Domestication of the Dog from the Wolf Was Promoted by Enhanced Excitatory Synaptic Plasticity: A Hypothesis

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Abstract

Dogs shared a much closer relationship with humans than any other domesticated animals, probably due to their unique social cognitive capabilities, which were hypothesized to be a by-product of selection for tameness toward humans. Here, we demonstrate that genes involved in glutamate metabolism, which account partially for fear response, indeed show the greatest population differentiation by whole-genome comparison of dogs and wolves. However, the changing direction of their expression supports a role in increasing excitatory synaptic plasticity in dogs rather than reducing fear response. Because synaptic plasticity are widely believed to be cellular correlates of learning and memory, this change may alter the learning and memory abilities of ancient scavenging wolves, weaken the fear reaction toward humans, and prompt the initial interspecific contact.

Key words: gray wolf, self-domestication, fear response, learning, memory.

Dogs have evolved unique social cognitive capabilities not found in their wolf progenitors (Hare et al. 2002; Miklósi et al. 2003; Topál et al. 2009). "Selection for communication" was proposed as the direct selective pressure that drove the evolution of these unusual abilities (Hare et al. 2002; Miklósi et al. 2003). Alternatively, the "correlated by-product" hypothesis proposed that these abilities was a by-product of selection for tameness toward humans, because tame foxes show greater skill in reading human gestures than control foxes (Hare et al. 2005), and hypothesized the reduced fearful-aggressive response, which largely shortened their distances from human presence, to be the prerequisite of dog domestication (Belyaev 1969). However, no genetic evidence has been reported that is directly associated with the precise aggressive-tame behavioral transformation, although several studies have identified genes that are involved in the neural system and are highly divergent from wolves (Saetre et al. 2004; Li et al. 2013; Wang et al. 2013).

Excess of Fixed Alleles within Stress-Related Genes in Dogs

We firstly compared published resequenced genomes of three wolves and ten dogs (including five ancient dogs and five modern dogs, supplementary material, Supplementary Material online) to identify the most significant genetic legacy in the dogs deviating from their progenitors. To avoid inaccurate estimation of population differentiation due to small sample size, we only count the single nucleotide polymorphisms (SNPs) that differentiate extremely between the wolves and the dogs (allele frequency is 1 in wolves but 0 in dogs, or vice versa), which were defined as fixed SNPs. We identified 204 genes that have at least six fixed SNPs (within

the 95% percentile rank). These genes showed an extremely significant lower level of nucleotide diversity and Tajima's *D* values ($P = 5.22E-05$ and 1.23E-30, respectively, Mann–Whitney *U* test) compared with other genes in the genome (fig. 1*A*), suggesting a potential selection effects on the divergence observed here. Because only a very small number of fixed SNPs (totally 26) were nonsynonymous substitutions, this may indicate that the positive selection operated mainly on

