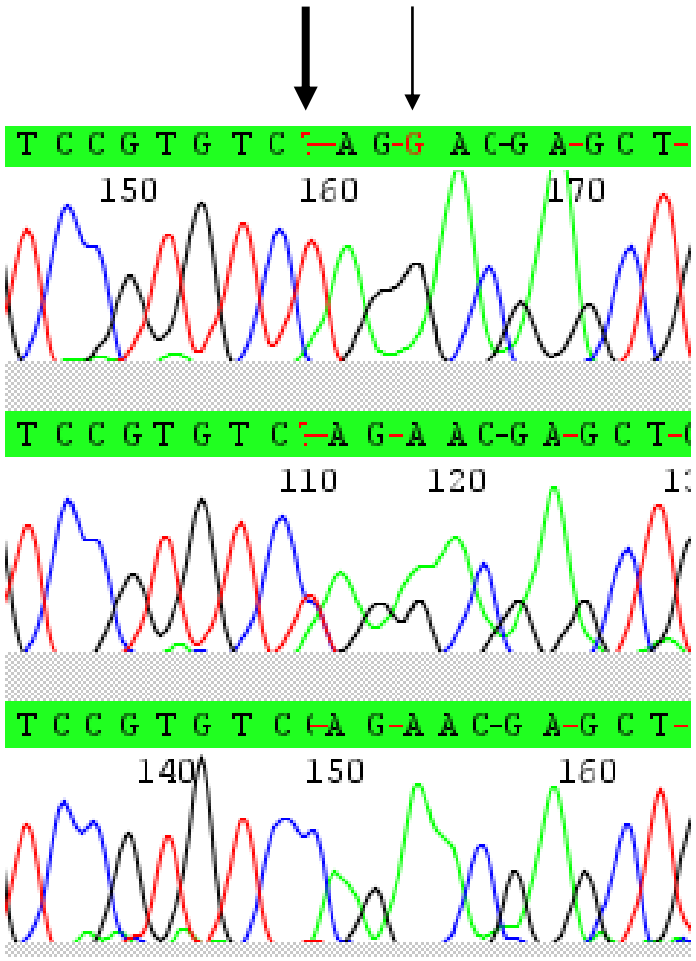
En/En



KIT exon 5

g.160T>C
(g.61620715T>C)

C/T A/G

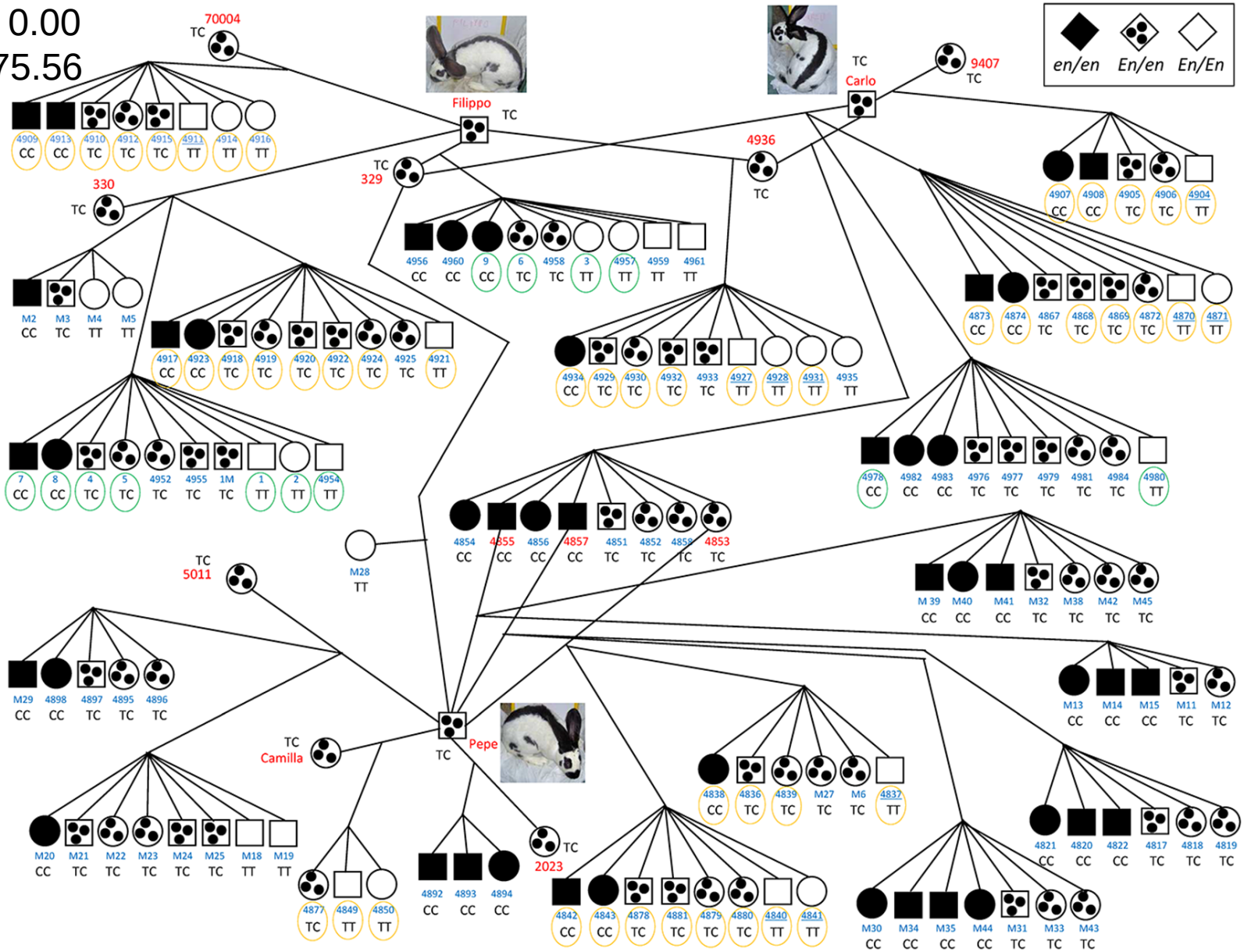


KIT exon 5 g.160T>C (g.61620715T>C)

