THE ALFORT JUMPER RABBIT: REVIEW OF THE SCIENTIFIC WORKS CONDUCTED FROM 1935 TO 2019

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ABSTRACT

The "Alfort jumper rabbit" is an original rabbit known since 1935 and easily recognized by its particularly acrobatic locomotion behavior and constant ocular lesions. The specific feature of this rabbit is an irregularity in its way of moving. Sometimes, the hind legs will lift, lose contact with the ground and the animal moves in an upright position, with hind paws and tail above the head. A lot of studies have been done on this rabbit since 1935. The jumper rabbit shows retinal dysplasia and early-onset congenital cataracts resulting in glaucoma, which are responsible for its blindness. The 'jumper' character is the expression of a major recessive gene (s^{am}) and its hereditary transmission is in accordance with a Mendelian distribution. A genomic study, demonstrated that the mutation is located in the *RORB* gene and that in “jumper” rabbits the Dmrt3 spinal population of neurons is misplaced. The histological observations of brain have shown a severe hypoplasia and an immature aspect of the cerebellum in young rabbits. Nowadays, more than 270 frozen embryos are stored in the national cryobank. The researchers that are interested in the gene (s^{am}) have to submit their program research to a scientific committee.

Key words: Alfort jumper rabbit, Ophthalmic lesions, Locomotion, s^{am} gene, RORB

INTRODUCTION

The "Alfort jumper rabbit" is an original rabbit easily recognized by its particularly acrobatic locomotion behavior and constant ocular lesions (Letard, 1935, Letard, 1943, Boucher, 1997a,b David, 1999). Saltatorial locomotion is a type of gait based on hopping that in mammals can be found among others in lagomorphs. The molecular mechanisms that control and fine tune the formation of this type of gait are unknown. Here, we take advantage of one breed of domesticated rabbits that exhibits an abnormal locomotion behavior characterized by the loss of the typical jumping that characterizes wild-type rabbits. Strikingly, individuals from this breed frequently adopt a bipedal gait using their front legs. In 1991, after a period when the "Alfort jumper rabbit" was almost forgotten in the French Veterinary school of Maisons-Alfort, some breeders have taken interest in this rabbit. They have created a group to preserve these animals and to study this specific character in collaboration with researchers (Boucher 1991). The aim of this paper is to summarize the different data evidenced in the work of the last years on this specific "jumper" character.

History of the strain

Four different populations of jumper rabbits have already been registered. One was raised in England, but this population seems to be definitively lost (Robinson, 1958). Two other populations, one from the hospice of Marseille (France) and one from a natural park in Italy, have been reported previously (Arnold, 1991). The population that we are studying originated from a single female of the breed "Normande" which was first observed in 1935 at the veterinary clinic of Maisons-Alfort (France) and mated to be multiplied (Letard, 1935). Nevertheless, E. Letard, professor of animal science at the Veterinary School of Alfort, had to abandon his rabbit rearing

during the Second World War. When he came back, there was only one male left from which he again constituted a strain that he classified as ”very prosperous” (Letard, 1943). The descendants of this male were registered in 3 strains: a dwarf strain to decrease the cost of *in situ* preservation, a medium size strain originated from various breed crosses and a homogeneous strain derived from all absorption cross on the synthetic line INRA 1077. At this moment we just preserve the medium size breed to study the “s^{am}” allele. Genetic material of other breeds are now frozen in nitrogen.

Description of the jumper character

The specific feature of this rabbit is an irregularity in its way of moving. This abnormality of locomotion behavior is not always visible especially not when the rabbit is at rest, he adopts a normal attitude on its four paws. Even when passing over a short distance, less than a few meters, it moves on its four paws as its congeners. When the rabbit jumps, the two hind paws don't move simultaneously, but have a tendency to place themselves alternatively as the common walk observed on the majority of other mammals. On the other hand, if the rabbit wants to run on a longer distance in a faster pace or if someone tries to catch him, the hind legs will lift, lose contact with the ground and the animal moves in an upright position, hind paws and tail above the head as a human acrobat would do when walking on the hands. The animal can walk like this around its cage, then the hind paws lightly touches the ground and then the animal again gets up on its front paws (Audigier, 1999).