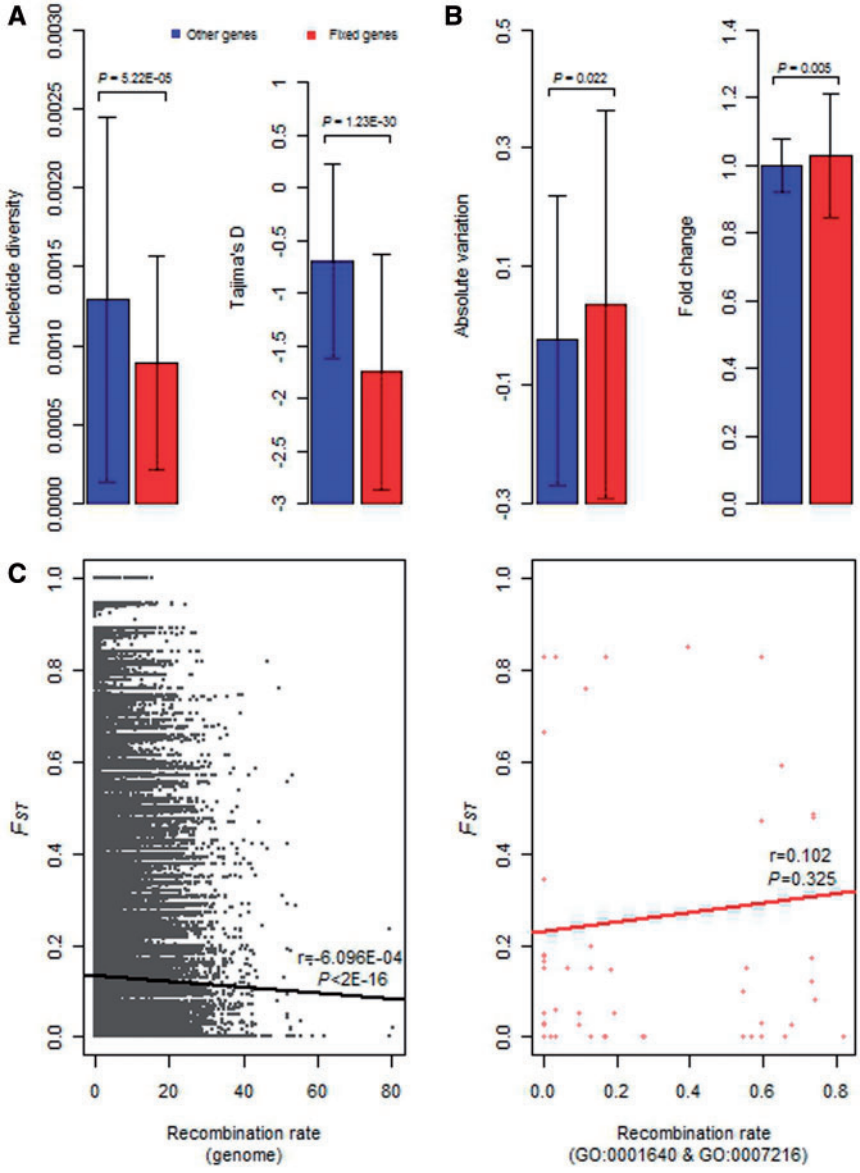

Fig. 1.—Analysis of selection in the dog genome. (*A*) Comparisons of the nucleotide diversity (left) and Tajima's *D* values (right) between genes containing large numbers of fixed SNP differences and other genes ± S.D. were presented. (*B*) Comparisons of the difference in expression levels between wolves and dogs between genes containing large numbers of fixed SNP differences and other genes. The expression value for each gene was log2 transformed. Left: Expression difference of each gene between the wolf and the dog was calculated by the transformed value in the dog minus the transformed value in wolf. Right: Difference of each gene between the wolf and the dog was calculated by the transformed value in the dog divided by the transformed value in the wolf. (*C*) Left: Negative correlation between F_{ST} values and recombination rates of genome wide SNPs. Right: Positive correlation between F_{ST} values and recombination rates of SNPs at genes in GO categories: GO: 0001640 and GO: 0007216, both of which contain only one gene: *GRIK3* in the Ensembl 72 dog annotation.

expressional regulation. Actually, the 204 genes showed appreciable changes in expression patterns between dogs and wolves than others for two different measurements: Absolute expression change and fold change ($P = 0.022$ and $P = 0.005$, respectively) (fig. 1*B*), based on the transcriptome data for the frontal cortex (Albert et al. 2012). These results suggest that expressional variation rather than structural variation in protein sequence is the major contributor to the currently observed differentiation between dogs and wolves.

GO (gene ontology) analysis of the 204 genes revealed most overrepresentation in categories referring to "multicellular organismal response to stress" ($P = 9.87E-4$ adjusted by Benjamini–Hochberg FDR, False Discovery Rate), "behavioral fear response" ($P = 1.41E-3$) and "behavioral defense response" ($P = 1.41E-3$, table 1), thus supporting the hypothesis that positive selection caused a behavioral shift as dogs diverged from wolves. The first category, multicellular organismal response to stress, contained five genes: *GRIK3*, *MECP2*, *BCL2*, *GRIK2*, and *GABRA5*, whereas the other two categories each contained these same genes except *GRIK3*. All five of these genes are associated with the metabolism of glutamate (table 2), which is an important neurotransmitter in the brain (Purves et al. 2001). Because none of the fixed SNPs detected within these five genes were nonsynonymous, this suggests that shifted fear behavior that occurred during the initial domestication of the dog might be an outcome of a change in expression of the glutamate-related genes. In addition to the above genes, the gene *HTR2C* (5-hydroxytryptamine receptor 2C), which is involved in serotonin and dopamine pathway (Stam et al. 1994; Alex et al. 2005), has ten fixed SNPs differences between dogs and wolves, and also belongs to the behavioral fear response categories in the GO Annotation (www.geneontology.org). It shared interacting genes with its paralogue HTR2A, which has been suggested to modulate cognitive process by enhancing glutamate release (Feng et al. 2001).

