ISSN 1819-7124, Neurochemical Journal, 2024, Vol. 18, No. 4, pp. 763–773. © Pleiades Publishing, Ltd., 2024.

EXPERIMENTAL ARTICLES

Selection Signal in C-Kit Ligand Gene Is Linked to Glucocorticoid-Regulated Neuroplasticity: A New View on Domestication Mechanisms

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Received June 4, 2024; revised June 11, 2024; accepted November 13, 2024

Abstract—Domestication profoundly shapes the evolutionary trajectories of both humans and animals. Despite significant scientific interest, the genetic underpinnings of domestication, particularly those related to behavior, remain elusive. This paradox may be reconciled by considering that behavior-associated genes have already been identified but categorized exclusively to other functional groups. Our investigation into this hypothesis utilized goat genome and human brain transcriptome data, focusing on the pigmentation gene *KITLG* due to its frequent association with domestication. Through analysis of interpopulation covariation between *KITLG* and candidate genes in the domestic goat genome (Capra hircus), we identified eight genes evolutionarily linked with *KITLG*. These genes were divided into three functional categories: (i) regulation of the glucocorticoid (GC) signal, (ii) initiation, and (iii) control of structural neuroplasticity. In the human brain, the regional expression patterns of the corresponding transcripts were complementary and most pronounced in areas associated with social interaction. We propose that a mutation in *KITLG* may decrease the activation threshold for GC-mediated neuroplasticity in these regions, enhancing the processing of social stimuli. The association of this allele with spotted coat patterns likely facilitated its selection, with the uniqueness of the pattern promoting selective social contacts. Consequently, the genomes of domesticated animals is, probably, more profoundly influenced by behavioral functions than previously believed. Further research could unveil novel functional attributes of the nervous systems in both animals and humans.

Keywords: glucocorticoid, neuroplasticity, domestication, limbic system, *KITLG*

DOI: 10.1134/S1819712424700417

INTRODUCTION

In the c-kit ligand gene (*KITLG*), signs of evolutionary selection are observed in almost all domesticated animal species. The gene product, a cytokine, acts through receptor tyrosine kinase to regulate the activation, proliferation, differentiation, and migration of various cell types, including melanocyte progenitors. A common mutation in a *KITLG* gene is associated with the emergence of color patterns characteristic of different species of domesticated animals, which is traditionally associated with its role in domestication [1]. But the value of such selection in the early stages of domestication is not obvious, and the assumption of its role in adaptation to solar radiation does not explain the selection of specific alleles exclusively in domesticated animals.

An allelic variant of a gene that provides an advantage in adaptation will thus be more common in the population. Therefore, the study of interpopulation allelic variation can serve as a tool for studying the mechanisms of adaptation. Goats are a good subject for studying genetic relationships that have arisen during domestication. This animal species was one of the first to be domesticated, but has retained a high genetic diversity because it has not been subjected to intensive artificial selection. The International Society for the Study and Protection of Genetic Resources has created a whole genome dataset of the domestic goat. It includes genotypes of more than 5,000 animals from nearly 200 populations distributed across the globe [2]. It includes both ancient and modern breeds. Thus, these data set can be used to search for allelic variation associated with the action of evolutionary selection.

The aim of the work was to investigate the hypothesis about the possible role *KITLG* in the formation of domesticated behavior. Three approaches were used for this. Firstly, genes regulating cerebral processes were identified in the genome of domestic goats, among which, based on the commonality of dispersion in the interpopulation distribution of alleles,

genes evolutionarily related to *KITLG* were found. Secondly, based on open data, the expression of mRNA of orthologs of the detected genes in the human brain was analyzed in order to identify the structures in which expression *KITLG* would be high and correlated with the expression of one or more of the noted genes. Thirdly, based on published works, the structural and functional characteristics of these genes and associated signaling pathways were analyzed.

MATERIALS AND METHODS

Analysis of genetic variation in the domestic goat. A combined genomic dataset from our previous work was used, which contains 38276 SNPs from 5176 animals of 188 domestic goat populations [3]. Genotyping of all populations was performed using the Goat 50K BeadChip (Illumina Inc., San Diego, CA, United States). Using PLINK 1.9, single nucleotide polymorphisms (SNPs) in the gene were searched for in chromosome coordinates obtained from the goat genome annotated in Ensembl (ARS1 assembly) *KITLG* and 30 genes potentially associated with behavior (Table 1). It included orthologs of human genes associated with the expression of personality traits, genes for receptors and transporters of serotonin and dopamine, oxytocin and its receptors, estrogen receptors, and steroid biosynthesis enzymes. Minor allele frequencies (MAFs) were calculated for the identified SNP markers in the world population as well as for each animal population of at least 10 individuals. The number of such populations was 178 with an average number of animals of 59 ± 2.2 ($M \pm SEM$). For all populations, the same allele was always considered minor based on its frequency in the world sample, even if it was predominant in a particular population. The mean (M), standard deviation (SD), standard error of the mean (SEM), skewness and kurtosis were calculated to assess the statistical distribution of the minor allele frequency of the studied genes (Table 1).

