Recent changes in candidate genes for domestication in humans in Europe: focusing on language

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Running title: Domestication and language evolution

Keywords: self-domestication, Late Neolithic/Bronze Age, Europe, nonsynonymous SNPs, language evolution

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Abstract

Human evolution resulted from changes in our biology, behavior, and culture. One source of these changes has been hypothesized to be our self-domestication (that is, the development in humans of features commonly found in domesticated strains of mammals, seemingly as a result of selection for reduced aggression). Signals of domestication, notably brain size reduction, have increased in recent times. In this paper we compare whole-genome data between Late Neolithic/Bronze Age individuals and modern Europeans and show that some genes associated with self-domestication and with neural crest development and function in mammals are significantly differently enriched in nonsynonymous single nucleotide polymorphisms between these two groups. We discuss how these changes might account for the exacerbation of features linked to self-domestication and more generally, together with other factors like dietary or social changes, for subtle changes in human cognition and behavior, including language.

Introduction

Human evolution has entailed multiple changes in our body, cognition, and behavior. These changes are expected to have resulted from selected mutations in selected genes (Grossman et al., 2013; Pääbo, 2014; Field et al., 2016) or from changes in the regulatory landscape of shared genes (Gokhman et al., 2014). Environmental factors, and particularly human culture resulting in a human-specific niche, are expected to have had an important impact on our genome too, because of the relaxation of natural selection, as well as the active selection resulting from some cultural practices (Laland et al., 2010). Beyond well-known cases mostly involving physiological adaptations (like lactase persistence, adaptation to cold climate, and adaptation to high altitude), the complex interaction between biology and culture during human evolution is poorly understood, particularly, regarding human cognition and some of its distinctive features, most notably human language. One recent hypothesis argues that many human distinctive features might have resulted from our self-domestication in response to an early selection towards increased in-group prosociality and reduced aggression (Hare, 2017; Wrangham, 2018). The parallels between domesticated animals and humans (including differences with extinct hominins) have been explored in detail by several authors (Shea, 1989; Leach, 2003; Somel et al., 2009; Zollikofer and Ponce de León, 2010; Herrmann et al., 2011; Plavcan, 2012; Stringer, 2016; Hare, 2017; Thomas and Kirby, 2018). This set of common features, impacting on the skull/brain, the face, or the skin, but also on development (paedomorphosis and neotenous behavior, reduction of sexual dimorphism, tameness) has been hypothesized to result from the hypofunction of the neural crest (NC) (Wilkins et al. 2014). Recent genomic analyses of dogs and domesticated foxes have revealed enrichments of genes linked to neural crest function (Pendleton et al., 2018; Wang et al., 2018). Signs of self-domestication in humans have increased in recent times (reviewed in Hare, 2017). Interestingly too, features of domestication are found abnormal (either exacerbated or attenuated) in clinical conditions impacting on our cognitive abilities, including language, like autism spectrum disorder (Benítez-Burraco et al., 2016) schizophrenia (Benítez-Burraco et al., 2017), or Williams syndrome (Niego and Benítez-Burraco, 2019). At the same time, genomic regions associated with dog-human communication contain genes related to human social disorders, particularly autism spectrum disorder (Persson et al., 2016). Not surprisingly, self-domestication has been invoked to account for the emergence of one of the most relevant human-specific traits, namely, our cognitive ability to learn and use languages (Benítez-Burraco et al., 2018), but also of the sort of languages we use nowadays for communicating (Benítez-Burraco and Kempe, 2018; Thomas and Kirby, 2018). In a nutshell, being able to learn and use a language depends on having a brain with the proper hardware, but also of living in a cultural environment with the proper triggering stimuli. Putting this differently, our cognition accounts for many aspects of the languages we speak, but some language features are an adaptation to the physical and human-made environment and impact in turn, more or less permanently, on our cognitive architecture. Interestingly, human self-domestication can contribute to both processes, because it gives raise to brain/cognitive changes (see Herrmann et al., 2010 for primates), but also contributes to the creation of the niche that enables the emergence of specific aspects of language complexity (like complex syntax) via a cultural mechanism (Benítez-Burraco and Kempe, 2018; Thomas and Kirby, 2018).