Selective Signatures of the Dog in Glutamate-Related Signaling Pathway Genes

If selection for stress response was an initial target during domestication, then these fixed alleles should keep in a near fixed state even with amplified sampling. To test this, we resequenced the genomes of an additional three wolves and three Chinese native dogs presenting very rich genetic diversity (see supplementary material, Supplementary Material online, for more details). The fixed SNPs in the five genes: *MECP2*, *BCL2*, *GRIK2*, *GABRA5*, and *GRIK3* identified above were present as a single allele or singleton in dogs. Furthermore, we calculated F_{ST} for each SNP between dogs and wolves to evaluate the population differentiation, and identified GO categories for genes containing SNPs with F_{ST} values statistically significantly higher than the average for SNPs for genome-wide genes. The GO categories showing the greatest statistical significance were "adenylate cyclase inhibiting G-protein coupled glutamate receptor activity" (GO: 0001640) and "G-protein coupled glutamate receptor signaling pathway" (GO: 0007216). Similarly, two pathways involved in glutamate receptor activity, "glutamate receptor signaling pathway" (GO: 0007215) and adenylate cyclase-inhibiting G-protein coupled glutamate receptor signaling pathway (GO: 0007196), were also among the top ten categories with greatest significances.

Because the F_{ST} parameter does not show the direction of selection, and cannot identify upon which lineage, dog or wolf, explains the divergence for these categories, we applied the parameter XP-EHH (Sabeti et al. 2007) to evaluate selection on the SNPs in the dog lineage after divergence form the

Table 1

GO Analysis of Genes Containing Large Numbers of Fixed SNP Differences between Wolves and Dogs

P Value	Gene Number	Term ID	Term Type	Term Name
9.87E-04	5	GO:0033555	BP	Multicellular organismal response to stress
1.41E-03	4	GO:0001662	BP	Behavioral fear response
1.41E-03	4	GO:0002209	BP	Behavioral defense response
3.51E-03	4	GO:0042596	BP	Fear response
6.82E-03	15	GO:0005975	BP	Carbohydrate metabolic process
1.94E-02	2	GO:0014041	BP	Regulation of neuron maturation
3.16E-02	3	GO:0042551	BP	Neuron maturation
4.18E-02	3	GO:0005605	CC	Basal lamina
4.78E-02	10	HP:0001417	hp	X-linked inheritance
5.00E-02	10	HP:0010985	hp	Gonosomal inheritance
2.29E-03	6	KEGG:04973	ke	Carbohydrate digestion and absorption
3.52E-03	5	GO:0019903	MF	Protein phosphatase binding
6.91E-03	3	GO:0017046	MF	Peptide hormone binding
5.00E-02	5	GO:0019902	MF	Phosphatase binding

NOTE.—BP, biological process; CC, cellular component; MF, molecular function; hp, human phenotype; ke, kegg pathway.