Analysis of mRNA expression in the human brain. mRNA expression data in the brains of six donors were provided by the Allen Human Brain Atlas [4]. As described, tissue samples for mRNA extraction were obtained by serial dissection. At the first stage, 0.5–1 cm thick brain slices were obtained, which were divided into blocks and stored at −80°C. Then, sections 25 μm thick were obtained on cryostats. Sections (every other one) were used for histological staining or further manual macrodissection and/or laser microdissection. Manual macrodissection was used for relatively large and easily identifiable brain structures, laser microdissection was used for smaller and irregularly shaped structures that required microscopic visualization. Regions sampled using macrodissection included the cerebral and cerebellar cortex, as well as large, well-shaped subcortical nuclei such as the caudate, putamen, and globus pallidus. Samples of other subcortical nuclei, in particular the amygdala, thalamus and hypothalamus, as well as cerebellar nuclei, were collected using laser microdissection. Neuroanatomical structures were identified based on histological Nissl or silver staining of the remaining sections. During macrodissection, 50 to 200 mg of tissue were excised depending on the region. The average size of cortical samples was 100 mg. Laser microdissection yielded samples with an average volume of 3.6 mm^2. In total, there were about 500 samples for each hemisphere of the brain. More details of these procedures, mRNA extraction methods, use of microarrays, expression data normalization, and donor data are available on the project website (Allen Human Brain Atlas, Documentation section). The ontology and nomenclature of microstructures was compiled in accordance with several sources and is described on the project website in the subsection "Ontology and Nomenclature." To obtain numerical data, on the main page of the brain atlas, we selected the option "Human brain," then "Microarray," entered the names of the genes of interest in the search window and for the search results, we selected the type of color scale of expression intensity with a resolution of microstructures, then selected the option "Download data." Expression values are presented as normalized values. To calculate paired parametric correlation coefficients between transcript levels, data from all donors were used simultaneously. Thus, intra- and inter-individual variation was taken into account.

Factor analysis was performed in SPSS Statistics v. 26. In the matrices used, the rows ("observations") corresponded to animal populations, and the columns ("variables") corresponded to minor allele frequencies. The Kaiser–Meyer–Olkin (KMO) test was used to check the adequacy of the sample. The number of factors to be identified was determined by an eigenvalue >1. When constructing factors, the principal component method with promax rotation and Kaiser normalization was used. The number of iterations during rotation was limited to 15. For identifying brain regions that synchronously express *KITLG* and other genes, we calculated the regression of their total dispersion factor for brain microstructures.

Structural and functional characteristics The *KITLG* genetic covariance products were compiled based on an analysis of literature data, including experimental and clinical studies. The biochemical class of molecules, participation in intracellular and intercellular signaling processes, and the relationship between genetic variation and the CNS phenotype were determined.

RESULTS

Identification of genes evolutionarily related to *KITLG* in a domestic goat. Table 2 shows the result of factor analysis of minor allele frequencies. *KITLG* and genes associated with behavioral regulation in the

Table 1. Characteristics of the distribution of minor allele frequencies

SNP	M	SD	SEM	Asymmetry	Excess
ABC_B1_SNP_1	0.48	0.23	0.02	–0.21	–0.43
ABC_B1_SNP_2	0.14	0.14	0.01	1.33	1.42
ANKK1	0.24	0.17	0.01	0.74	0.03
APOE_1	0.39	0.23	0.02	0.18	–0.71
APOE_2	0.31	0.19	0.01	0.62	0.30
BDNF	0.16	0.14	0.01	1.23	1.83
CDH13_11	0.46	0.18	0.01	0.09	–0.11
CDH13_12	0.23	0.19	0.01	1,12	1.15
CDH13_13	0.40	0.22	0.02	0.14	–0.60
CNR1_1	0.21	0.23	0.02	0.96	–0.23
CNR1_2	0.33	0.19	0.01	0.62	–0.06
COMT_1	0.22	0.18	0.01	1.07	1.19
COMT_2	0.42	0.26	0.02	0.26	–0.87
CYP11A1	0.22	0.22	0.02	1.02	0,00
CYP17A1A_SNP_1	0.35	0.35	0.03	0.49	–1.25
CYP17A1A_SNP_2	0.33	0.33	0.02	0.63	–1.00
CYP19A1	0.35	0.19	0.01	0.59	0.20
CYP1A1	0.44	0.19	0.01	0.31	–0.32
CYP26B1_SNP_1	0.24	0.19	0.01	0.62	–0.20
CYP26B1_SNP_2	0.49	0.24	0.02	–0.01	–0.66
CYP26B1_SNP_3	0.34	0.23	0.02	0.62	–0.29
DGKH_1	0.39	0.21	0.02	0.01	–0.47
DGKH_2	0.46	0.25	0.02	0.18	–0.85
DGKH_3	0.49	0.22	0.02	0.25	–0.27
DRD2_1	0.43	0.19	0.01	0.19	–0.35
DRD2_2	0.50	0.17	0.01	–0.10	–0.08
E2R_1	0.43	0.30	0.02	0.66	–0.82
E2R_2	0.32	0.24	0.02	0.66	–0.39
E2R_3	0.43	0.30	0.02	0.47	–0.98
E2R_4	0.48	0.28	0.02	–0.16	–1.13
E2R_5	0.41	0.29	0.02	0.09	–1.28
FAAH_1	0.43	0.24	0.02	0.25	–0.79
FAAH_2	0.20	0.19	0.01	0.95	–0.18
GABRA2_1	0.44	0.26	0.02	0.12	–0.95
GABRA2_2	0.42	0.18	0.01	–0.10	0.25
HSD11B1_1	0.48	0.20	0.02	–0.42	–0.50
HSD11B1_2	0.35	0.26	0.02	0.18	–0.95
HTR2A	0.44	0.26	0.02	0.22	–0.67
KITLG	***0.23***	***0.27***	***0.02***	*1.06*	*0.03*
LEP_1	0.41	0.21	0.02	0.39	–0.11
LEP_2	0.12	0.16	0.01	1.95	4.13
NPY	0.46	0.21	0.02	–0.02	–0.44
OXT_1	0.40	0.21	0.02	0.31	–0.45
OXT_2	0.36	0.19	0.01	0.23	–0.11
OXTR_1	0.43	0.25	0.02	0.25	–0.78

Table 1. (Contd.)