Overall, the evidence reviewed above suggests that self-domestication could be considered a process with different degrees of completion. Nonetheless, because of the attested effect of environmental factors, and more generally, our mode of life, on our morphology, physiology, and behavior, as noted above, it is not clear whether the observed differences between ancient anatomically-modern humans (AMHs) and present-day AMHs resulted from the enhancement of our self-domestication, or are instead an unrelated consequence of our adaptation to new, human-made environments.

As also noted, we have detailed characterizations of the genetic differences between humans and our closest relatives, namely, Denisovans and Neanderthals (Grossman et al., 2013; Pääbo, 2014; Field et al., 2016). We also have tentative accounts of the genetic and epigenetic changes important for the emergence of our language-readiness (Boeckx and Benítez-Burraco, 2014a, 2014b, Benítez-Burraco and Boeckx, 2015), as well as a preliminary hypothesis about how these changes could have been translated to changes in the sort of cognitive abilities that are needed for acquiring and mastering a

language (Murphy and Benítez-Burraco 2018a, b). One recent genetic research has shown that candidate genes for domestication in mammals are overrepresented among the genes under positive selection in modern humans compared to extinct hominins (Theofanopoulou et al., 2017). However, no evidence of when these changes were selected is available. Actually, because features of self-domestication have intensified with time, as also noted, we regard of interest to check whether genomic signals of domestication have also intensified recently. If this was the case, one could argue that some late changes in human evolution with an impact on language are certainly associated with our self-domestication, rather than simply with changes of life.

In a recent paper (Chekalin et al., 2019) we compared whole-genome data between Late Neolithic/Bronze Age individuals from 6000 years ago and modern Europeans and showed that several biological pathways were significantly differently enriched in nonsynonymous single nucleotide polymorphisms (SNPs) in these two groups. We argued that these changes, with an impact on metabolism, immune response, physical behavior, perception, reproduction, and cognition, could have been triggered and shaped by cultural practices, particularly, by important changes occurred in Europe at that age. In this paper, we have asked whether a genetic signature of enhanced self-domestication can be found that accounts for the attested enhancement of domestication features in late modern humans. To answer this question, we have analyzed the same two samples of Europeans (Late Neolithic/Bronze Age and modern ones), in order to compare the numbers of nonsynonymous mutations in the groups of genes associated with self-domestication and NC development and function.

Materials and Methods

Our four different sets of candidates for domestication resulted from i) merging the list we compiled for our paper on features of domestication in schizophrenia (Benítez-Burraco et al. 2017) with the list compiled by Theofanopoulou and collaborators (2017). The merged list includes 764 genes (Supplemental table 1). We also considered ii) the 41 genes highlighted by Theofanopoulou and collaborators as showing evidence of positive selection in modern humans compared to Neanderthals/Denisovans (Supplemental table 1). In view of the suggested role of the NC in the emergence of features of domestication, we considered as well iii) genes important for NC development and function, which we also compiled for our paper on domestication and schizophrenia (Benítez-Burraco et al., 2017). This list encompasses 89 genes (Supplemental table 1), which we gathered using pathogenic and functional criteria: neurochristopathy-associated genes annotated in the OMIM database (http://omim.org/), NC markers, genes that are functionally involved in NC induction and specification, genes involved in NC signaling (within NC-derived structures), and genes involved in cranial NC differentiation. Finally, we considered as well iv) the "core" genes highlighted by Wilkins and collaborators (2014) as key candidates for the "domestication syndrome" in mammals (Supplemental table 1).