F1 = 131 rabbits

Theta = 0.00

LOD = 75.56



Genotypes of the g.61620715T>C SNP in different rabbit breeds

Checkered Giant

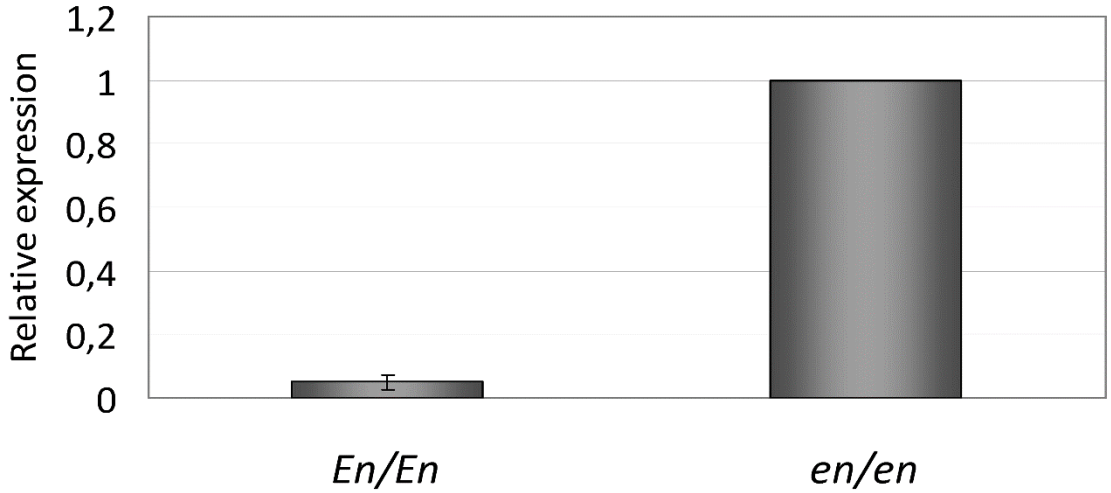
Rhinelander

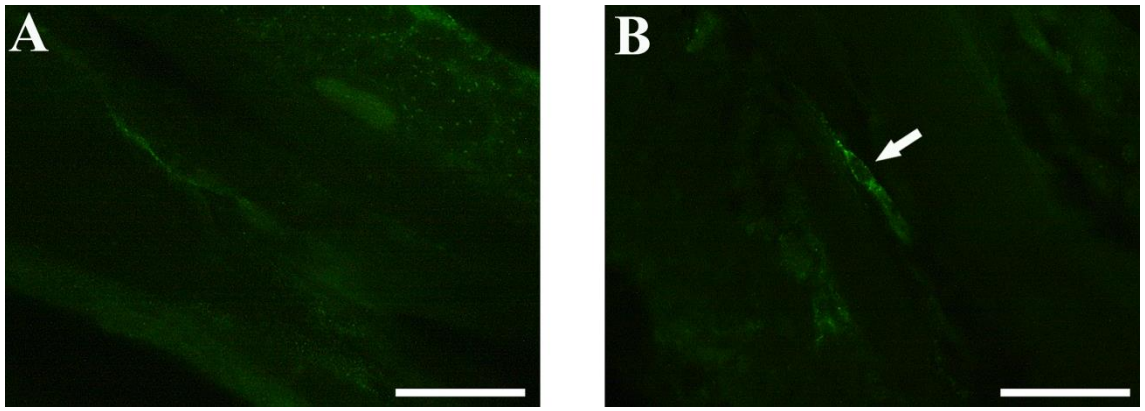
English spotting

Dutch

Breeds	No. of animals	Genotypes		
		TT	TC	CC
Giant Grey	6	3	3	0
Giant White	2	0	2	0
Checkered Giant	20	0	20	0
Champagne d'Argent	12	0	0	12
Giant Chinchilla	12	0	3	9
Vienna Blue	13	9	2	2
New Zealand White	4	0	0	4
Californian	20	1	3	16
Rhinelander	3	0	3	0
English spotting	8	0	0	8
Dutch	6	1	2	3
Japanese	1	0	0	1
Total	**107**	**14**	**38**	**55**

KIT gene expression in colon

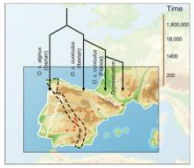




Cells of Cajal (ICC)

Locus	Gene symbol	Gene name	Alleles	Mutations	References
Coat colour loci					
Extension	MC1R	melanocortin 1 receptor	E^{+} (wild type)	Two wild type alleles differing by two SNPs: c.[333A>G;555T>C]	Fontanesi et al. (2006, 2010b)
			E^{D} or E^{S} (dominant black or steel)	6 bp-in-frame deletion: c.280_285del6	
			e (red, non-extension of black)	30 bp-in frame deletion: c.304_333del30	
			e^{J} (Japanese brindling)	6 bp-in frame deletion flanked by a G>A transition in 5': c.[124G>A;125_130del6]	
Agouti	ASIP	agouti-signalling protein	A (light-bellied agouti; wild type)	Wild type allele	Fontanesi et al. (2010a)
			a (recessive black nonagouti)	c.5_6insA	
			a^{t} (black and tan)	p.L55M and p.L89P	
C (albino)	TYR	tyrosinase	C (fully coloured)	Wild type allele	Aigner et al. (2000)
			c^{Ch} (Chinchilla)	p.E294G and p.T358I	
			c^{H} (Himalayan albinism)	p.E294G	
			c (albino, total lack of pigments)	p.T373K	
Dilute	MLPH	melanophilin	D (wild type, intense black and red)	Several wild type alleles	Fontanesi et al. (2014a)
			d (dilution of blck to blue and red to yellow)	g.549853delG	
			d (dilution of blck to blue and red to yellow)	Two exon skippin mutation	Lehner et al. (2013)
Brown	TYRP1	tyrosinase-related protein 1	B (wild type)	Several wild type alleles	Utzeri et al. (2014)
			b (brown)	p.Trp190ter	
English spotting	KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	en (solid coloured, wild type, recessive)	Wild type sequences	Fontanesi et al. (2014b)
			En (English spotted; partially dominant)	g.93948587T>C (in complete linkage disequilibrium with the segregating alleles)	
Hair and coat structure loci					
Rex 1	LIPH	lipase member H	R^{1} (wild type allele)	Wild type sequence	Diribarne et al. (2011)
			r^{1} (mutated allele)	1362delA (deletion in exon 9)	
Angora	FGF5	fibroblast growth factor 5	L (wild type allele)	Wild type sequence	Mulsant et al. (2004); Chantry-Darmon et al. (2006)
			l (mutated allele(s))	In frame insertion of 3 bp (exon 3); T>C SNP	
Other loci					
Yellow fat	BCO2	beta-carotene oxygenase 2	Y (white fat)	Wild type sequences	Strychalski et al. (2015)
			y (yellow fat)	A three-bp deletion in exon 6	
Watanabe heritable hyperlipidemia	LDLR	low density lipoprotein receptor	Two alleles in the Watanabe population	In-frame deletion of 12 bp (mutated allele)	Yamamoto et al. (1986)

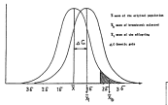
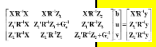
Evolutionary history of the domestic rabbit










