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Accepted version

A novel homozygous nonsense mutation in *ITGB4* gene causes epidermolysis bullosa in Mouton Vendéen sheep

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Junctional Epidermolysis Bullosa (EB) is a severe genetic skin disorder in humans and animals where any mechanical trauma can cause painful blisters. In sheep, this recessive disease affecting limb extremities and mucous membranes causes perinatal death of affected lambs and was previously associated to mutation in *LAMC2* and *ITGB4* genes in German black-headed mutton and Spanish Churra sheep, respectively [1, 2]. Multiple observations of EB cases were recently reported in the French Mouton Vendéen meat sheep breed. Skin biopsies of 6 affected dead lambs and when available, blood samples from the parents (n = 7) and unaffected full-sib lambs (n = 4) were collected for genomic DNA extraction. Based on the hypothesis of a recessive transmission of a deleterious variant, we have performed an Illumina HiSeq paired-end WGS (ENA accession number PRJEB37460; BWA alignment, ≈10X coverage) of 2 unrelated EB-affected lambs (supposed homozygous carriers) and 1 unaffected full-sib (supposed heterozygous or non-carrier). The strategy focused on 13 candidate genes already associated with EB or skin fragility syndrome in several species, and mainly belonging to the collagen, laminin, integrin and keratin families. After GATK variant analysis of these 13 genes fitting with the mutation segregation hypothesis, we have identified a novel SNP (OAR11_v4.0, g.54799925G>A) in the exon 23 of the *ITGB4* gene of the integrin family whose variant allele causes a premature stop codon (p.Arg885*). By a specific RFLP assay (DdeI digestion, Figure

1), we have determined that all EB-affected lambs were homozygous for this variant allele, their parents were heterozygous and the full-sibs were either heterozygous or non-carrier, fitting well with a recessive mutation segregation (Figure 1). Through a large set of genotyping of renewal ewe lambs from the same annual cohort, the population allele frequency was estimated at 6.3% (Table 1). The same frequency was observed for service rams (5.2%) and adult ewes (6.0%) picked-up randomly in commercials flocks (Table 1). The discovery of a new mutation in ovine *ITGB4* enhances the role of this gene in EB etiology and is an important molecular tool to improve the selection scheme management of the Mouton Vendéen breed to limit the dissemination of this disease.

Acknowledgments

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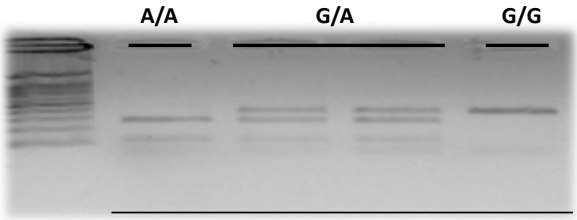
References

1. Mömke et al. (2011) PloS ONE 6, e18943
2. Suarez-Vega et al. (2015) PloS ONE 10, e0126416

Figure 1. Genotyping of EB cases and their relatives. (A) Specific RFLP results (DdeI digestion) for OAR11_v4.0, g.54799925G>A mutation in *ITGB4* for homozygous A/A case n°3, its heterozygous sire and dam (G/A) and non-carrier full-sib (G/G). (B) Genotyping results of the initial sampling from 6 cases (*whole-genome sequenced animals, NA not available).

A



B

	Affected lamb	Sire	Dam	Full-sib
Case 1	A/A*	NA	NA	NA
Case 2	A/A	NA	NA	NA
Case 3	A/A*	G/A	G/A	G/G*
Case 4	A/A	G/A	G/A	G/A
Case 5	A/A	G/A	G/A	G/G
Case 6	A/A	G/A	NA	G/A

50 Table 1. Genotyping of g.54799925G>A in *ITGB4* in the Mouton Vendéen population.

	Number of animals	Number of heterozygous carriers	Allele frequency
Renewal ewe lambs	1335	168	6.3%
Adults ewes	1683	203	6.0%
Service rams	1200	126	5.2%

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