For all four sets of genes, we performed the calculations analogous to those done in the paper of Chekalin et al., 2019. Briefly, we calculated the significance of the differences in the counts of synonymous and nonsynonymous SNPs between genomes of ancient and modern Europeans. In case these differences have been found, we assessed their nature (accumulation of mutations in the modern group in comparison to ancient one or, in the opposite, reducing the number of mutations). Despite the fact that it is widely accepted that mutations in cis-regulatory regions play a very important role in evolution (King and Wilson, 1975 and many others), the functions of most of the SNPs in the regulatory regions are not yet known, and no confident database of these sort of changes in the human lineage is currently available. For this reason, our analysis was restricted by genome coding regions only. We used differential SNP enrichment scores (DSSE for synonymous SNPs and DNSE for nonsynonymous SNPs) as measures of these differences (Chekalin et al., 2019). The pathways were considered to be differentially enriched if absolute value of the differential SNP enrichment score > 4, and the adjusted p-value < 0.01 (Bonferroni correction). Negative score values indicated accumulation of mutations in genomes of modern Europeans in comparison with ancient Europeans, while positive score values indicated an opposite pattern.

Results

We compared whole genome data from 150 ancient samples dated between 3,500 and 1,000 BCE (Allentoft et al., 2015; Gamba et al., 2014; Haak et al., 2015; Mathieson et al., 2015) with data on 305 modern Europeans genotyped in the framework of the 1,000 Genomes Project (Genomes Project et al. 2015), under the assumption that modern Europeans are genetic descendants of the Bronze Age Europeans, as described and discussed in detail in Chekalin et al. (2019) (Figure 1).

[FIGURE 1 ABOUT HERE]

As expected, we have found no significant differences between groups in synonymous SNP enrichment (Table 1), taking into account the neutral character of these mutations. At the same time, we have found a significant enrichment in nonsynonymous SNPs between the Bronze Age and present-day European individuals. Specifically, we have found that candidates for domestication have been accumulating nonsynonymous mutations during the past 6,000 years, whereas candidates for NC exhibit fewer nonsynonymous mutations in present-day humans than in Bronze Age humans. By the reasons we provide in our 2019 paper, these differences are not expected to be caused by an insufficient sequence coverage of Bronze Age individuals or by general inter-population differences between the two groups. By contrast, we have found no significant selection signals in domestication candidates positively selected after our split from Neanderthals and Denisovans, nor in "core" candidates for the domestication syndrome (Table 1).

[TABLE 1 ABOUT HERE]

Discussion

Self-domestication has been claimed to account for key aspects of human evolution, including the creation of the cultural niche that allowed complex languages to emerge. Although signals of domestication have seemingly increased recently, as showed by the paleoanthropological record (Leach 2003; Zollikofer and Ponce de León, 2010; Stringer, 2016), it is not clear if they resulted from genomic changes that incidentally enable as well to provide a more precise chronological account of the self-domestication events, as it has been possible with several domesticated mammal species (Driscoll et al., 2007; Nomura et al., 2013; Orlando et al., 2013; Freedman et al, 2014; Qiu et al., 2015; Botigué et al., 2017). At present, only one study has addressed this issue, concluding that statistically significant overlaps exist between selective sweep screens in anatomically-modern humans and several domesticated species (Theofanopoulou et al., 2017). Nonetheless, this study is inconclusive about the timing of the self-domestication events, as it relies on previously published (but limited) comparisons between anatomically-modern humans and Neanderthals and Denisovans by Prüfer et al. (2014), Racimo (2016) and Peyrégne et al. (2017).

In this paper, we have shown that two sets of genes associated with self-domestication and NC development and function, respectively, have been selected during the last 6,000 years in Europe, a period when important changes in human behavior and culture occurred, including the spread of agricultural practices and sedentism, urbanization, increasing in population density, development of trading routs, globalization etc. These changes reshaped not only the gene pool of Europe, but also modified its linguistic landscape, because Neolithic languages were almost totally replaced by Indo-European languages (Bouckaert et al., 2012; de Barros et al., 2018; Mathieson, 2018, among many others).