Time line

Domestication

VII century

XX century

Modern Fancy breeds

1970

Application of quantitative genetics theory

1990

BLUP Animal Model

2007

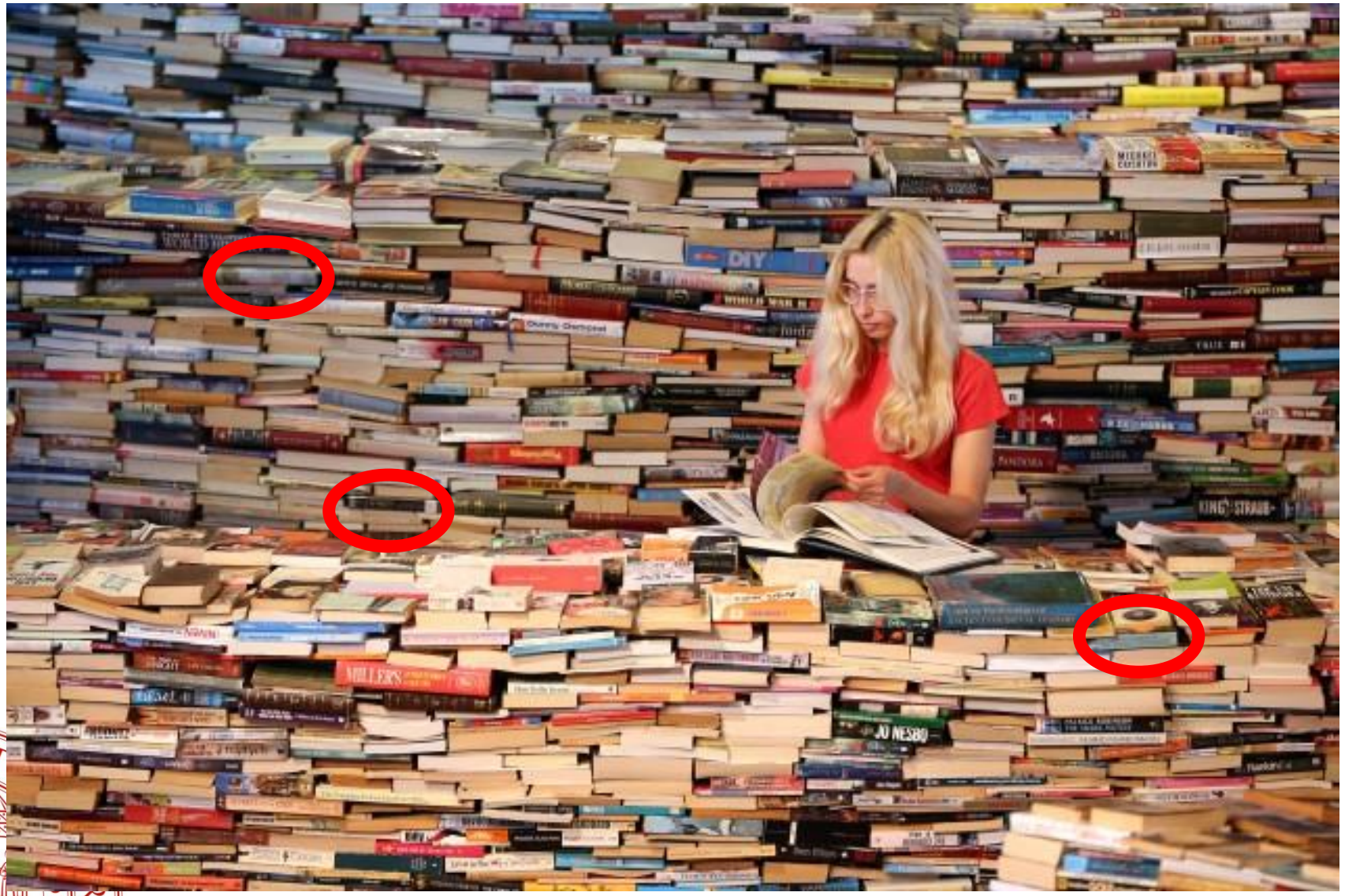
OryCun1.0

2016

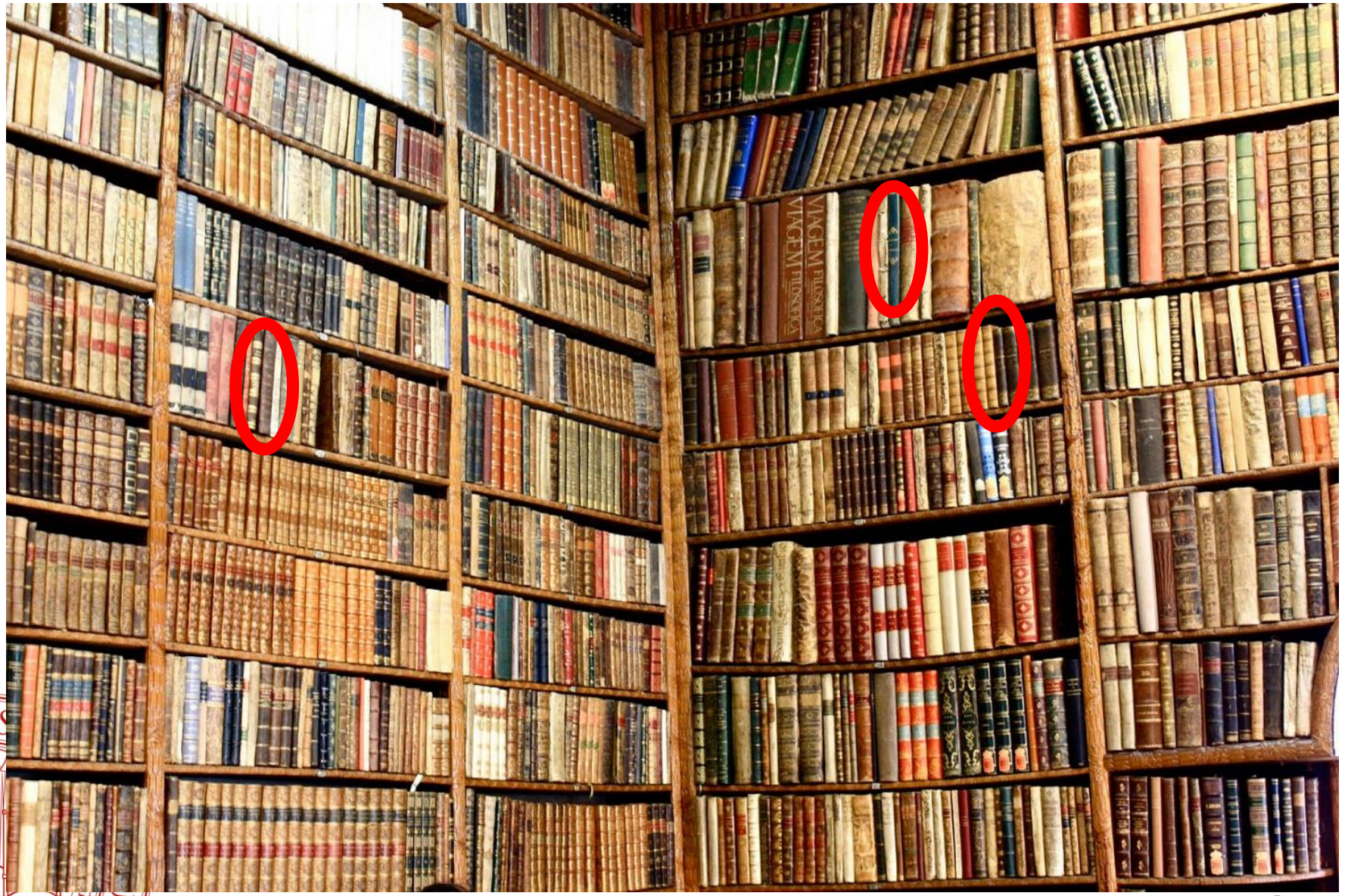
Genomic tools

Candidate gene analysis era for quantitative traits

The candidate gene approach



The candidate gene approach



?

