Brief Note

Exclusion of adrenoceptor alpha 2 variants in a horse insensitive to medetomidine

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Running title: Equine alpha 2 adrenoceptor genes

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Background: Patients may react in different ways to drugs and genetic factors have to be considered when observing variability in drug responses.[1] Drugs acting as agonists for the alpha 2 adrenoceptor (formerly called α_2 adrenergic receptor), such as xylazine, detomidine, medetomidine, or romifidine are regularly used for sedation, premedication and analgesia in veterinary medicine.[2,3] Three genes encode for separate subtypes of alpha 2 adrenoceptors, *ADRA2A*, *ADRA2B,* and *ADRA2C*.[4] Alpha 2 adrenoceptors modulate the regulation of blood pressure, renal function, insulin release, cognition, memory and behaviour.[5] *Adra2a* mutant mice (α_{2A}D79N) are resistant to sedation with dexmedetomidine.[6,7]

Own analysis: A 9-year old Swiss Warmblood horse was presented due to anorexia. Since the horse was highly aggressive, clinical examination was only deemed possible under general anaesthesia. Therefore, tiletamine-zolazepam (2mg/kg) and medetomidine (0.04 mg/kg) were administered intramuscularly by blowpipe darting. While the drug-related side effects such as sweating, polyuria, tremor and ataxia were observed, the sedative effect remained absent. Therefore 35 minutes later a second dart containing tiletamine-zolazepam (1 mg/kg) and medetomidine (0.04 mg/kg) was shot, again without noticeable sedative effects. We sequenced the genome of this horse at 28x coverage as described (study accession PRJEB14779, sample accession SAMEA104357351).[8] We called private variants with respect to 80 genomes from other horses of different horse breeds (Table S1). This analysis yielded 26,416 private variants, 222 of them predicted to be protein-changing (Table S2). During this analysis we recognized that *ADRA2A*, *ADRA2B* and *ADRA2C* contain gaps and/or are not correctly annotated in the current EquCab 2 assembly. Therefore, our automated bioinformatics pipeline for variant detection would not necessarily have detected all possible variants within these genes. Based on preliminary data from the ongoing efforts to produce an EquCab 3 assembly we designed PCR primers for the amplification of the entire *ADRA2A*, *ADRA2B* and *ADRA2C* genes (Table S3). We Sanger sequenced these genes from the medetomidine-resistant horse and a control horse and deposited curated reference sequences for these 3 genes in the European Nucleotide Archive (accessions LT935786 – LT935788). We did not detect any protein-changing variant in the medetomidine-resistant horse.

Comments: Coding variants in *ADRA2A*, *ADRA2B* and *ADRA2C* can be excluded for the observed insensitivity to medetomidine in a Swiss Warmblood horse. We provide new genomic reference sequences for these three genes.

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Supplementary data

Table S1. Accession numbers of horse genome sequence data.

Table S2. Private variants in the medetomidine-resistant Swiss Warmblood horse.

Table S3. Primer sequences for the amplification of the equine *ADRA2A*, *ADRA2B*, and *ADRA2C* genes.