The group of genes that are candidates for domestication in mammals have demonstrated the accumulation of nonsynonymous mutations in the genomes of present-day Europeans in comparison to Bronze Age ones. However, it is worth noticing that this group consists of 764 genes which can be responsible for a number of different biological processes. Further detailed study of this group with its subsequent division into smaller subsets will probably allow us to reveal more diverse patterns of

selections for these genes. We have also found the decrease in nonsynonymous mutations in the modern group in comparison to ancient Europeans in the candidate genes for NC development and function. This can be the evidence of negative or, on the opposite, strong positive selection in the genes responsible for development and function of NC.

Enhanced self-domestication has been recently claimed to contribute to the transition from the so-called esoteric languages, typically spoken by close-knit, small human communities that share a considerable amount of knowledge about the environment, to exoteric languages, better designed for communicating decontextualized information to strangers (Benítez-Burraco and Kempe, 2018). In brief, self-domestication seemingly resulted in a less aggressive behaviour that facilitated the establishment of larger and more complex social networks and enhanced contacts with strangers, which are factors that favour the emergence of exoteric features in languages (phonological simplification, morphological transparency and regularity, expanded vocabularies, more complex syntax). Likewise, self-domestication resulted in an extended juvenile period that increased language learning by children and language teaching by caregivers, which seemingly enables the mastering of exoteric languages, which are most costly to process and learn (see Benítez-Burraco, in press for details). Importantly, whereas self-domestication seemingly contributed to create (together with other factors, like changes in food supply or climatic changes) the human niche that enabled languages to acquire the features linked to exotericity, language evolution itself (and particularly, the type of languages spoken at some point during our evolution) also contributed to our self-domestication, particularly, because verbal interactions seemingly reduce in-group physical aggression (Progovac and Locke 2009).

Our hypothesis is that for the reasons mentioned above, in Europe (and possibly in other parts, but this needs to be checked) this transition to exotericity could be linked to the increased domestication features found among Europeans in that period. Importantly, exoteric languages demand some cognitive adaptation, because their more complex syntax and expanded vocabularies need an enhanced working memory capacity, more executive control, and improved declarative knowledge to be learnt and mastered (see Benítez-Burraco and Kempe, 2018 for a detailed discussion). Interestingly, we previously found in our European samples evidence of selection of two pathways related to cognition, particularly, to long-term potentiation and dopaminergic synapse, which underlies synaptic plasticity and ultimately, memory and learning abilities (Chekalin et al., 2019). Importantly too, these two pathways do not have any shared genes with NC genes. Therefore, the common pattern for these two groups (decrease in nonsynonymous mutations during the last 6,000 years) is due to not shared genetic background but, probably, to common external factors. We then suggested that this selection might be related to changes in ways of information presentation, perception, and transmission. Now, we hypothesize that this external factor might be (also) related to the transition from esoteric to exoteric languages in Europe.

By contrast, we have found no signals of selection in "core" candidates for domestication (Wilkins et al. 2014), many of which are involved in NC development and function. This suggests that, although the NC is seemingly involved in the manifestation of domestication features also in our species, changes in NC development and function could mostly account for early stages of our self-domestication, considering that features of self-domestication, although attenuated, are already present in early anatomically-modern humans (see Theofanopoulou et al., 2017 for discussion). Interestingly too, we have found that the candidates for domestication that show signals of positive selection in anatomically-modern humans compared to Neanderthals and Denisovans have not been subject to selection in Europeans during the last 6,000 years. This lack of selection suggests that they might have been selected earlier in our history, plausibly accounting for the milder domesticated phenotype exhibited by early modern humans compared to present-day humans, and that recent self-domestication events have resulted from selection in other genes, plausibly in response to selection factors that might be different from the ones operating during our speciation.