SNP	M	SD	SEM	Asymmetry	Excess
OXTR_2	0.37	0.19	0.01	0.45	0.12
P2RX7_1	0.22	0.18	0.01	0.86	–0.05
P2RX7_2	0.40	0.21	0.02	–0.08	–0.17
PER3	0.06	0.09	0.01	3.11	15.04
SLC6A4	0.34	0.17	0.01	0.37	0.42

world domestic goat populations. A total of 12 factors were identified, explaining 71% of the total variance. Minor allele frequency *KITLG* was included in the first factor, explaining 15% of the total variance, which indicates a significant proportion of the total variability associated with *KITLG*. When this variable was excluded, the matrix ceased to be positively definite. Thus, MAF *KITLG* determined the structure of the factor matrix and the very possibility of its construction. This confirms the assumption that the role *KITLG* in the evolution of domesticated animals could be associated with the regulation of behavior. In addition to *KITLG*, the first factor included the allele frequencies of 8 genes: *CYP11A1* and *HSD11B1*, genes of enzymes of synthesis and local transformation of glucocorticoids; genes *CNR1* and *FAAH*, endocannabinoid receptor and its ligand degradation enzyme; genes *DGKH* and *P2RX7*, diacylglycerol and purine receptor kinases that regulate the activities of intracellular Ca^{++}-dependent signaling pathways; gene *GABRA2*, GABA receptor subunits, as well as the gene *CDH13*, T-cadherin, which, like *KITLG*, is a trophic factor and regulator of chemotaxis in the central nervous system.

Analysis of expression of *KITLG* and evolutionarily associated genes in the human brain. In the human brain (Allen atlas), the expression of the 8 genes noted above and *KITLG* had a complementary regional profile, unidirectional with *CNR1*, *CDH13*, *DGKH*, *GABRA2*, *HSD11B1*, and multidirectional with *P2RX7*, *FAAH*, *CYP11A* (Table 3 and 4). According to the correlation module, *HSD11B1*, *DGKH* and *FAAH* were associated to the greatest extent with *KITLG* expression (Table 4). Figure 1 shows the distribution of the latent variable of the commonality of expression variance of the three specified genes in 407 microstructures. It is clear that it deviates from random: in the region of high values, two inflection points stand out (0.60 and 0.95), to the left of which the slope of the distribution function increases – that is, the value of the factor in these structures higher than would be expected from its distribution. The number of structures with a factor value greater than 0.95 was 23 (Table 5). According to these data, the highest synchronous expression of these genes was observed in the cingulate and paraterminal gyri, parahippocampal gyrus, insular cortex, anterior frontotemporal cortical regions of the limbic system, in the lateral and basolateral nuclei of the amygdala in the caudal subgroup of the intralaminar group of nuclei of the thalamus, amygdalohippocampal transition zone, and field CA1 of the hippocampus. Minimal expression was observed in the lower diencephalon, facial nerve nuclei, white matter, and the midbrain as a whole. In the dentate gyrus, the values of the total variance factor were also low: –0.98 on the right and –0.86 on the left.

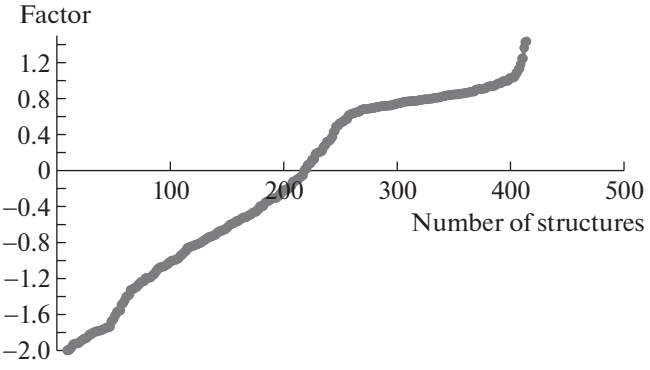

Fig. 1. Distribution of the total dispersion factor of mRNA expression levels of genes *KITLG*, *FAAH*, *11BHSD1*, and *DGKH* in the microstructures of the human brain

Functional characteristic of genetic covariance of *KITLG*. Table 6 shows the structural and functional characteristics of the products of the studied genes that revealed an association with *KITLG*.

DISCUSSION

We identified genes potentially involved in the behavior evolution during domestication, as well as brain regions where synchronous expression of their corresponding transcripts was observed. Of greatest interest is the joint functional activity of these genes, which contributed to interspecies behavioral adaptation. Gene *KITLG* and all 8 genes associated with it were found to be linked to neuroplasticity processes—which is natural, since any gene expressed in the nervous system is involved in one way or another in neuroplasticity—that is, in adaptation to the external and internal environment at the level of nervous tissue. The association of the noted genes with neuroplasti-

Table 2. Factor analysis of minor allele frequencies of behavioral genes and *KITLG* in goat populations (factor loadings are given)