Table 2

Description of the Functions of Five Genes Potentially under Selection in the Dog

Genes	Performance in Functional Assay	Reference	Observed Expression Profiles Estimated by the FPKM Value		Changing Direction of Expression Pattern		
			Wolf	Dog	Observed Direction	Assumed Direction for Enhanced Synaptic Plasticity or Learning and Memory Ability	Assumed Direction for Reduced Fear or Anxiety
GRIK2	*GRIK2* deficiency showed significant reduction in anxiery and fear memory.	(Ko, et al. 2005)	23.88 (1.22*)	29.86 (5.70*)	+	+	–
	GRIK2 knock-out animals showed deficits in mossy fiber LTP.	(Breustedt and Schmitz 2004; Contractor, et al. 2001)					
GRIK3	*GRIK3* coassembles with *GRIK2*.	(Dingledine, et al. 1999)	15.24 (1.08*)	16.35 (1.15*)	+	+	
	GRIK3 knock-out animals showed deficits in mossy fiber LTP.	(Contractor et al. 2001; Pinheiro et al. 2007)					
MECP2	*MECP2* deficiency related with increased anxiety, reduced learning, memory, and LTP; Over expression show reduced anxiety, enhanced learning, memory, synaptic plasticity, and LTP (but see Tau-Mecp2).	(Na et al. 2013)	4.15 (1.29*)	6.92 (2.18*)	+	+	+
	MECP2 deficiency enhances glutamate release.	(O'Driscoll et al. 2013)					
GABRA5	Anxiety correlates with hippocampal *Gabra5* mRNA increase.	(Clement et al. 2012)	19.57 (0.90*)	17.50 (−2.05*)	–		–
	Decreased *Gabra5* associated with increased fear.	(Ponder et al. 2007)					+
	Reverse memory deficits by inhibiting *GABRA5*.	(Wang et al. 2012)				–	
BCL2	Fear decreased with overexpressed *BCL2*.	(Rondi-Reig, et al. 1997)	6.43 (0.88*)	5.71 (−0.91*)	–		+
	Reduced *BCL2* levels with significant increase of anxiety-like (fear) behaviors.	(Einat et al. 2005)					+
	Overexpression of *BCL2* was detected with impaired learning and memory.	(Wei et al. 1996)				–	
	Transgenic mice with overexpression of *BCL2* have learning deficits.	(Rondi-Reig et al. 1997; Rondi-Reig and Mariani 2002)				–	
	Negative correlation between the *BCL2* expression and glutamate concentration.	(Schelman et al. 2004)					

NOTE.—"+" represents increased expression level in dog relative to wolf. "–" represents decreased expression level in dog relative to wolf. "*" in the blanket stands for the *Z*-score.

wolf. XP-EHH values on the dog lineage for genes involved in the glutamate receptor pathway retained statistically significant high values, suggesting that positive selection on these glutamate receptor pathway genes potentially occurred during the domestication of dog from wolf, and account for their change in behavior.

A considerable proportion of selective signatures was due to hitchhiking accompanied with the high intensity of artificial selection on a selected few genes. Accordingly, we next examined whether the observed signature of selection seen in glutamate metabolism genes was due to selection or hitchhiking. The Hill–Robertson effect states that selection is most effective when variants freely recombine (Hill and Robertson 1966). Selective sweeps are expected to extend less far in regions of higher recombination rate, and thus allele frequency differentiation is expected to be negatively correlated with recombination rate under hitchhiking. At the genomic level in dogs, the evolutionary rate for a SNP correlates negatively with its recombination rate (fig. 1*C*, $r = -6.096e-04$, $P < 2e-16$), which is consistent with the overall pattern observed in rice (Lu et al. 2006) and humans (Keinan and Reich 2010). In contrast, SNPs within GO: 0001640 category (the most divergent category) showed positive correlation between evolutionary rate and recombination rate, although the correlation was not statistically significant as it referred to only one gene (fig. 1*C*, $r = 0.102$, $P = 0.325$). Furthermore, GO:0007216 category from Ensembl version 74 (containing four genes: *GRIK3*, *GRM5*, *GRM6*, and *TRPM1*) showed a statistically significant positive correlation ($r = 0.014$, $P = 0.00133$). Thus, our result indicated that positive selection occurred on glutamate metabolism genes during the domestication of the dog.