Overall, our results suggest that human self-domestication is an ongoing process, contributing to important recent changes in the human body and particularly, in human behavior, culture, and perhaps

cognition, with a potential impact on language evolution, and that different genes account for the different stages of the human self-domestication process.

Acknowledgements

This research was funded by the Spanish Ministry of Economy and Competitiveness (grant FFI2016-78034-C2-2-P [AEI/FEDER, UE] to ABB). We thank Adam Wilkins for some valuable commentaries on a previous version of this manuscript.

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Figure legends

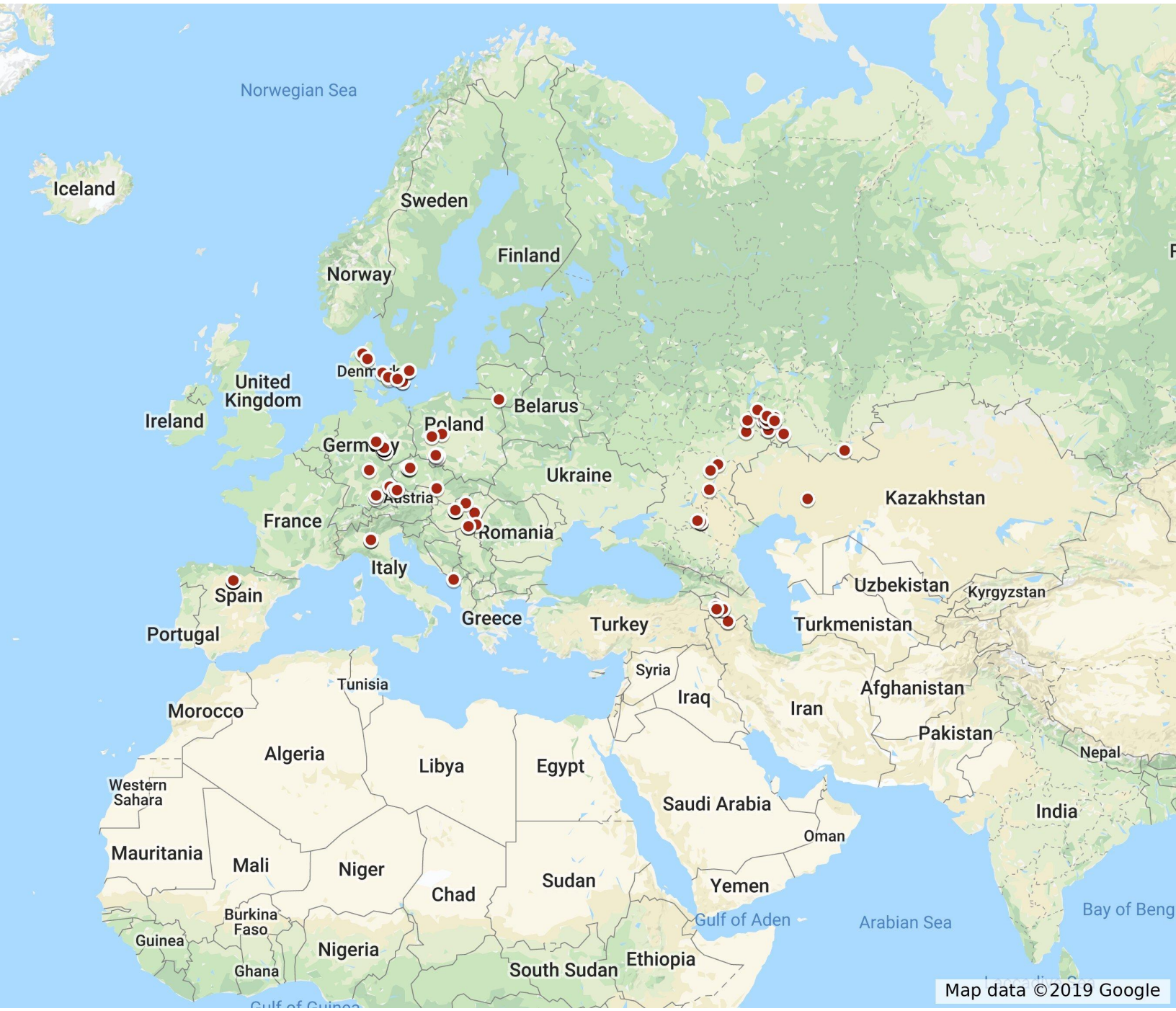
Figure 1. Location of ancient samples analyzed in the study.