	Factor											
	I	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**	**X**	**XI**	**XII**
	% explained dispersion											
	15.2	14.3	6.3	4.4	4.2	4.1	3.3	3.2	3.1	3.1	2.9	2.8
KITLG	**0.91**	0.15	−0.07	−0.20	0.01	−0.16	−0.05	0.01	0.08	−0.02	0.09	−0.05
CNR1_1	**0.84**	−0.17	0.07	−0.02	0.13	0.13	0.02	−0.12	−0.05	−0.05	0.19	−0.02
FAAH_2	**0.83**	−0.02	0.06	0.07	0.30	−0.21	0.03	0.20	0.10	−0.21	−0.10	−0.14
DGKH_2	**0.75**	−0.08	−0.02	−0.27	0.11	−0.09	−0.03	0.09	0.12	0.01	−0.24	0.02
CYP11B1_2	**−0.69**	−0.46	−0.09	0.03	0.39	−0.11	−0.05	−0.14	0.02	0.06	−0.01	−0.10
CYP26B1	**−0.64**	−0.09	−0.03	0.06	−0.31	−0.17	−0.15	0.19	−0.09	0.33	0.01	0.09
P2RX7_1	**0.62**	−0.27	−0.09	0.13	−0.17	0.33	−0.02	0.12	0.23	0.06	0.14	−0.08
HSD11B1_1	**−0.57**	−0.18	0.03	−0.02	−0.09	−0.11	0.00	0.40	0.20	0.25	−0.08	0.14
GABRA2	**−0.55**	0.30	0.00	0.28	0.16	0.02	0.05	0.08	0.38	0.05	−0.05	−0.02
CDH13_12	**0.53**	0.00	0.00	0.38	0.21	−0.04	−0.09	−0.03	−0.14	0.05	−0.04	0.02
DRD2_2	−0.18	**−0.79**	0.06	−0.30	0.30	0.03	0.08	0.20	0.10	−0.02	0.12	0.10
LEP_2	−0.08	**0.76**	−0.01	−0.17	0.14	−0.21	−0.13	0.20	0.10	0.06	0.13	−0.05
COMT_2	0.35	**0.73**	−0.02	0.01	0.11	−0.07	0.06	0.02	0.02	0.21	0.05	0.21
PER3	0.13	**0.64**	0.04	−0.19	−0.17	0.08	−0.09	−0.09	0.16	0.18	−0.02	−0.17
ABC_B1_SNP_1	0.18	**−0.58**	−0.07	−0.08	−0.05	−0.22	−0.04	−0.02	−0.06	0.19	−0.13	−0.01
APOE_1	−0.53	**0.54**	0.03	−0.06	−0.11	0.00	0.14	−0.08	−0.16	0.11	−0.05	−0.13
COMT_1	−0.26	**0.48**	0.05	0.10	0.22	0.09	0.10	0.06	−0.17	0.21	0.03	0.31
CYP17A1A_2	−0.08	**0.43**	−0.18	0.00	0.34	0.17	−0.18	0.32	−0.23	−0.28	−0.30	0.06
E2R_4	0.03	−0.01	**0.93**	0.05	0.01	−0.13	0.23	0.00	−0.08	0.01	−0.04	−0.04
E2R_1	0.00	−0.03	**−0.92**	−0.09	−0.07	−0.03	0.00	−0.04	0.07	−0.12	−0.03	0.28
E2R_3	−0.01	−0.04	**−0.88**	−0.02	0.04	0.09	0.19	−0.02	−0.08	−0.04	0.00	0.14
E2R_5	−0.03	−0.08	**0.62**	−0.04	0.06	0.05	−0.53	−0.08	−0.05	0.01	−0.06	0.07
SLC6A4	−0.28	−0.03	0.04	**0.88**	0.26	0.44	−0.02	0.06	0.11	0.01	−0.06	−0.12
FAAH_1	−0.01	−0.05	0.08	**0.78**	0.17	−0.26	0.12	0.01	0.10	−0.22	0.11	0.05
DGKH_3	−0.28	0.04	−0.05	**0.53**	−0.41	−0.02	−0.02	−0.13	−0.02	−0.26	0.06	0.22
HSD11B1_2	0.32	−0.25	−0.03	**0.35**	−0.18	−0.29	0.03	0.16	−0.08	−0.07	−0.27	−0.07
ABC_B1_2	0.24	0.02	0.06	0.28	**0.84**	0.00	−0.15	0.03	0.02	−0.26	0.03	0.00
HTR2A	−0.04	0.35	−0.07	0.16	**0.49**	−0.14	−0.03	−0.17	0.38	0.11	0.01	−0.06
DRD2_1	−0.11	−0.02	0.25	−0.17	**−0.34**	0.22	0.28	0.02	0.13	−0.16	−0.13	0.19
ANKK1	−0.04	0.16	−0.03	−0.29	**0.33**	0.03	−0.03	−0.28	0.30	0.03	0.00	0.04
P2RX7_2	0.26	−0.10	−0.10	0.01	−0.08	**0.78**	−0.18	0.10	−0.07	0.15	0.23	0.04
APOE_2	−0.22	0.13	−0.06	0.08	0.05	**0.77**	0.04	0.00	0.04	0.01	0.00	−0.16
OXTR_1	−0.03	−0.06	0.09	0.12	−0.15	−0.02	**0.93**	−0.03	−0.08	0.02	0.05	−0.25
E2R_2	0.04	0.11	0.45	0.11	0.10	0.13	**−0.76**	0.00	0.10	0.06	−0.01	0.05
OXTR_2	−0.03	−0.07	0.07	0.13	0.30	0.10	**0.33**	−0.03	−0.31	0.21	0.09	−0.07
CDH13_9	−0.10	0.00	0.00	−0.04	−0.02	−0.06	0.04	**−0.93**	−0.04	−0.02	0.16	0.25
GABA2	0.00	0.19	0.02	0.00	−0.02	0.02	0.08	**0.64**	**0.52**	−0.11	0.27	−0.06
BDNF	0.16	0.03	−0.03	0.12	0.03	0.02	−0.10	0.18	**0.98**	0.18	0.27	0.13
NPY	0.38	−0.11	−0.03	0.18	0.27	−0.08	0.07	0.00	−0.24	**−0.90**	0.21	0.08
CYP11B1_1	0.30	0.26	0.10	−0.27	−0.02	0.17	0.09	0.02	−0.07	**0.43**	0.03	−0.03

Table 2. (Contd.)

