The callipyge phenomenon, a genetic curiosity

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Because it defies the laws of Mendelian inheritance, the callipyge trait observed in certain sheep is of great interest due to its mode of transmission. Only heterozygous individuals carrying the mutation on the paternal allele display the characteristics associated with this phenotype: muscular hypertrophy. This phenomenon has been studied for many years in the Unit of Animal Genomics of GIGA at the University of Liege by Michel Georges' team. New results have been published in PLOS ONE.

The callipyge phenomenon is a mystery that has fascinated genetics experts. Observed for the first time in 1983 in the US, this phenotype can be found in sheep and is characterized by a muscular hypertrophy. Animals with the callipyge phenotype - which means "beautiful buttocks" in Greek - have an increased muscle mass of 30%! This phenomenon appears in both sexes when the lambs are around one month old and results in a larger proportion and greater diameter of fast-twitch muscle fibers. These fast-twitch muscle fibers have a higher level of contraction but a weak fatigue resistance, in contrast with slow-twitch muscle fibers which are mobilized for weak-level contractions but which are very fatigue resistant. "Callipyge sheep would probably be very good sprinters", says a smiling Haruko Takeda, a post-doctoral student in the Unit of Animal Genomics of GIGA at the University of Liege, directed by Professor . You might reasonably think that animals affected by this phenomenon represent an advantage for sheep breeders in view of the larger amounts of meat they offer. "Unfortunately, the meat from callipyge sheep is not tender and is therefore not a popular choice", explains Haruko Takeda. The callipyge phenomenon is therefore not interesting from an economic point of view even though it is a scientific curiosity.

From the phenotype to the genotype

At the beginning of the 1990s, a long and fruitful collaboration began. Michel Georges, who was in Genmark in the US at that time, was approached by Dr. Noelle Cockett of Utah State University who enlisted his help in finding the gene responsible for the callipyge phenotype. Since then, Michel Georges has returned to Belgium but the collaboration has continued to this day. The reason for this collaboration: identifying the genetic mechanisms behind the callipyge phenomenon is no mean feat. First of all, the mutation which is responsible is discretely located in a large non-coding section of the genome. This mutation is called CLPG and was independently highlighted in 2002 by an American team as well as Michel George's team. But, in addition to the difficulty of identifying this mutation, the callipyge phenomenon has a very singular particularity: its unique mode of heredity transmission. This is what makes it so interesting in the eyes of geneticists.

In order to properly understand this particularity, we first need to return to the common way genetic transmission takes place, known as the Mendelian laws of inheritance. We can greatly simplify Mendel's laws as follows: each individual possesses two versions or alleles of each gene: the maternal version and the paternal version. According to whether or not the parents are carriers of a gene mutation, four possible types of scenarios exist for their offspring. Imagine a gene "A" which we will call "a" in its mutated version. Four combinations (or genotypes) are possible: "AA", "Aa", "aA" or "aa". In "Aa" individuals, the mutated allele "a" is transmitted by the father; in "aA" individuals, the mutated allele has been transmitted by the mother. The mutation is therefore absent in individuals who are carriers of the "AA" genotype and present in the three other cases. If the mutation 'a' is dominant, the individuals of the "Aa", "aA" and "aa" genotypes will express the associated phenotype. If the mutation "a" is recessive, only the "aa" individuals will express the phenotype.
But genetics would be too simple if this law was always applied to the letter. The callipyge phenomenon follows its own rules and does not comply with the Mendelian mode of inheritance. In order for an animal to present with the muscular hypertrophy that characterizes this phenotype, it must be the carrier of a unique version of the mutated gene and this must come from the father. This mode of inheritance had never been observed before its discovery in 1996 and was given the name “polar overdominance”. This observation was published by Noelle Cockett and Michel Georges in the journal *Science*. Since then, experts think that this mode of inheritance could be much more frequent than was previously thought. It could also contribute to a predisposition to genetically complex common illnesses in humans.
When the alleles come into conflict

Haruko Takeda joined Michel Georges' team in 2002, and, for the last nine years, has been specifically concentrating on the study of the mechanisms underlying the polar overdominance of the callipyge phenotype. Why does an individual inheriting the mutation from the father express the phenotype while an individual inheriting the mutation from the mother does not? Why does an individual inheriting the mutation from his father and mother not present with the characteristics of the callipyge phenotype? These are the questions that scientists have been trying to answer for years. Discoveries in relation to this subject are fascinating and the mechanisms involved are astonishing. The researchers notably identified the involvement of an area of the genome subjected to what is called the "parental imprint". "The genes subjected to this imprint are genes of which only the paternal or maternal version is expressed", explains Haruko Takeda. "The CLPG mutation - which is responsible for the callipyge phenomenon - affects the expression of the two genes (DLK1 and PEG11) that code for proteins from the paternal chromosome and a large number of non-coding genes from the maternal chromosome", she continues. "Over time, we have shown that polar overdominance is in fact the reflection of a conflict between maternal and paternal alleles during which the micro-RNAs produced from the maternal allele target the coding genes for the proteins produced from the paternal allele". This is the main reason why the individuals which are carriers of two mutated CLPG alleles do not express the callipyge phenotype: the mutation situated on the paternal allele is neutralized by the excess of the micro-RNAs produced by the mutated maternal allele.
Getting to the bottom of the mystery

Haruko Takeda and her colleagues have recently published new results in the journal PLOS ONE (1). "We had already demonstrated that the expression of the DLK1 gene causes a muscular hypertrophy in transgenic mice. However, we did not yet know if the second gene (PEG11) affected by the CLPG mutation also played a role in the appearance of the phenotype", says the scientist. In order to verify that, the researchers created a line of transgenic mice that expressed the PEG11 protein in the skeletal muscles of the mice pups. "In this way, we were able to demonstrate, by means of measurements and histological analyses of the muscles, that these mice clearly presented a muscular hypertrophy", reveals Haruko Takeda. These results suggest that the PEG11 gene plays a non-negligible role in the callipyge phenotype observed in sheep. Moreover, later results that have not yet been published by the researchers, suggest that the two genes DLK1 and PEG11 could be acting in synergy with each other.

Despite decades of research and discoveries about the callipyge phenotype, the latter has still not revealed its secrets. "We would particularly like to understand which intermediary leads to the muscular hypertrophy through the expression of the DLK1 and PEG11 genes", continues Haruko Takeda. "But also, on a broader level, we would like to know at which point polar overdominance becomes a frequent genetic phenomenon, what its contribution to natural selection or the predisposition to disease in humans is". Can the callipyge phenomenon be classed as a scientific curiosity? Certainly, but it is a curiosity that could provide a lot of unexpected answers to genetic mysteries.

(1) Xuewen Xu, Fabien Ectors, Erica E. Davis, Dimitri Pirottin, Huijun Cheng, Frédéric Farnir, Tracy Hadfield, Noelle Cockett, Carole Charlier, Michel Georges, Haruko Takeda. Ectopic Expression of Retrotransposon-Derived PEG11/RTL1 Contributes to the Callipyge Muscular Hypertrophy. PLOS ONE.10.1371/journal.pone.0140594