Tables

Table 1. Differently enriched sets of genes in ancient and modern groups

Set of genes	Ancient SNPs count	Modern SNPs count	Enrichment score	p-value	p-value adjusted Bonferroni	Enriched Bonferroni 0.01 threshold
Synonymous SNPs						
Domestication	2165	3759	1.24	0.2138	1	No
Neural crest	194	315	1.19	0.2353	1	No
Domestication syndrome	49	76	0.98	0.326	1	No
Positive selection in AMH	144	268	-0.25	0.8012	1	No
Nonsynonymous SNPs						
Domestication	2440	4844	-4.32	1.58×10^{-5}	0.005	Modern
Neural_crest	213	240	5.01	5.36×10^{-7}	2×10^{-4}	Ancient
Domestication syndrome	61	73	2.49	0.0127	1	No
Positive selection in AMH	138	231	0.69	0.4885	1	No

Note. Positive enrichment score values correspond to pathways that have more SNPs in genomes of ancient individuals, while negative DNSE values correspond to pathways that have more SNPs in genomes of modern Europeans. AMH refers to anatomically-modern humans (compared to Neanderthals and Denisovans)


Norwegian Sea
Iceland
Sweden
Finland
Norway
United Kingdom
Ireland
Belarus
Poland
Ukraine
France
Romania
Italy
Spain
Portugal
Greece
Turkey
Kazakhstan
Uzbekistan
Kyrgyzstan
Turkmenistan
Syria
Iraq
Iran
Afghanistan
Pakistan
Nepal
India
Tunisia
Morocco
Algeria
Libya
Egypt
Western Sahara
Saudi Arabia
Oman
Yemen
Mauritania
Mali
Niger
Chad
Sudan
Burkina Faso
Guinea
Nigeria
Ghana
South Sudan
Ethiopia
Gulf of Aden
Arabian Sea
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Domestication	Domestication	Neural crest (I	Core candidates for the domestication syndrome (Wilkins et al., 2014)
ABAT	AMBRA1	ALX1	BAZ1B
ABCA10	BRAF	ALX3	CHD7
ABCA5	CACNA1D	ALX4	EDN3
ABCB10	COA5	ASCL1	EDNRB
ABCG1	COL11A1	BDNF	FGF8
ABCG2	COQ10B	BMP2	FOXD3
ABHD1	DLGAP1	BMP4	GDNF
ACA64	ERBB4	BMP7	KIT
ACAD8	FAM172A	CAD7	MAGOH
ACMSD	GGT7	CDH2	MIITF
ACOT11	GRIA1	CDH6	PAX3
ACOT13	GRIK3	CMYC	RET
ACOT8	HSD3B7	COL1A2	SOX10
ACOX2	HSPD1	COL2A1	SOX2
ACOX3	HSPE1	CRKL	SOX9
ACSF3	ITGA9	DCT	TCOF1
ACSM5	LRP1B	DLX5	
ACSS2	LYST	DLX6	
ACTA1	MOB4	EDN1	
ADAM2	MYLK3	EDN3	
ADAMDEC1	NCOAS	EDNRA	
ADAMTS13	NEK4	EDNRB	
ADAMTSL3	NT5DC2	EFNB1	
ADRB2	NTM	EFNB2	
AHCY	PLAC8L1	ETS1	
AHCYL2	PPAP2A	FGF2	
AK1	PPAPDC1B	FGF8	
AKAP1	PRR11	FOXD3	
ALDH16A1	PVRL3	GBX2	
ALDH18A1	RETN2	GDNF	
ALDH1L2	RNPC3	GFAP	
ALK	SF3B1	GJB1	
ALS2CR12	SKA2	GLI3	
AMACR	SNRPD?	GSC	
AMBRA1	STAB1	HDAC	
ANK1	SYTL1	HES1	
ANKDD1A	TAS2R16	HES5	
ANKRD2	TEX14	HOXA1	
ANKRD49	TP53BP1	HOXA2	
ANKRD50	ZMYND10	HOXA3	
ANKS4B	ZNF521	HOXB1	
APEH		ID3	
APOBEC4		ISL1	
APOPT1		ITGB1	
ARHGAP26		KIF1B	
ARID1B		LHX1	