	Factor											
	I	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**	**X**	**XI**	**XII**
	% explained dispersion											
	15.2	14.3	6.3	4.4	4.2	4.1	3.3	3.2	3.1	3.1	2.9	2.8
CNR1_2	0.34	–0.10	0.08	0.33	0.01	–0.17	0.13	–0.14	0.39	**0.41**	–0.09	0.15
DGKH_1	0.13	0.06	–0.03	0.04	0.04	0.16	0.07	–0.08	0.36	–0.18	**0.93**	0.07
LEP_1	–0.37	0.12	0.05	–0.04	–0.11	–0.34	–0.05	0.02	–0.13	–0.21	**0.50**	–0.18
OXT_2	–0.10	–0.05	–0.35	0.00	–0.08	–0.07	–0.24	–0.22	0.17	–0.02	0.04	**0.77**
OXT_1	–0.06	–0.07	0.48	–0.09	0.04	–0.12	–0.16	–0.12	0.04	–0.23	0.04	**0.54**

The Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy was 0.73, and the Bartlett's test of sphericity was 4464 ($p < 0.001$)

Table 3. Correlations of normalized gene expression values in the human brain ($n = 417$, ** $p < 0.01$)

	KITLG	*GABRA2*	*CYP11A*	*HSD11B*	*CNR1*	*DGKH*	*P2RX7*	*FAAH*	*CYP11B*	*CDH13*
KITLG	1.00	0.375**	–0.227**	0.483**	0.068**	0.317**	–0.048**	–0.265**	00.00	0.328**
GABRA2	0.375**	1.00	–0.237**	0.657**	0.512**	0.277**	–0.078**	–0.210**	0.01	0.452**
CYP11A	–0.227**	–0.237**	1.00	–0.255**	–0.391**	–0.168**	0.100**	0.173**	–0.126**	–0.112**
HSD11B	0.483**	0.657**	–0.255**	1.00	0.352**	0.033*	0.124**	–0.134**	–0.120**	0.698**
CNR1	0.068**	0.512**	–0.391**	0.352**	1.00	0.209**	–0.207**	–0.127**	0.079**	0.077**
DGKH	0.317**	0.277**	–0.168**	0.033*	0.209**	1.00	–0.300**	–0.119**	0.078**	–0.308**
P2RX7	–0.048**	–0.078**	0.100**	0.124**	–0.207**	–0.300**	1.00	0.569**	–0.087**	0.386**
FAAH	–0.265**	–0.210**	0.173**	–0.134**	–0.127**	–0.119**	0.569**	1.00	–0.045**	0.02
CDH13	0.328**	0.452**	–0.112**	0.698**	0.077**	–0.308**	0.386**	0.02	–0.114**	1.00

city was pronounced and was noted in other studies as their key characteristic. The functions of these genes, critical for the implementation of neuroplasticity, allow us to classify them into three categories of processes in relation to it:

(1) Initiation and implementation: *KITLG*, *CDH13*, *P2RX7*, and *DGKH*.

(2) Glucocorticoid-dependent regulation: *HSD11B1* and *CYP11A1*.

(3) Control and inhibition: *CNR1*, *FAAH*, and *GABRA2*.

The association between *KITLG* and *HSD11B1* was the most expressed of all gene combinations both at the level of genomic covariance and as a complementary expression profile in the human brain. *KITLG* may mediate the effect of GC on neuroplasticity processes, since it contains a glucocorticoid-responsive element (GRE). Binding of GRE to the nuclear GC receptor causes inhibition of expression *KITLG* [21]. Based on this, it could be hypothesized that the mutation in *KITLG* affected the GRE site, weakening the control of *KITLG* expression and thereby facilitating the implementation of neuroplasticity processes. However, in the human limbic system *KITLG* and *11HSDB1* were expressed synchronously (Table 4). This suggests that their effects have the same direction. Experimental data allow us to identify such a mechanism in the hippocampus, where glucocorticoids are central regulators of neuroplasticity [22]. The *KITLG* promoter also contains the NfKB binding site. Simultaneous binding of NfKB and GRE causes a transient increase in *KITLG* expression, preceding inhibition [21]. Activation of NFkB by cytokines has traditionally been associated with inflammation. However, in the hippocampus, interleukin 1β (IL1β) is secreted constitutively by neurons [23]. In the dorsal hippocampus, acute stress induces a rapid release of IL1β that is mediated by *P2RX7* [24]. Interestingly, *KITLG* functions in embryogenesis, during blastocyst implantation into the endometrium, are also related to punctate remodeling of the extracellular matrix with IL1β expression [21].

The signaling pathway common to the 8 genes studied and *KITLG* is the *KITLG*-activated phosphatidyl inositol signaling pathway. Presence of glucocorticoid-responsive elements in promoter regions of *KITLG* and *CDH13*, which jointly regulate focal adhe-

Table 4. Regional expression levels in the human brain (normalized values). In the color gradient, red corresponds to high expression values. The bottom line shows the correlation coefficients (for all, $p < 0.01$)

