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Study on a novel nonsense variant in *MTNR1A* identified in Vietnamese native buffalo using a knock-in wild-derived mouse model

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Abstract

Domestic buffaloes play a vital role in rural economies in many developing countries, including Vietnam. However, they suffer from low productivity, particularly in fertility and growth. We previously identified a nonsense variant in melatonin receptor 1A (*MTNR1A*) that could lead to the complete loss of its receptor functionality, specific to Vietnamese native buffalo. Melatonin and its receptors are known to play a role in regulating circadian rhythms, reproduction, and energy metabolism in various species, highlighting the importance of understanding the functional implications of this variant in buffaloes. In this study, we generated knock-in mice with this variant and analyzed its effects on growth, fertility, and behavior using a melatonin-proficient wild-derived mouse strain. Homozygous mice carrying the mutation were successfully created, and offspring with homozygous (KI/KI), heterozygous (KI/+), and wild-type (+/+) genotypes were used for comparative analyses. Our results revealed no significant differences in puberty onset, testis weight and histology, and sperm quality among KI/KI and KI/+ mice compared to +/+ mice. Interestingly, significant phenotypic changes were observed in body weight and behavior. Specifically, KI/KI male mice exhibited significantly increased body weight ($p < 0.05$), which can imply a beneficial trait in meat production. KI/KI mice displayed reduced locomotor activity and reduced anxiety-like behaviors in a novel environment ($p < 0.05$), suggesting a calmer temperament. These findings reveal the novel variant in *MTNR1A* as a promising genetic marker in breeding programs for improving productivity and manageability, while further studies are required to confirm the actual effects of this variant in buffaloes.

Keywords: Knock-in mice, melatonin receptor 1A, nonsense variants, Vietnamese native buffalo