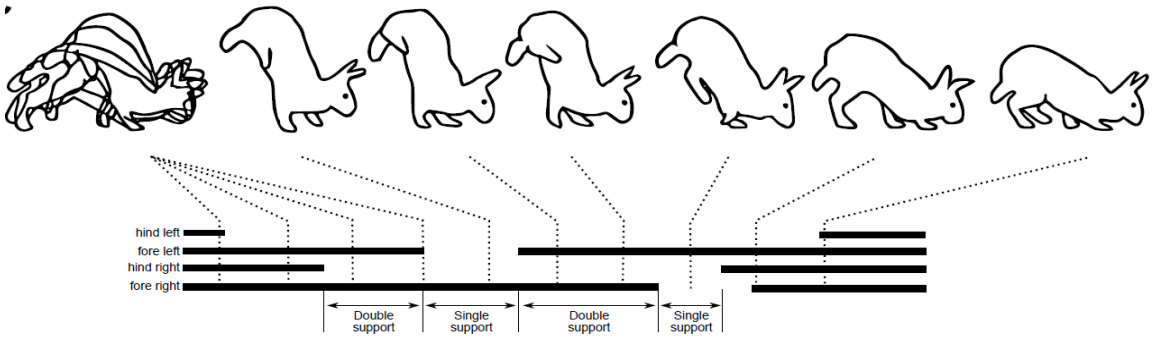

***Figure 1**: Representation of bimania in the jumping rabbit (Audigier, 1999)*

***Figure 2**: Young Alfort jumper rabbit during saltation*

Moreover, severe ocular lesions are always associated with the 'Jumper" character (Theret, 1961). The association of such ophthalmologic and locomotor abnormalities is most often lethal. The jumping rabbit is an exception in this respect. Theret (1961) was the first researcher to emphasize the interest of the “jumper" rabbit in order to study the hereditary anomalies of eyes (cataract) that was slightly binded with the "jumper" character. Thus, this rabbit was used in the Veterinary School of Alfort as model animal in order to study the evolution of cataract and to implement the techniques of ocular

microsurgery usable on pets. Since 1991, different types of ocular malformations have been observed: abnormal retina with bilateral papillary coloboma and a reduction of pupillary reflex only on the 'jumper" homozygous (s^{am} /s^{am}) animals; a bilateral cataract with luxation of crystalline lens, glaucoma, entropion and ectropion as well on homozygous and heterozygous (+ /s^{am}) animals. The present selection of the “jumper" rabbit strains shows a clear regression in the number of eyelids malformations and it has raised the age when the cataract occurs even though it develops when animal is 2 or 2.5 years old. But at this time, the jumper rabbit shows retinal dysplasia which are responsible for its blindness (Simon-Mennerat, 2003).