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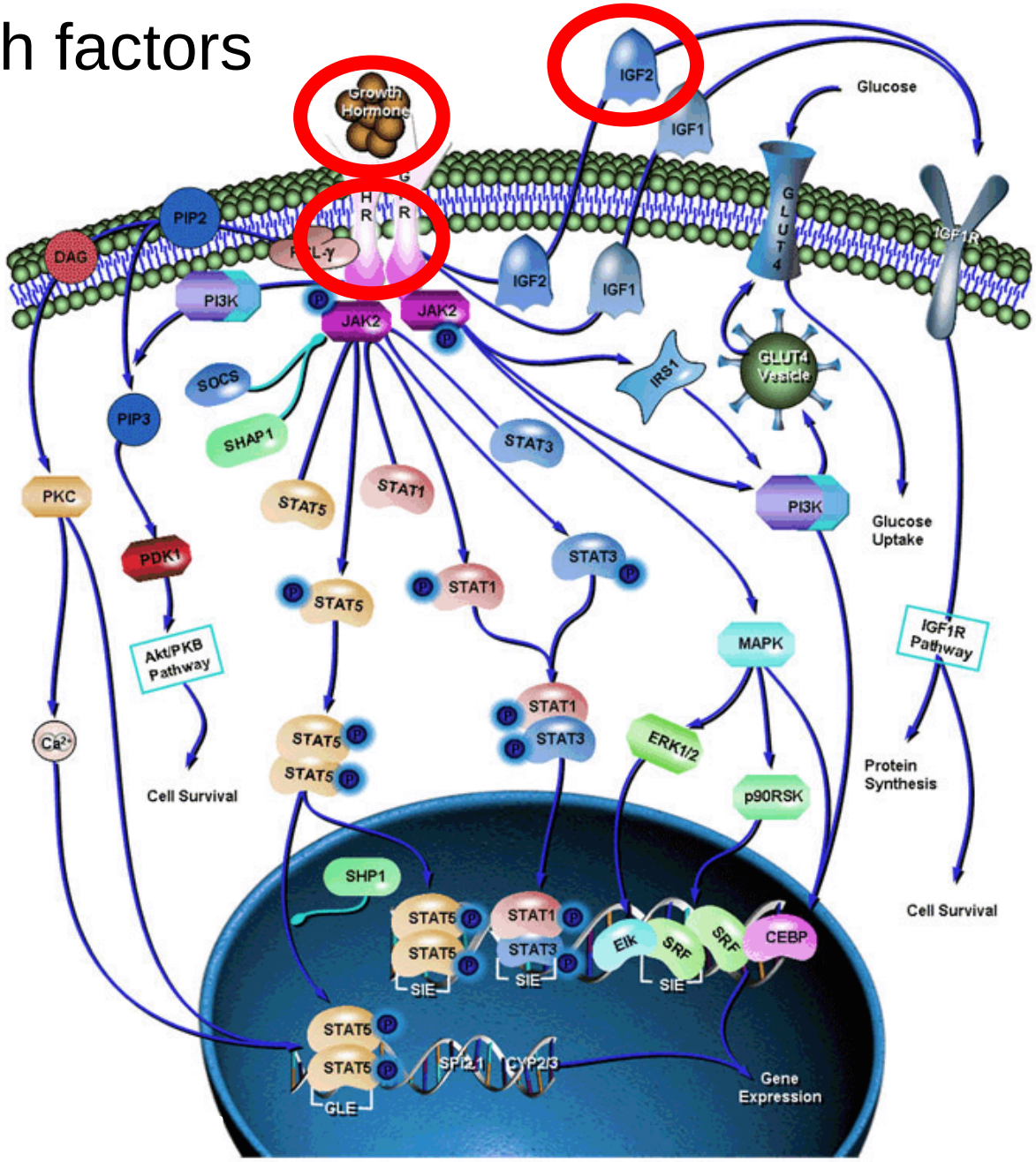
Growth factors



Gene symbol	Gene name	Polymorphisms	Populations	Associated traits	References
Growth and meat production traits (carcass and meat and fat quality traits)					
FTO	Fat mass and obesity associated	3 SNPs in exon 3 (2 missense mutations)	New Zealand, Ira and Champagne rabbits	Body weight at 35, 70, and 84 d; intramuscular fat	Zhang G.W. et al. (2013a)
GH1	Growth hormone	SNP in a putative regulatory region	Commercial meat rabbit line	Finishing weight	Fontanesi et al. (2012a)
GHR	Growth hormone receptor	Missense mutation (SNP)	Commercial meat rabbit line	Finishing weight	Fontanesi et al. (2016)
GHR	Growth hormone receptor	Missense mutation (SNP)	New Zealand, Ira and Champagne rabbits	Eviscerated weight, semi-eviscerated weight, eviscerated slaughter rate, and semi-eviscerated slaughter rate, pH24, weight at 84 d	Zhang et al. (2012)
IGF2	Insulin-like growth factor 2	Indel in a putative regulatory region	Commercial meat rabbit line	Finishing weight	Fontanesi et al. (2012c)
IRS1	Insulin receptor substrate 1	2 synonymous SNPs	New Zealand rabbits	Body weight at 35, 70, and 84 d	Zhang et al. (2014)
MC4R	Melanocortin 4 receptor	Missense mutation (SNP)	Commercial meat rabbit line	Finishing weight	Fontanesi et al. (2013)
MSTN	Myostatin	Missense mutations	Commercial meat rabbit line	None (analysed only finishing weight)	Fontanesi et al. (2011)
MSTN	Myostatin	1 SNP in 5'-flanking region	Ira, Champagne, and Tianfu Black rabbit breeds	Body weight at 84 d	Peng et al. (2013)
MSTN	Myostatin	1 SNP in intron 1	Giant Grey x New Zealand F2 population	Several carcass traits[1]	Sternstein et al. (2014)
NPY	Neuropeptide Y	1 SNP in intron 1	Ira, Champagne, and Tianfu Black rabbit breeds	Eviscerated slaughter percentage, semi-eviscerated slaughter percentage	Liu et al. (2014)
PGAM2	Phosphoglycerate mutase	1 synonymous SNP on exon 1	Ira, Champagne, and Tianfu Black rabbit breeds	Body weight at 84 d, average daily gain	Wu et al. (2015)
POMC	proopiomelanocortin	1 SNP in intron 1	Ira, Champagne, and Tianfu Black rabbit breeds	84 d body weight, eviscerated weight, semi-eviscerated weight, ripe meat ratio	Liu et al. (2014)
POU1F1	POU class 1 homeobox 1	1 SNP in intron 5	Hyla, Champagne, and Tianfu Black rabbit breeds	pH1, cooking loss, intramuscular fat	Wang et al. (2015)
TBC1D1	TBC1 domain family member 1	1 missense mutation in exon 1	European White and New Zealand white rabbits	Body weight at 35 days	Yang et al. (2013)
Reproduction traits in does					
OVGP1	Oviductal glycoprotein 1	1 missense SNP in exon 11 and a microsatellite	F2 cross of two lines divergently selected for uterine capacity	Total number of kits born, number born alive, number of implanted embryos, foetal prenatal embryo survival and development	Merchán et al. (2009); García et al. (2010)
PGR	Progesterone receptor	5 SNPs in two haplotypes	F2 cross of two lines divergently selected for uterine capacity	Embryo implantation and litter size, expression of progesterone receptor isoforms	Peiró et al. (2008); Peiró et al. (2010)
TIMP1	TIMP metallopeptidase inhibitor 1	1 SNP in the promoter region	F2 cross of two lines divergently selected for uterine capacity	Embryo implantation	Estellé et al. (2006); Argente et al. (2010)
Disease/disorder resistance traits					
DECTIN1 (CLE7A)	C-type lectin domain family 7 member A	ss707197675A>G	New Zealand white (case and control study)	Nonspecific digestive disorder	Zhang G.W. et al. (2013a)
IL10	Interleukin 10	Synonymous SNPs in exon 3	New Zealand white, Fujian yellow and their reciprocal crosses	Immune parameters[2]	Wan et al. (2014)
JAK3	Janus kinase 1	1 missense mutation (exon 9) and 1 synonymous SNP (exon 21)	New Zealand white (case and control study)	Nonspecific digestive disorder	Fu et al. (2014)
MYD88	myeloid differentiation primary response 88	Synonymous SNP in exon 4	Yaan and Chengdu populations (case and control study)	Nonspecific digestive disorder	Chen et al. (2013)
NLRP12	NLR family, pyrin domain containing 12	1 missense mutation in exon 3	New Zealand white (case and control study)	Nonspecific digestive disorder	Liu et al. (2013)
NOD2	Nucleotide-binding oligomerization domain containing 2	1 synonymous SNP in exon 10	New Zealand white (case and control study)	Nonspecific digestive disorder	Zhang W.X. et al. (2013)
STAT3	signal transducer and activator of transcription 3	2 synonymous SNPs (exons 4 and 8)	New Zealand white (case and control study)	Nonspecific digestive disorder	Fu et al. (2014)
TLR4	Toll-like receptor 4	5 SNPs (2 synonymous and 3 non-synonymous): 2 haplotypes	New Zealand white (case and control study)	Nonspecific digestive disorder	Zhang et al. (2011)
TYK2	Tyrosine kinase 2	2 haplotypes	New Zealand white (case and control study)	Nonspecific digestive disorder	Fu et al. (2015)