Structure_name	*KITLG*	*GABRA2*	*CDH13*	*HSD11B*	*CNR1*	*DGKH*	*P2RX7*	*FAAH*	*CYP11A*
Dorsal thalamus	1.73	−0.74	0.01	−0.31	−2.32	0.98	0.26	0.08	0.54
Occipital lobe	0.63	0.32	0.46	0.43	−0.02	−0.25	0.20	−0.34	−0.71
Parietal lobe	0.56	0.39	0.66	0.67	0.18	−0.25	0.13	−0.34	−0.44
Frontal lobe	0.52	0.44	0.80	0.83	0.40	−0.19	0.09	−0.23	−0.44
Cingulate gyrus	0.44	0.56	0.77	0.85	0.51	−0.11	0.17	−0.22	−0.24
Amygdala	0.42	1.64	0.12	0.74	0.72	0.18	−0.36	−0.03	0.33
Parahippocampal gyrus	0.38	0.72	0.45	0.80	0.43	0.28	0.04	−0.08	−0.25
Epithalamus	0.37	−0.83	−1.39	−1.74	−1.23	−1.39	−0.77	−0.67	1.30
Temporal lobe	0.37	0.52	0.66	0.82	0.38	−0.15	0.11	−0.30	−0.54
Insula	0.27	0.63	0.94	0.86	0.52	−0.01	0.11	−0.27	−0.52
Claustrum	0.05	1.35	−0.08	0.86	−0.05	1.03	1.11	0.03	−0.23
Hippocampal formation	−0.15	1.15	−0.55	0.15	0.56	1.04	−0.99	0.14	0.09
Striatum	−0.24	0.85	−1.10	−0.25	0.86	2.11	−0.36	0.18	0.30
Sulci & spaces	−0.39	−5.80	−3.47	−2.00	−3.57	−1.95	−2.79	1.57	2.41
Cerebellar nuclei	−0.46	−1.55	−0.26	−1.39	−0.60	−1.06	1.15	0.68	0.74
Basal forebrain	−0.51	0.81	−0.23	−0.38	0.24	0.17	−0.12	0.58	0.49
Cerebellar cortex	−0.56	−1.26	−2.23	−1.52	0.66	0.78	−1.21	−0.42	−0.62
Basal part of pons	−0.81	−1.67	−1.11	−0.38	−3.12	−0.75	−0.28	−0.20	2.07
Myelencephalon	−0.83	−0.99	−0.05	−0.79	−0.75	−0.89	0.54	0.88	1.36
Ventral thalamus	−0.83	−1.22	1.08	−0.83	−0.95	−0.81	2.17	2.33	0.56
Hypothalamus	−0.88	0.17	−0.05	−0.58	−0.16	−0.61	−1.03	−0.43	0.08
Mesencephalon	−0.99	−1.02	−0.08	−0.98	−0.51	−0.46	0.25	0.33	0.80
Pontine tegmentum	−1.30	−0.76	−0.27	−1.02	−0.54	−1.01	0.41	0.40	1.01
White matter	−1.67	−1.78	−0.91	−2.36	−2.31	−1.88	3.46	3.33	−0.75
Globus pallidus	−2.06	−0.71	−0.34	−1.09	−0.97	−1.22	2.25	1.13	0.34
Subthalamus	−2.16	−1.78	0.06	−0.62	0.68	−1.51	1.28	1.57	0.40
R	***1***	***0.39***	***0.23***	***0.58***	***0.14***	***0.53***	***−0.40***	***−0.61***	***−0.23***

sion and chemotaxis, as well as the links of these genes with enzymes that enhance the intracellular glucocorticoid signal (*CYP11A1*, *HSD11B1*), indicates that GCs act as regulators of *KITLG*-mediated neuroplasticity, which is, probably, associated with the reorganization of neural networks.

Thus, the data of the present work indicate a profound role of glucocorticoids and *KITLG* in domestication suggesting that a mutation in the *KITLG* gene led to a change in glucocorticoid control over neuroplasticity processes in brain areas associated with social interaction, thereby increasing its effectiveness. Spotting, also a result of mutation in *KITLG*, could have become a catalyst for domestication, since it allowed individuals of different species to easily distinguish each other and thus interact long-term and selectively.

The connection discovered between *KITLG*, a gene initially associated with pigmentation, and genes regulating neuroplasticity indicates that the genome of domesticated animals may be more specialized in regulating behavioral processes than previously was shown. In fact, even a minimal link between a gene and behavior could determine its further selection if the gene polymorphism also had a phenotypic manifestation detectable by humans. Thus, during the process of domestication, the association of many genes with behavior may have been strengthened as a result of the selection of new and previously existing alleles,

Table 5. Structures with the highest values of the total dispersion factor of mRNA expression of the genes *KITLG*, *FAAH*, *11BHSD1*, *DGKH* in the human brain

Microstructure	Normalized common variance for expression values *KITLG*, *FAAH*, *11BHSD1*, *DGKH*
Parolfactory gyri, right	1.435756
Lateral nucleus, right	1.42779
Frontal pole, right, medial aspect	1.363383
Frontal pole, left, medial aspect	1.245791
Frontal pole, right, inferior aspect	1.245178
Temporal pole, right, superior aspect	1.183644
Basolateral nucleus, left	1.135082
Frontal pole, right, superior aspect	1.12694
Superior rostral gyrus, right	1.091031
Amygdalohippocampal transition zone, right	1.082773
Lateral nucleus, left	1.054398
Long insular gyrus, right	1.034494
Basomedial nucleus, left	1.033235
Medial orbital gyrus, right	1.032336
Superior frontal gyrus, right, medial bank of gyrus	1.029286
Inferior rostral gyrus, right	1.023999
Inferior frontal gyrus, opercular part, left	0.999864
Superior rostral gyrus, left	0.996167
Posterior orbital gyrus, right	0.995277
Inferior frontal gyrus, opercular part, right	0.994522
Temporal pole, right, medial aspect	0.993474
Temporal pole, left, superior aspect	0.991006
Parolfactory gyri, left	0.974587
Occipital pole, left, lateral aspect	0.970754
Paraterminal gyrus, right	0.968393
Supramarginal gyrus, right, superior bank of gyrus	0.967676
Basolateral nucleus, right	0.960092
Cingulate gyrus, frontal part, left, superior bank of gyrus	0.952045

while in other species it was less significant and, perhaps, not described.

CONCLUSIONS

The links identified suggest that *KITLG* is a plagiotropic gene that links animal coloration and neurochemical regulation of neuroplasticity by glucocorticoid hormones in the limbic system, particularly in areas of the brain involved in regulation of social behavior. Thus, a new mechanism of domestication can be proposed, and new related features of the functioning of the nervous system of animals and humans can be revealed. The findings also suggest that the genome of domesticated animals may be more specialized for social behavior than previously thought.

FUNDING

This work was supported by the Russian Science Foundation, project no. 22-76-10053.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval. This article does not contain any studies using animals as subjects.

