Demographically-Based Evaluation of Genomic Regions Under Selection in Domestic Dogs

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Description of additional candidate genes

Brain function/behavior

The 27th region overlaps or is proximate to several genes including MARK3 (see below); BAG5, which interacts with Parkinson's disease-related genes LRRK2 [1] and Parkin [2]; and CKB, which shows increased transcription in the brain during development and co-expression with MBP in rats [3] (but also appears to play an important role in bone resorbtion in osteoclasts [4]). CUX2 (the only gene overlapping the 37th region as well as the peak in $CMS_{1\text{-}FDR}$ signal) is a key marker of neuronal fate during mammalian cortex development [5] whose knockout in mice shows deficits in working memory [6]. Mutations in ARID1B (the only gene in the 39th region, also overlapping with the $CMS_{1\text{-}FDR}$ peak) cause developmental delays, and the absence of 5th finger and toenail, suggesting a connection to both behavior and formation of the dewclaw [7]. The peak of the $CMS_{1\text{-}FDR}$ signal in the 42nd region overlaps with LRRN3, and is an autism candidate gene [8]. The only other gene (IMMP2L) found within this large 430kb region is at the opposite end and far from the peak signal. TMEM132D is a large gene overlapping the 45th region in its entirety and is the sole gene that intersects this region. Mutations in TMEM132D are associated with anxiety phenotypes [9], and it was identified in a selection scan as domestication candidate gene in cattle [10].

Two g-coupled protein receptors lie at either end and just outside of the 53rd region, which does not intersect directly with any gene annotations. However, GPR139 is proximate to the peak in $CMS_{1\text{-}FDR}$ signal, and is associated with inattention/ADHD [11]. SEMA3D is the only gene within the 69th region, and spans its entire length. This gene is involved in peripheral axon guidance during development [12], and mutations within it may be associated with schizophrenia [13]. MBD2 is the only gene of three (including POLI and STARD6) that overlaps with the peak in $CMS_{1\text{-}FDR}$ in the 88th region. It activates glucocorticoid receptor, in doing so modulates patental care in rats, and hippocampal expression of MBD2 increases in response to maternal licking [14]. Although a small gene of unknown function is contained within the 98th region, it is spanned in its entirety by PARK2. PARK2 produce the protein parkin, and mutations in PARK2 are associated with Parkinson's disease (http://omim.org/entry/602544).

Diet/lipid metabolism

ADRB2 (23rd) is an andrenergic receptor that regulates energy balance, and belongs to a class of receptors that stimulates lipid mobilization in adipose tissue. Mutations in and downregulation of ADRB2 are associated with obesity [15,16]. Melanin concentrating hormone receptor 2 (MCHR2, 95th) plays a role in behavioral aspects of food intake, and energy homeostasis [17], and may act antagonistically to MCHR1 so as to reduce food intake and diet-induced obesity [18]. However, MCHR2 was also recently identified as a candidate gene in a GWAS on age of menarche onset [19] so which phenotype might have been acted on by selection remains unclear. RAPH1 (99th) has been associated with both mood disorders [20] and bloodstream concentrations of butyrylcholinesterase [21], the activity of which influences lipid concentrations levels and obesity.

Supplementary References

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