A mouse model for polar overdominance?

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The callipyge mutation (CLPG) is responsible of a muscular hypertrophy phenotype in sheep and is characterized by a particular mode of inheritance, called polar overdominance, where only heterozygous individuals having received a paternal mutation exhibit the muscular hypertrophy.

The CLPG mutation has been mapped to the DLK1-GTL2 imprinted domain and is an A to G transition in a 12bp motif, conserved between Eutherian mammals and present in an intergenic region, 32kb 5' from the *GTL2* gene.

Expression studies performed on skeletal muscle from sheep of the four CLPG genotypes at different developmental stages, allowed us to propose the hypothesis that the mutation invalidates a regulatory element shared by genes belonging to the central part of the domain. This element is muscle-specific and is supposed to be requested for the post-natal repression of those genes. The muscular hypertrophy phenotype is due to the lack of repression of paternally expressed genes (DLK1 and/or PEG11) in this tissue. We recently demonstrated that the observed polar overdominance phenomenon is the result of a *trans*-inhibition of the paternally expressed genes mediated by the maternally expressed non-coding RNAs.

A mouse model, recapitulating this polar overdominance phenomenon is essential for the detailed analysis of its molecular basis. For that purpose, two transgenic lines have been produced by homologous recombination in ES cells. The first line corresponds to a knock-in of the point mutation (A>G) and the second is harbouring a deletion of the conserved 12 bp motif (Δ12).

A detailed spatio-temporal expression profile of the genes orthologous to the ones affected by the CLPG mutation in sheep is underway in mice from the four genotypes at the mutated locus, for both transgenic lines (A>G and Δ12).