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Reproduction traits in does					
OVGP1	Oviductal glycoprotein 1	1 missense SNP in exon 11 and a microsatellite	F2 cross of two lines divergently selected for uterine capacity	Total number of kits born, number born alive, number of implanted embryos, foetal prenatal embryo survival and development	Merchán et al. (2009); García et al. (2010)
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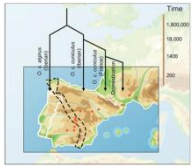
Growth and meat production traits

Reproduction traits in does

Disease/disorder resistance traits

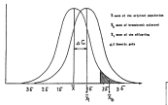
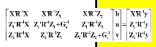
Evolutionary history of the domestic rabbit










Time line

Domestication

VII century

XX century

Modern Fancy breeds

1970

Application of quantitative genetics theory

1990

BLUP Animal Model

2007

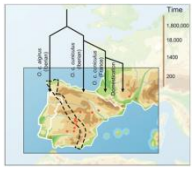
OryCun1.0

2016

Genomic tools

Candidate gene analysis era for quantitative traits

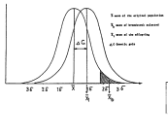
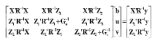
Evolutionary history of the domestic rabbit







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Genomic data and tools era

Genomic data and tools era

SNPs

ANIMAL GENETICS Immunogenetics, Molecular Genetics and Functional Genomics
SHORT COMMUNICATION
doi: 10.1111/age.12121

High-throughput SNP discovery in the rabbit (*Oryctolagus cuniculus*) genome by next-generation semiconductor-based sequencing

F. Bertolini*, G. Schiavo*, E. Scotti*, A. Ribani*, P. L. Martelli†‡, R. Casadio†‡ and L. Fontanesi*‡

*Department of Agricultural and Food Sciences (DISTAL), Division of Animal Sciences, University of Bologna, Viale Fanin 46, Bologna, 40127, Italy. †Biocomputing Group, Department of Biological, Geological and Environmental Sciences (BiGeA), University of Bologna, via San Giacomo 9/2, Bologna, 40126, Italy. ‡Centre for Genome Biology, University of Bologna, Bologna, 40126, Italy.

EVOLUTIONARY GENOMICS

Rabbit genome analysis reveals a polygenic basis for phenotypic change during domestication

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Science AAAS
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Science **345**, 1074 (2014);
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Genomic data and tools era

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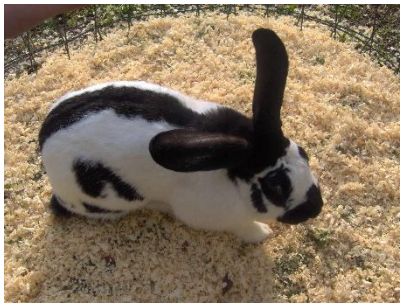
SNP chip: 200K

affymetrix
part of Thermo Fisher Scientific

M. Carneiro,
C.J. Rubin
….
L. Fontanesi,
L. Andersson

Rabbit is a key species

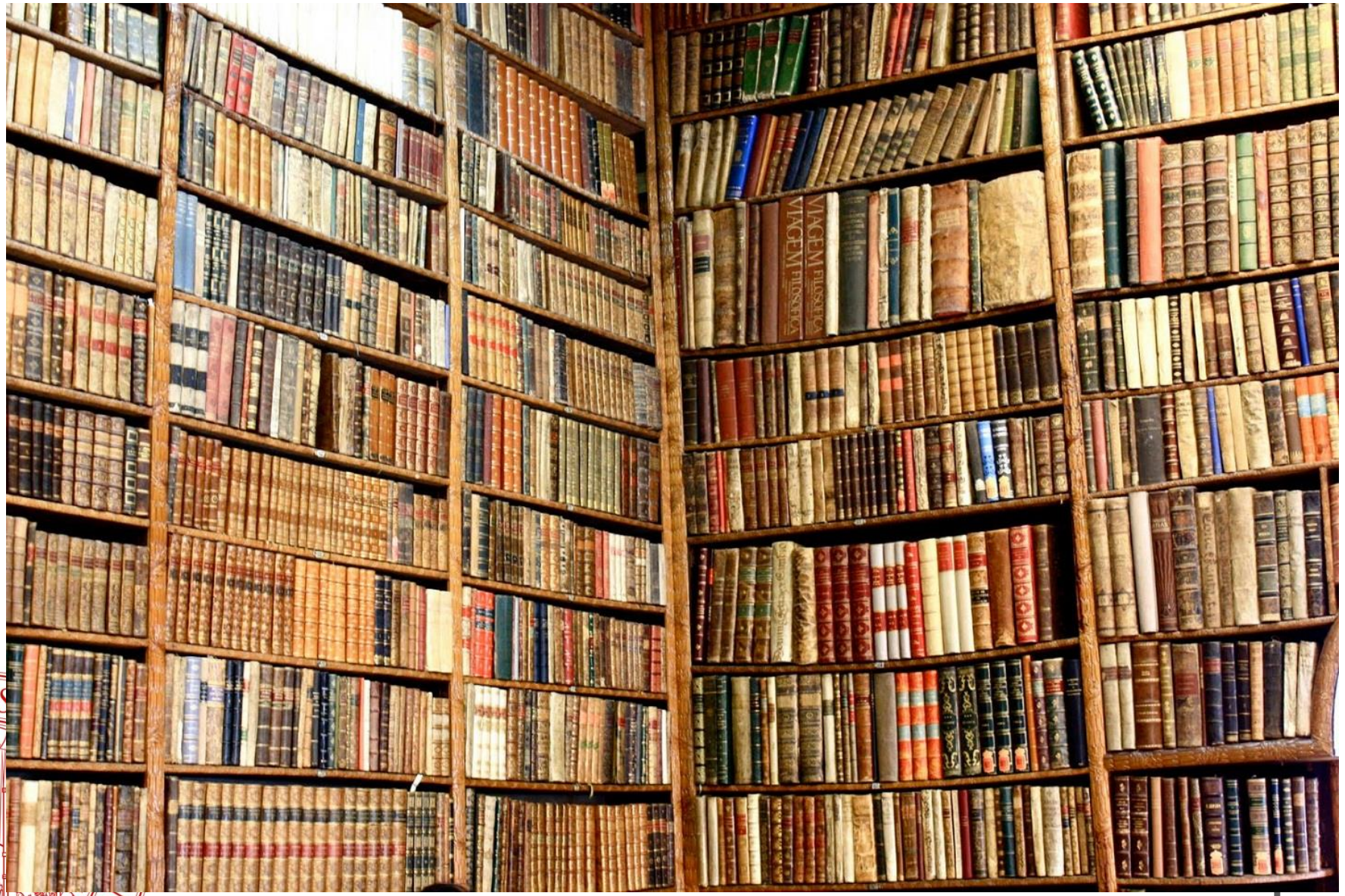
- Livestock resource
  - Meat, fur, pet, fancy breeds
  - European meat market: 1.6 billion €
- Animal model and bioreactor
  - Model of prolific livestock species (pig)
  - Basic biology
  - Human diseases
  - Biotechnology applications
  - World antibodies production: 3-5 billion €
- Wild resource
  - Ecology, game species, pest
  - Related species (wild lagomorphs)



Meat production

Genomic selection in rabbits ?