ARID3B
ARL6IP1
ARL9
ART3
ASAP1
ASB11
ASIP
ASTN1
ASTN2
ATL1
ATXN7L1
B3GALTL
B3GLCT
BAG5
BARD1
BAZ1B
BCAP31
BMP15
BMPR1B
BPI
BRAF
BRCA1
BTAF1
C11orf54
C11orf63
C15orf60
C16orf71
C17orf67
C1orf109
C22orf31
C2orf40
C2orf62
C3orf62
C4orf33
C5orf15
C7orf72
C8B
C9orf89
C9orf96
CACNA1C
CACNA1D
CADM2
CAGE1
CALCB
CASP7
CAST
CAV1
LHX2
MASH1
MAX
MITF
MSX1
MSX2
NEUROD
NEUROG1
NF1
NFKB
NOTCH
NRP1
NRP2
OLIG1
OLIG2
PAX3
PAX7
PHOX2B
PHOX2B
PMP22
POMT1
RET
RHOB
ROBO1
ROBO2
SDHB
SDHD
SNAIL1
SNAIL2
SOX10
SOX5
SOX9
TBX1
TFAP2A
TMEM127
TWIST
VHL
WNT1
WNT3a
WNT6
WNT7B
WNT8
ZEB2
ZIC1

CAV2
CBD118
CBD121
CBD122
CBX2
CCDC38
CCDC64B
CCDC67
CCDC70
CCDC82
CCNJ
CCNT2
CD27
CD36
CD48
CD93
CDH1
CDH6
CDK5RAP1
CDKL3
CDRT1
CDRT4
CELA1
CENPE
CENPM
CEP68
CEP97
CERS3
CETN3
CHD7
CHMP4B
CIB4
CKB
CKM
CLCA3
CLDN17
CLEC5A
CLK3
CNGA2
CNTN6
COA5
COBL
COG6
COIL
COL11A1
COL14A1
COL22A1

COL6A3
COL9A3
COMMD1
COQ10B
COX4I1
COX4I2
CPEB3
CRH
CROCC
CRTC3
CRYM
C-SKI
CSPP1
CTTN
CUL1
CUX2
CXCL10
CYB5R1
CYFIP1
CYP1A1
CYP1A2
CYP26A1
CYP26C1
CYP27B1
DACT1
DAPK1
DBI
DCC
DCST1
DDC
DEFB103B
DEFB119
DEFB122
DGAT1
DHDH
DLGAP1
DLL3
DMRT3
DNAH3
DNAH9
DNAJA1
DNAJB9
DNTTIP2
DOCK2
DPEP3
DSCAM
DTD1

DUSP19
ECHDC1
EDC3
EDN3
EDNRB
EEA1
EHBP1L1
EIF2S2
ELF2
EMC2
ENKUR
ENTPD1
ENTPD7
EPHB4
EPS15
ERBB4
ETNPPL
ETV4
EVC2
EYA1
F9
FABP5
FAF1
FAIM3
FAM107B
FAM114A2
FAM131B
FAM172A
FAM179A
FAM40B
FAM69A
FANCA
FANCB
FAT4
FBN3
FBXL22
FBXO10
FBXO28
FBXO31
FBXW10
FBXW11
FCHSD2
FCRL4
FER
FGA
FGD6
FGF13