Informed consent. This article does not contain any studies involving human subjects.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Table 6. Structural and functional characteristics of *KITLG* and associated genes

Gene	Product	Biochemical functions	Signaling pathways, intercellular interactions. Effects of genetic variation on CNS function (if described)
KITLG	KIT ligand, stem cell factor (SCF), c-kit ligand	Cytokine, c-kit agonist. receptor tyrosine kinase. Factor of survival and positive chemotaxis.	A signal of positive chemotaxis, differentiation and activation. In culture, it supports the survival of rat and chicken neurons that express the c-kit receptor [5]. In the brain, the highest levels of *KITLG* mRNA are found in the thalamus, neocortex and cerebellum [6]. In addition, c-kit is expressed in neuroproliferative zones [7]. The *KITLG* receptor is a tyrosine kinase that activates the regulatory subunit of phosphatidylinositol 3-kinase, a key mediator of stress-induced plasticity processes in the hippocampus, including neurogenesis and synaptogenesis [8, 9]. Stimulates the migration of neuronal progenitor cells into the area of action of the stress factor [10], activates microglia, stimulates the release of vesicles.
CDH13	T-cadherin	An atypical member of the cadherin family, it does not contain a cytoplasmic domain.	Two fatty acids in the hydrophobic phosphatidylinositol group anchor T-cadherin to the cell membrane. It acts as a signaling receptor involved in environmental sensing and regulation of cell motility, proliferation and phenotype. T-cadherin expression levels correlate with cell proliferative potential. T-cadherin acts as a negative chemotiaxis signal. Acts as a negative regulator of axonal growth during neuronal differentiation [11]. Genetic variation has been linked to autism and attention deficit/hyperactivity disorder [12]. It is localized in inhibitory presynaptic endings where it modulates GABA transmission. In mice, during embryogenesis, it regulates the migration of 5-HT neurons from the raphe nuclei to the prefrontal cortex, and gene knockout enhances serotonin innervation in the prefrontal cortex. [11], which potentially links the role of the gene with the formation of selectivity of serotonin effects in the prefrontal cortex. T-cadherin is also specifically expressed in Golgi cells in the cerebellar cortex, and inhibition of its expression in the cerebellum does not affect motor functions but disrupts cognitive functions and increases the frequency of social interactions, but at the same time leads to a loss of selectivity of the latter [11]. The T-cadherin gene contains a GC-responsive element that inhibits its expression.
CYP11B1	11β-hydroxylase	Adds an OH group to 11-deoxycortisol and 11-deoxycorticosterone, converting them into cortisol and corticosterone.	Catalyzes the final reaction of glucocorticoid biosynthesis, key regulators of hippocampal neuroplasticity [13]. Genetic variation has been associated with autism spectrum traits and Asperger syndrome [12].

Table 6. (Contd.)

Gene	Product	Biochemical functions	Signaling pathways, intercellular interactions. Effects of genetic variation on CNS function (if described)
11β-HSD	11β-hydroxysteroid dehydrogenase type 1	Locally restores cortisol from corticosterone	Reconstituting cortisol from corticosterone amplifies local glucocorticoid action in most mammals, for which cortisol serves as the primary glucocorticoid hormone [14]. In the brain, it is expressed by neurons and microglia, participating in the regulation of stress response and neuroinflammatory reactions. Since the enzyme helps accelerate the action of glucocorticoids, it may contribute to both more effective termination of the neuroinflammatory response under the influence of glucocorticoids and the damaging effects of these hormones with prolonged exposure to them. Mediates differential regulation of memory depending on the stressor. The activity of the enzyme is enhanced by epileptogenesis [15].
DGKH	diacylglycerol kinase eta	Phosphorylates diacylglycerol (DAG) to form d-phosphatidic acid	Regulator of intracellular Ca-associated signaling pathways. It interrupts the signaling of DAG, which together with inositol triphosphate (IP3) diacylglycerides are formed from membrane phospholipids as a result of phospholipase C activity. IP3 diffuses into the cell where it causes the release of calcium from the endoplasmic reticulin, DAG remains bound to the membrane due to its hydrophobicity, but also potentiates calcium-dependent processes, facilitating the activation of protein kinase. By displacing the enzyme from the membrane into the cytoplasm *DGKH* transfers the phosphoric acid residue to the free carbon atom of glycerol, forming phosphatidic acids, which also participate in the regulation of Ca-dependent processes, in particular, facilitating the formation of vesicles by changing the properties of its membrane. In the absence of phosphorylation, diacylglycerides are hydrolyzed to form fatty acids, in particular arachidonic acid, which is a precursor to anandamide and other endocannabinoids. It regulates LTP and LTD, genetic variation has a strong association with the risk of developing bipolar personality disorder [16].
P2RX7	Purinoreceptor 7	Ligand-gated ion channel	*P2X7R* is expressed by glutamatergic pyramidal neurons of the hippocampus and non-neuronal cells: astrocytes, oligodendrocytes and microglia. [17]. Opens the gates into the cytoplasm for divalent cations by binding purines. Recognizes extracellular ATP-dependent apoptosis. Regulator of intracellular Ca-associated signaling pathways. Regulator of neuroinflammation. It activates myeloid cells, induces the expression of Interleukin-1-beta, causes degranulation of mast cells and activation of microglia. Regulator of neuroinflammation. It causes long-term enhancement of LTP [18].
CNR1	Endocannabinoid receptor type 1	G protein-coupled receptor of the endocannabinoid system	The central element of the endocannabinoid system. The level of endocannabinoids increases under the influence of GC, and the endocannabinoids themselves limit the development of the stress response, including neuroinflammation. Mediates the effects of glucocorticoids on the consolidation of aversive memories [19].
FAAH	Fatty acid amide hydrolase	Integral membrane enzyme that hydrolyzes endocannabinoids and related signaling lipids	The main catabolic enzyme of fatty acid amides, particularly anandamide and other endocannabinoids. It is highly expressed in the limbic system. Inhibits the activity of endocannabinoids. Dexamethasone regulates endocannabinoid metabolism by inhibiting FAAH activity [19].

Table 6. (Contd.)