Genomic data and tools era: Genomic Selection



Genomic data and tools era: Genomic Selection

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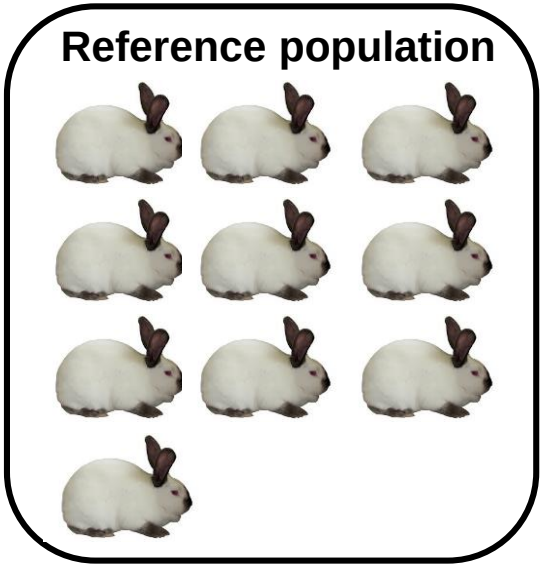
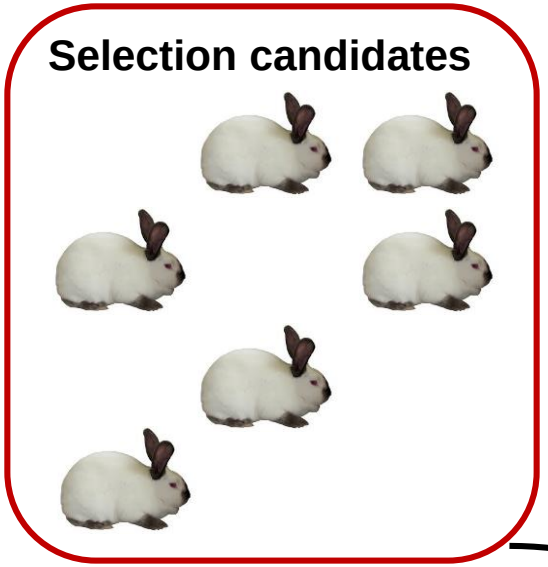
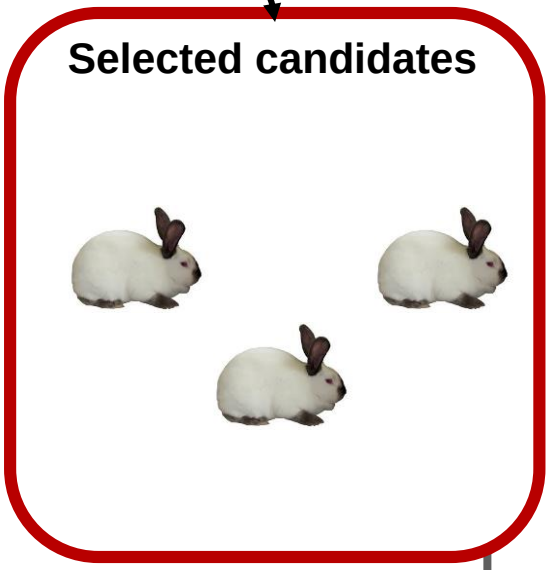
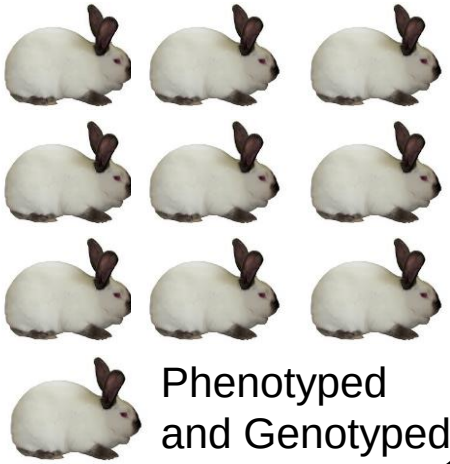






Genomic Selection

Reference population



Phenotyped and Genotyped

Selection candidates

Only Genotyped

Prediction Equation

Genomic Breding Value =
$t_1x_1 + t_2x_2 + t_3x_3 + \ldots$

Selected candidates

using Genomic Breeding Values

Meat production

Genomic selection in rabbits ?

$$\Delta G = (i * r * \sigma_g) / L$$

Meat production

Genomic selection in rabbits ?

Genetic progress

$$\Delta G = (i * r * \sigma_g) / L$$

Generation interval

Meat production

Genomic selection in rabbits ?

Genetic progress

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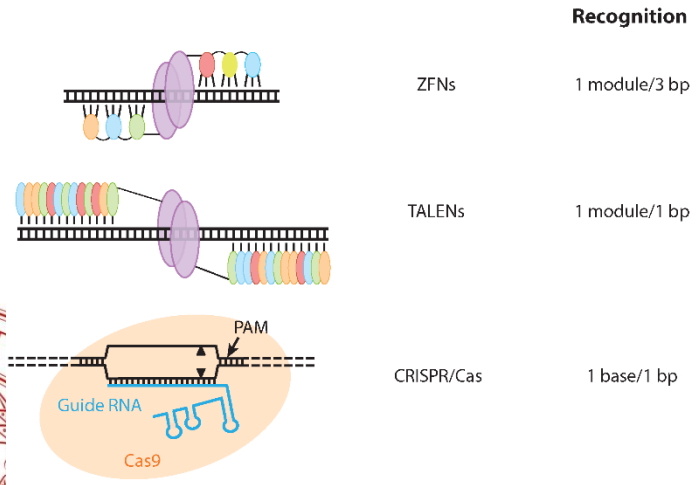
Meat production

Gene editing in rabbits ?



Carroll D. 2014.
Annu. Rev. Biochem. 83:409–39

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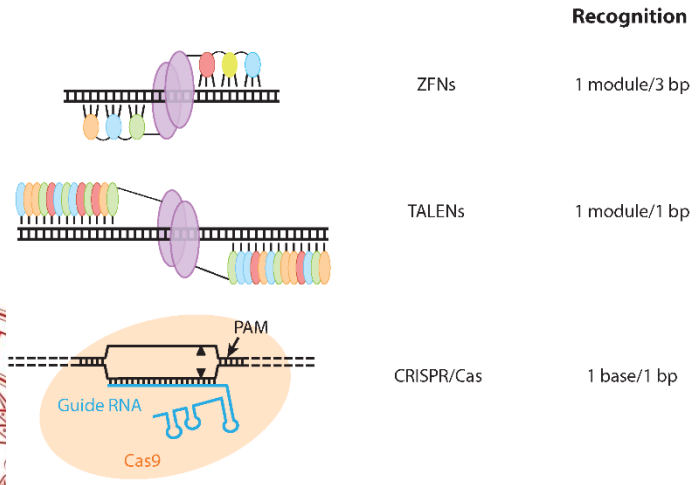

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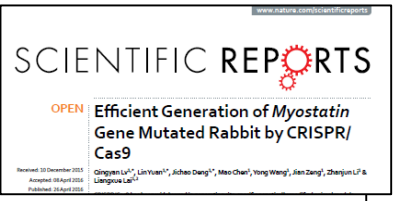