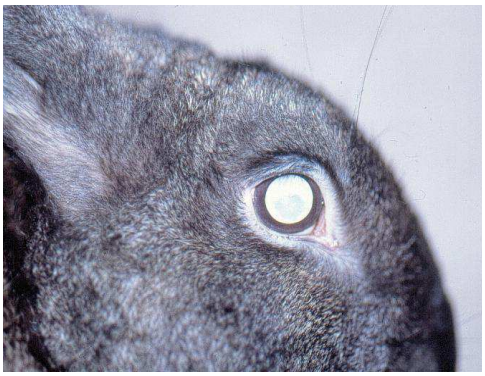

Figure 2*: Cataract with crystalline luxation and mydriasis (photo S. Boucher)*

Even though Letard (1943) only had one jumper rabbit buck in 1941 and about forty rabbits in 1943, he figured that the 'Jumper" character was the expression of a typical recessive major gene. Classical experiments of crossbreeding and adoption confirmed that the anomaly has nothing to do with learning by experiments (Letard, 1943; Boucher 1997 b). Robinson (1958) described a British strain with a locomotion behavior very similar to that of "Alfort jumper". Different crossbreeding experiments were designed to ascertain the genetic determinism of this character (Boucher *et al* 1996). The results confirmed that the 'jumper' character is the expression of a major gene (s^{am}) recessive in comparison with the wild gene (S^{am} +) whose heredity transmission is in accord with a Mendelian principle.
The karyotype analysis of the 'jumper' rabbits was performed in 1992 by Berland (Ecole Nationale Vétérinaire de Toulouse, France) (Boucher *et al*, 1996). The strip chromosome coloration technique was used and did not show any major anomalies on the chromosomes of these animals.
Recently, using a combination of experimental crosses and whole genome sequencing, we show that a single locus containing the ROR related orphan receptor Beta gene (*RORB*) explains the atypical gait of these rabbits (Carneiro *et al*. 2020 in preparation). We found that a splice-site mutation in an evolutionary conserved site of *RORB* results in several aberrant transcript isoforms incorporating intronic sequences. This mutation leads to a drastic reduction of RORB-positive neurons in the spinal cord, as well as defects in differentiation of the DMRT3-expressing population of interneurons, which are known to play an essential role in regulating gait across species (Andersson *et al*. 2012).

The examination of histological sections was performed on the brain and the eyes of the 'jumper' rabbit by Plassiart (Laboratoire d'Anatomie Pathologique Vétérinaire, Metz, France) and Breton (Ecole Nationale Vétérinaire de Nantes) (Boucher *et al* 1996). They have observed dysplasia or non-differentiated retina and cataracts with luxation on the eyes of the animals at different ages. In some cases, a prolapse of the optic nerve and a hypertrophy of the pigmentary epithelium of the retina were evidenced. Few lesions were observed on the brains of very young rabbits, with severe hypoplasia and an immature aspect of the cerebellum.

Preservation ex situ

Embryos freezing at low temperature allow, for a long time, the storage of genetic materials in liquid nitrogen (-196°C) with any decrease of the cellular viability (Joly *et al*, 2012). Homozygous (s^{am}/s^{am}) or heterozygous (+/s^{am}) animals were sampled and treated by superovulation methods used to enhance the production of freezable embryos per female. Then, they were mated with homozygous buck (s^{am}/ s^{am}). After the sacrifice of the females, embryos were collected at compacted morulae-blastocyst stage

(65- 72 hours post *coïtum*) by perfusing the genital tract. Classical slow-freezing procedure was carried out in a programmable freezer. The results showed that 90% of treated females produced embryos of a good quality (in average, 30.4 frozen embryos/donor female). These values are higher for the 'jumper' rabbit and one of the higher for all other populations treated (Joly *et al.,* 2012). The viability of these stored embryos were evaluated *in vivo* after thawing and transfer of 10 embryos in a pre-synchronized recipient. One-month later, 3 offspring (1 with a genotype s^{am} / s^{am} and 2 with a genotype +/ s^{am}) were born alive in normal condition.
Nowadays, more than 270 frozen embryos are stored in the national cryobank. The persons that are interested in the gene (s^{am}) have to submit their program research to a Scientific Committee. After an agreement by the commission, they can easily have access to the frozen embryos stored in the cryobank.

CONCLUSION

The "jumper" rabbit has been known since 1935 but the molecular mechanisms causing the locomotion and ophthalmic phenotypes are still unknown. Since 1935, many researchers including many veterinarians have contributed to a better knowledge of this animal and a better description of its phenotype. Scientific advances in recent years have finally revealed the gene involves and showed that ocular problems and locomotion are linked. This article has reviewed the work carried out from 1935 to 2019 on this amazing rabbit, the jumping rabbit, now preserved *ex situ* and made available to interested researchers.

ACKNOWLEDGEMENTS

Thanks to Gérard Chauvet, breeder, who has been voluntarily producing jumping rabbits for research.

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