FGF18
FGF4
FGF5
FGF8
FGFBP3
FHL1
FMO3
FN3K
FOXD3
FOXI1
FOXJ3
FRMD6
FRMD7
FRMPD1
FSTL4
GABRA5
GAK
GALR1
GAPDHS
GCNT7
GDNF
GEMIN7
GGT6
GGT7
GLRA1
GNAT3
GNG10
GNG4
GNPTAB
GOLGA1
GP2
GPATCH8
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GRIA2
GRID1
GRIK2
GRIK3
HADH

HAS2
HEATR5B
HECA
HEPACAM2
HEPH
HERC2
HIPK2
HMGA2
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HS3ST4
HS6ST2
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IGF2
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IGSF1
IGSF3
IGSF9B
IKZF1
IMMP2L
INHBC
INPP4B
INPP5J
IPO4
IQCB1
ISG15
ITGA2B
ITGA9
ITGBL1
ITPR3
JAM3
JMJD1C
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KITLG
KLF4
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KRIT1
KRT71
KYNU
LAMC2
LAMC3
LAP3
LATS2
LCAT
LCLAT1
LEPREL1
LHFPL3
LIAS
LILRA6
LIMD1
LIN28B
LINC01927
LINGO2
LMF1
LRIG3
LRP1B
LRRC32
LRRC36
LRRN3
LSM3
LTF
LYST
MAFK
MAGOH
MAOA
MAOB
MAP3K1
MAP3K4
MAP7D2
MAP7D3
MAPK10
MARCH10
MARCH7

MARK2
MARK3
MARVELD3
MATN2
MBD2
MBP
MC1R
MC2R
MC4R
MCF2
MCHR2
MED23
MERTK
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METTL22
METTL8
MFAP3
MGAM
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MIIP
MINOS1
MITF
MKKS
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MOB4
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NEK1
NEK4
NFAM1
NFKBIZ
NID2
NINJ1
NIPA2
NIPBL
NKAIN2
NOCT
NOL4
NOLC1
NOSTRIN
NOTCH2
NPAS3
NPFFR2
NPTX1
NR2F2
NR3C1
NR3C2
NRF1
NRG2
NRG4
NRSA2
NRXN1
NT5DC2
NTAN1
NTM
NUDT15
NUMB
NUP133
NUP54
NXPE3
OLIG1
OMA1
OPCML
OPTC
OR10K1
OR13C8
OR2B11
OR4D6
OR51A7

OR9A4
OTOF
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PARP12
PARVG
PAX2
PAX3
PCDH18
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PCDHB4
PCSK5
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PDE4DIP
PDE5A
PDE7B
PDILT
PDRG1
PDXDC1
PEX7
PHF2
PHF20
PHLDB3
PIK3C3
PITRM1
PJA2
PKD1L1
PLA2G2E
PLA2G3
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RABGAP1L
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RALGAPA2
RALY
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RCSD1
REEP1
RELL1
RELT
RET
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TCOF1
TCTN1
TCTN3
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THEGL
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THYN1
TLX3
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TPH1
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TRDN
TRIM16
TRIM59
TRIO
TRMT61A
TRPM1
TRPV6
TRY1
TRY2

TRY3
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TVP23C
TXN2
TXNRD2
TYK2
TYRP1
U2
UBE2B
UBXN10
ULBP3
UMOD
UNC93A
URB2
USP45
UVRAG
V1R
VDAC1
VEZT
VPS26B
VRK1
VWC2
VWDE
WASF3
WDR17
WDR62
WDR90
WFDC8
WIPF2
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WNK2
WWC1
XCR1
XPBP
XPC
XPO6
YSK4
YWHAH
ZC3H3
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