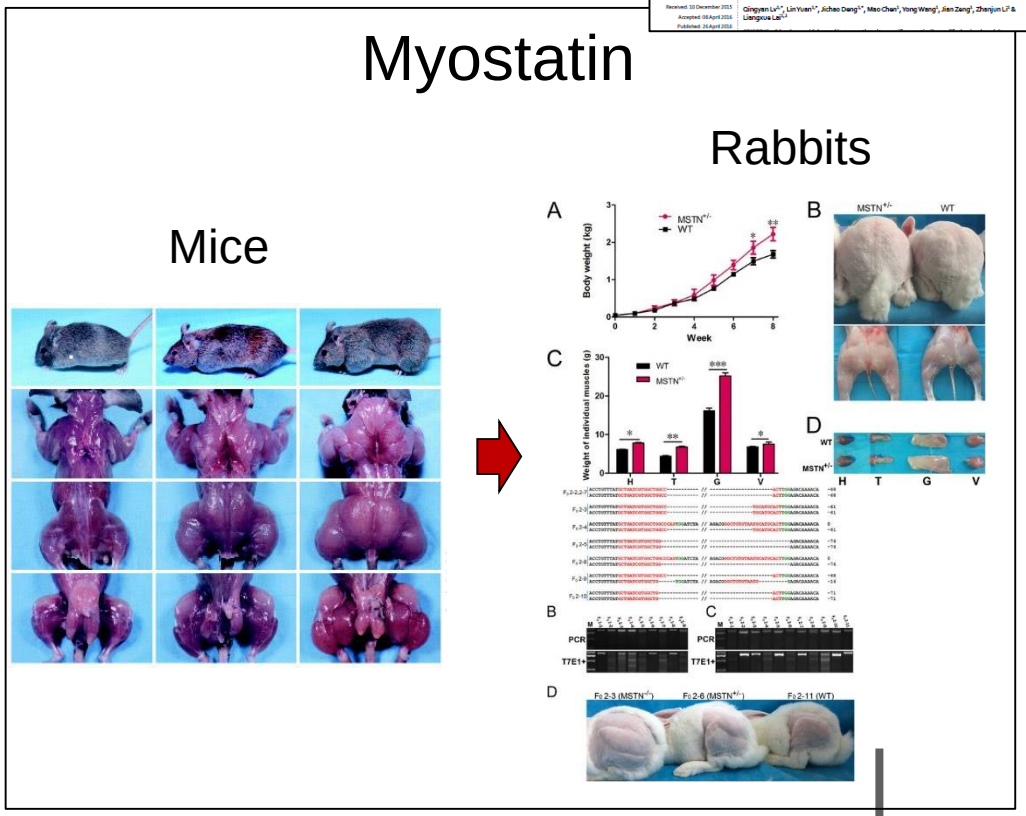

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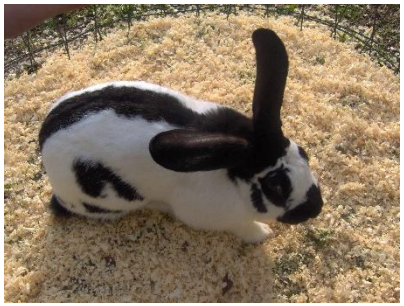

Animal model / Biotech

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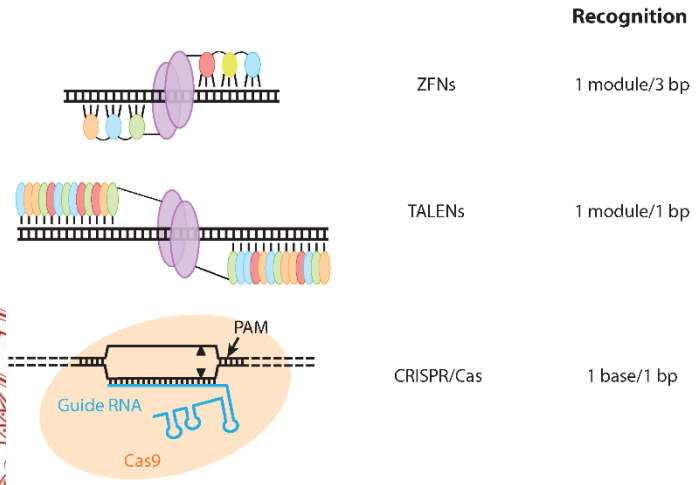

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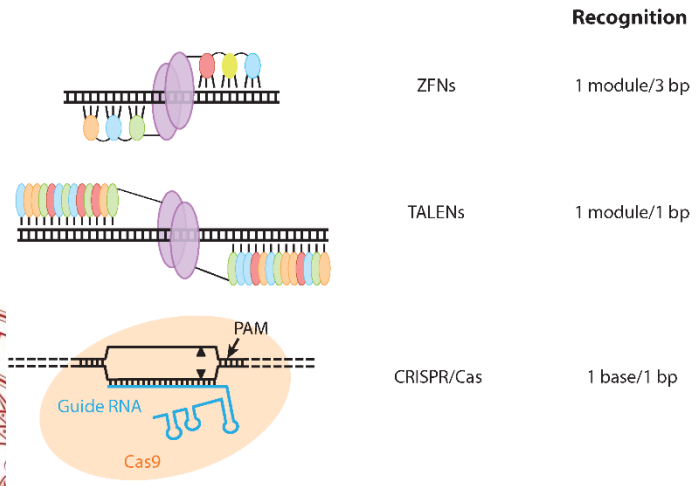

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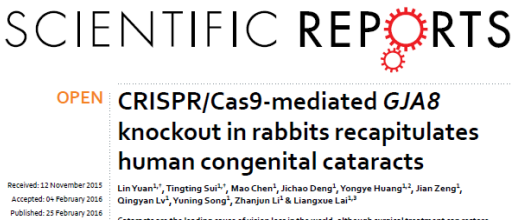
Yan et al. Cell Regeneration 2014, 3:12
http://www.cellregenerationjournal.com/content/3/1/12
CELL REGENERATION
RESEARCH Open Access

Generation of multi-gene knockout rabbits using the Cas9/gRNA system

Quanmei Yan[1†], Quanjun Zhang[1†], Huaqiang Yang[1], Qingjian Zou[1], Chengcheng Tang[2], Nana Fan[1*] and Liangxue Lai[1,2*]

www.nature.com/scientificreports


SCIENTIFIC REPORTS
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CRISPR/Cas9-mediated *GJA8* knockout in rabbits recapitulates human congenital cataracts

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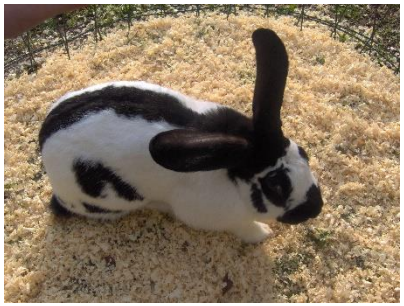
Many potential applications ….

Rabbit is a key species

- Livestock resource
  - Meat, fur, pet, fancy breeds
  - European meat market: 1.6 billion €



- Animal model and bioreactor
  - Model of prolific livestock species (pig)
  - Basic biology
  - Human diseases
  - Biotechnology applications
  - World antibodies production: 3-5 billion €

- Wild resource
  - Ecology, game species, pest
  - Related species (wild lagomorphs)

«Dedomestication genetics – Project »

Dedomestication has been defined as switch of domestic animals back into wild or semi-wild forms

The rabbit has also been widely translocated by humans, and feral rabbits occur worldwide.

Feral rabbits often originate from released rabbits from different domestic breeds, occasionally in combination with strains of wild rabbits

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LAGOMORPHA

Ochotonidae

Pikas

Ochotona (30)

Leporidae

Jackrabbits and Hares

Lepus (32)

Rabbits

Amami Rabbit	*Pentalagus* (1)
Rock Hares	*Pronolagus* (3)
Volcano Rabbit	*Romerolagus* (1)
Hispid Hare	*Caprolagus* (1)
European Rabbit	***Oryctolagus* (1)**
Cottontails	*Sylvilagus* (17)
Pygmy Rabbit	*Brachylagus* (1)
Riverine Rabbit	*Bunolagus* (1)
Bunyoro Rabbit	*Poelagus* (1)
Sumatran and Annamite striped Rabbits	*Nesolagus* (2)

