LARGE OFFSPRING SYNDROME, A BOVINE MODEL FOR THE HUMAN LOSS-OF-IMPRINTING OVERGROWTH SYNDROME BECKWITH-WIEDEMANN

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ABSTRACT

Beckwith-Wiedemann syndrome (BWS) is a human loss-of-imprinting syndrome primarily characterized by macrosomia, macroglossia, and abdominal wall defects. BWS has been associated with misregulation of two clusters of imprinted genes. Children conceived with the use of assisted reproductive technologies (ART) appear to have an increased incidence of BWS. As in humans, ART can also induce a similar overgrowth syndrome in ruminants which is referred to as large offspring syndrome (LOS). The main goal of our study is to determine if LOS shows similar loss-of-imprinting at loci known to be misregulated in BWS. To test this, *Bos taurus indicus* × *Bos taurus taurus* F1 hybrids were generated by artificial insemination (AI; control) or by ART. Seven of the 27 conceptuses in the ART group were in the > 97th percentile body weight when compared to controls. Further, other characteristics reported in BWS were observed in the ART group, such as large tongue, umbilical hernia, and ear malformations. *KCNQ1OT1* (the most-often misregulated imprinted gene in BWS) was biallelically-expressed in various organs in two out of seven overgrown conceptuses from the ART group, but shows monoallelic expression in all tissues of the AI conceptuses. Furthermore, biallelic expression of *KCNQ1OT1* is associated with loss of methylation at the KvDMR1 on the maternal allele and with down-regulation of the maternally-expressed gene *CDKN1C*. In conclusion, our results show phenotypic and epigenetic similarities between LOS and BWS, and we propose the use of LOS as an animal model to investigate the etiology of BWS.