Gene	Product	Biochemical functions	Signaling pathways, intercellular interactions. Effects of genetic variation on CNS function (if described)
GABRA2	Alpha subunit of the GABA-A receptor	Ligand-gated Cl-channel, GABA receptor (subunit)	Like endocannabinoids, it acts as a protective element against the damaging effects of own reactions caused by social stress. Activation of the receptor reduces anxiety and inhibits neuroinflammatory reactions. The variation is associated with anxiety disorders, Asperger's syndrome, bipolar disorder and schizoaffective disorder [20].

REFERENCES

1. Talenti, A., Bertolini, F., Williams, J., Moaeen-Ud-Din, M., Frattini, S., Coizet, B., Pagnacco, G., Reecy, J., Rothschild, M.F., Crepaldi, P., and Italian Goat Consortium, *J. Hered.,* 2018, vol. 109, no. 3, pp. 315–319.
2. Stella, A., Nicolazzi, E.L., Van Tassell, C.P., Rothschild, M.F., Colli, L., Rosen, B.D., Sonstegard, T.S., Crepaldi, P., Tosser-Klopp, G., Joost, S., and the AdaptMap Consortium, *Genet. Sel. Evol.,* 2018, vol. 50, p. 61.
3. Mukhina, V., Svishcheva, G., Voronkova, V., Stolpovsky, Y., and Piskunov, A., *Animals (Basel),* 2022, vol. 12, no. 3, pp. 221.
4. Shen, E.H., Overly, C.C., and Jones, A.R., *Trends Neurosci.,* 2012, vol. 35, no. 12, pp. 711–714.
5. Hirata, T., Morii, E., Morimoto, M., Kasugai, T., Tsujimura, T., Hirota, S., Kanakura, Y., Nomura, S., and Kitamura, Y., *Development (Cambridge, England),* 1993, vol. 19, no. 1, pp. 49–56.
6. Zhang, S.C. and Fedorof, S., *J. Neurosci. Res.,* 1997, vol. 47, no. 1, pp. 1–15.
7. Jin, K., Ma, X.O., Sun, Y., Xie, L., and Greenberg, D.A., *J. Clin. Investigation,* 2002, vol. 110, no. 3, pp. 311–319.
8. Lennartsson, J. and Ronnstrand, L., *Physiol. Rev.,* 2012, vol. 92, no. 4, pp. 619–649.
9. Yang, Z., Shi, H., Ma, P., Zhao, S., Kong, Q., Bian, T., Gong, C., Zhao, Q., Liu, Y., Qi, X., Zhang, X., Han, Y., Liu, J., Li, Q., Chen, H., and Su, B., *Mol. Biol. Evol.,* 2018, vol. 35, no. 9, pp. 2272–2283.
10. Guijarro, P., Wang, Y., Ying, Y., Yao, Y., Jieyi, X., and Yuan, X., *Dev. Neurobiol.,* 2013, vol. 73, no. 12, pp. 871–887.
11. Tantra, M., Guo, L., Kim, J., Zainolabidin, N., Eulenburg, V., Augustine, G.J., and Chen, A.I., *Genes Brain Behav.,* 2018, vol. 17, no. 6.
12. Kuwahara, N., Nicholson, K., Isaacs, L., and MacLusky, N.J., *Androg. Clin. Res. Ther.,* 2021, vol. 2, no. 1, pp. 216–230.
13. Gulyaeva, N.V., *Biochemistry (Moscow),* 2023, vol. 88, pp. 565–589.
14. Olusola, A.A. and Sapolsky, R.M., *Neuroendocrinology,* 1999, vol. 69, no. 2, pp. 138–144.
15. Li, X., Qiu, W., Deng, L., Lin, J., Huang, W., Xu, Y., Zhang, M., Jones, N.C., Lin, R., Xu, H., Lin, L., Li, P., and Wang, X., *J. Transl. Med.,* 2022, vol. 20, no. 1, p. 406.
16. Lee, D., Kim, E., and Tanaka-Yamamoto, K., *Front. Cell Dev. Biol.,* 2016, vol. 4, p. 92.
17. Zhao, Y.F., Tang, Y., and Illes, P., *Front. Mol. Neurosci.,* 2021, vol. 14, p. 641570.
18. Kesavan, J., Watters, O., de Diego-Garcia, L., Mendez, A.M., Alves, M., Dinkel, K., Hamacher, M., Prehn, J.H.M., Henshall, D.C., and Engel, T., *Purinergic signalling,* 2023, p. 1007.
19. Granja-Galeano, G., Dominguez-Rubio, A.P., Zappia, C.D., Wolfson, M., Sanz-Blasco, S., Aisemberg, J., Zorrilla-Zubilete, M., Fernandez, N., Franchi, A., Fitzsimons, C.P., and Monczor, F., *Neuropharmacology,* 2023, vol. 239, p. 109674.
20. Melroy, W.E., Stephens, S.H., Sakai, J.T., Kamens, H.M., McQueen, M.B., Corley, R.P., Stallings, M.C., Hopfer, C.J., Krauter, K.S., Brown, S.A., Hewitt, J.K., and Ehringer, M.A., *Behav. Genet.,* 2014, vol. 44, no. 4, pp. 356–367.
21. Da, SilvaC.A., Heilbock, C., Kassel, O., and Frossard, N., *FASEB J.,* 2003, vol. 17, no. 15, pp. 2334–2336.
22. Gulyaeva, N., *Neurochem. Res.,* 2019, vol. 44, pp. 1306–1322.
23. Dutta, S.S., Andonova, A.A., Woellert, T., Hewett, S.J., and Hewett, J.A., *Neurobiol. D.,* vol. 168, no. is. 2022, p. 105689.
24. Pena-Altamira, L.E., Polazzi, E., Giuliani, P., Beraudi, A., Massenzio, F., Mengoni, I., Poli, A., Zuccarini, M., Ciccarelli, R., Di Iorio, P., Virgili, M., Monti, B., and Caciagli, F., *Neurochem. Int.,* 2018, vol. 115, pp. 37–49.