Lagomorph Genomics Consortium

American Genetic Association

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Perspective
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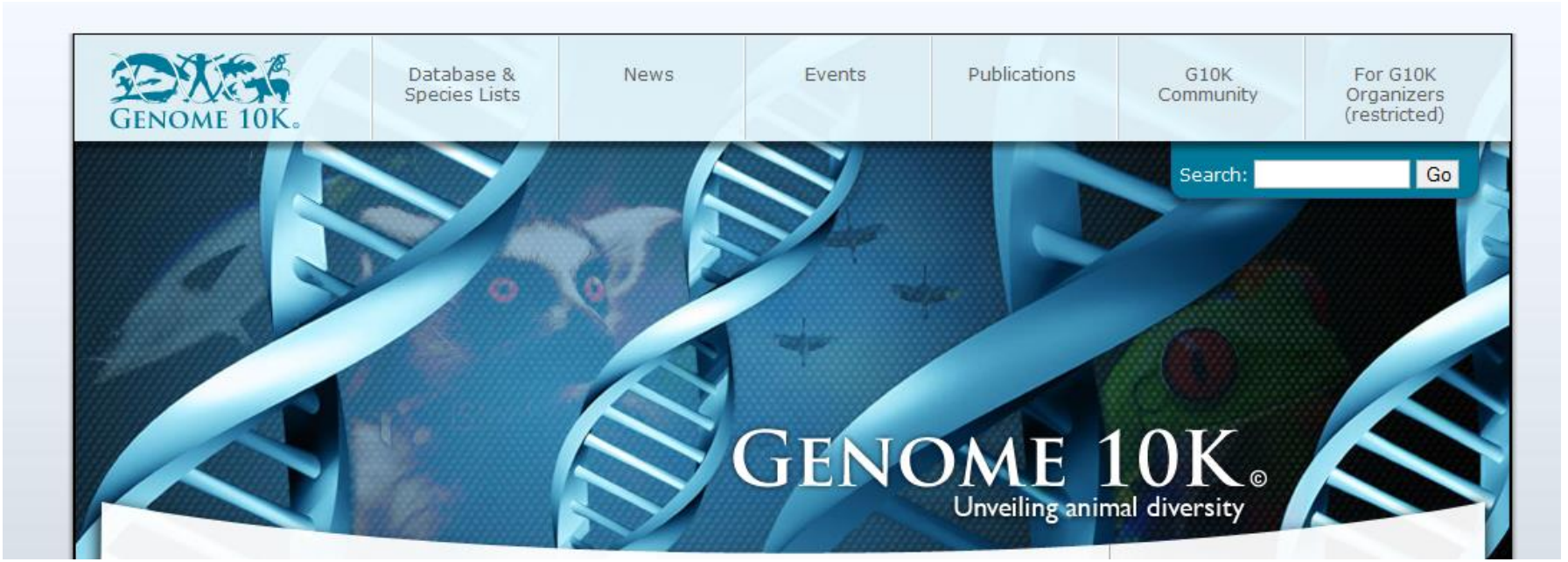
OXFORD

Perspective

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

Luca Fontanesi, Federica Di Palma, Paul Flicek, Andrew T. Smith, Carl-Gustaf Thulin, Paulo C. Alves, and the Lagomorph Genomics Consortium*



Conclusions

Needs:

- Refinement of the rabbit genome
- Functional annotation: FAANG
- Deep phenotyping

Potentials:

- To be further exploited

Future:

- Bright or dark?

Outlooks

What next ?.....

Outlooks

What next ?.....

From the Genetics Round Table:

International Network on Rabbit Genome Biology

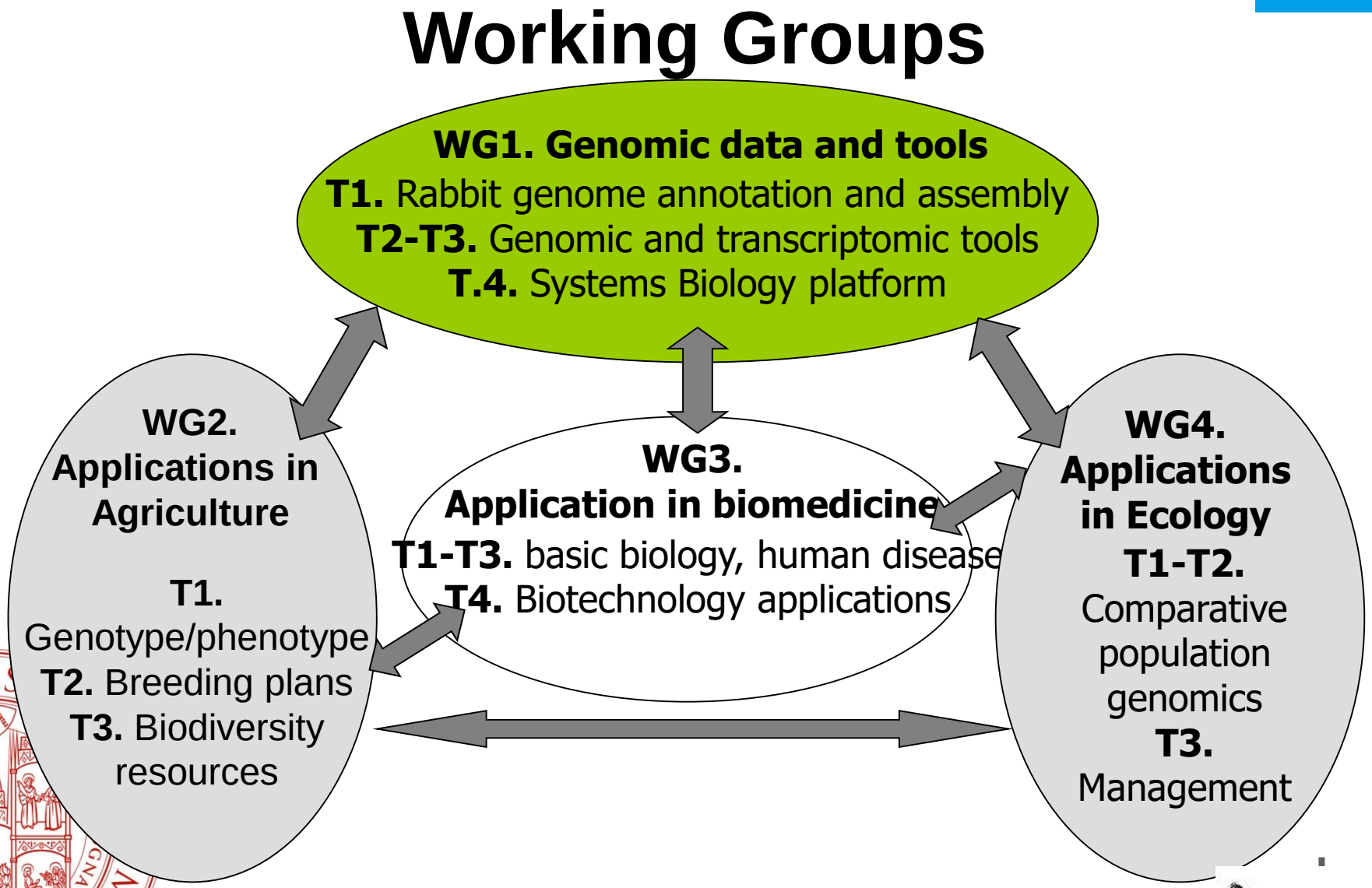
From the Genetics Round Table

A Collaborative European Network on Rabbit Genome Biology

cost
EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

What is a COST Action ?
It is a science and technology network with a duration of four years funded by the European Union.
It is organised through a range of networking tools, such as workshops, conferences, training schools, short-term scientific missions, publications, etc. in order to create opportunities for scientific collaborations worldwide

From the Genetics Round Table



From the Genetics Round Table

International Network on Rabbit Genome Biology
Activities/Objectives

1) Mapping all meat rabbit genetic resources/lines in the world
2) Update FAO DAD-IS database for rabbit breeds/lines
3) Constitute a database of rabbit biotech resources
4) Database of papers /strains of rabbits used as animal model
5) Network on gene editing in rabbits (Crispr/CAS9)

Thank you! 谢谢

The rabbit in the genomics era: applications and perspectives in rabbit biology and breeding

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