Potential Function of Candidate Genes with Changed Expression Direction

Glutamate is the major excitatory neurotransmitter in the brain that regulates many kinds of behaviors and emotions and plays a key role in cognitive ability, including learning and memory through influencing short- and/or long-term potentiation (LTP) (Purves et al. 2001). Both *GRIK2* (glutamate receptor, ionotropic, kainate 2) and *GRIK3* (glutamate receptor, ionotropic, kainate 3) are glutamate receptors. *GRIK2* knock-out mice exhibit significant reduction in anxiety and fear memory (Ko et al. 2005). Although no clear function has been identified for *GRIK3*, it coassembles with GRIK2 to form the kainate glutamate receptor (Dingledine et al. 1999), and deficits in mossy fiber LTP were observed in *GRIK2* and *GRIK3* knock-out animals (Contractor et al. 2001; Schmitz et al. 2003; Breustedt and Schmitz 2004; Pinheiro et al. 2007). Our analysis of the frontal cortex transcriptome data showed that *GRIK2* is expressed at a significantly higher level in the frontal cortex of the dog than in the wolf ($P = 0.0006$ by the Mann–Whitney *U* test). Intriguingly, we also found a consistent up-regulation of *GRIK2* in other domesticated animals compared with wild counterpart (student's *t*-test), including chicken ($P = 0.249$), rat ($P = 0.068$), guinea pig ($P = 0.045$, data from Albert et al. [2012]), and rabbit ($P = 0.381$, data from Albert et al. [2012]) (supplementary table S1, Supplementary Material online), which showed a convergent evolution among domesticated animals. Increased transcription of *GRIK2* should increase anxiety and fear memory (table 2). Consistent with the changes in *GRIK2*, *BCL2*, and *GABRA5* also present changes (but no statistical significance) in their levels of expression in dogs compared with wolves that should increase the fear response in dogs (table 2).

We note that the changes in expression levels for these divergent genes were moderate, but they presented changes that contradict the expected expression pattern by the correlated by-product hypothesis, which proposed the fear reduction in the primary dogs to explain the prerequisite of the domestication. These moderate changes may be attributed to the minor effects of many genes underlying the selective targets, which may often occurred during the initial phase of domestication. Actually, according to the weighted gene coexpression network analysis (WGCNA) analysis (Langfelder and Horvath 2008), *GRIK2*, *GRIK3*, *GABRA5*, and *MECP2* showed coexpression pattern and belonged to the same gene coregulatory network (e.g., module) which presented special positive correlation with the frontal cortex of wolf and dog ($P = 4e-05$ and 6e-05, respectively) (see supplementary fig. S1 and material, Supplementary Material online, for details). Moreover, *GRIK2*, *GRIK3*, and *GABRA5* all present to be hub genes in this module (MM = 0.943, 0.914, and 0.917, respectively), indicating their important functions within this module on nervous system.

A Hypothesis of "Enhanced Excitatory Synaptic Plasticity"

It should be noted that the roles predicted for these genes in the fear response research (table 2) were all tested under Pavlovian fear conditioning, from which fear (the conditioned response) was trained to accompany a noxious stimuli. These Pavlovian tests contrast with both the fox experiment (Trut 1999) and dog domestication, where punishments were not received when the animals became close to humans. Additional pleiotropic functions of glutamate may have also contributed to the successful domestication of the wolf. The direction of change in the expression of the five genes should tend to cause excitatory synaptic plasticity in neural cells and/or benefit memory ability (although gene *MECP2* locates in X chromosome, the equal sex ratio for both the domesticated and wild groups should eliminate the sex-linked effects on dosage). Consistent with this suggestion, dogs exhibit more excitatory behaviors than wolves, which sometimes becomes an overreaction yielding anxiety, or even obsessive-compulsive disorder, which may be associated with glutamate-related

genes (Sampaio et al. 2013). Changes in synaptic plasticity are thought to be associated with changes in learning and memory abilities, by affecting short- and LTP (Purves et al. 2001). Thus, our results partially support the selection for communication hypothesis, where a strengthened learning ability should help the skill of reading human communicative behaviors. However, interspecific communication would only begin after a long period of scavenging life that enhanced the interactions between humans and wolves. In the "self-domestication" model, wolves domesticated themselves into dogs overtime of scavenging lifestyle (Coppinger and Coppinger 2001). In such a wild environment, the reduced fear response proposed by the correlated by-product hypothesis may be hard for these dog progenitors to survive. It therefore could be reasoned that during the early stages, the wolves with better learning and memory abilities would come close to human settlements more frequently, acquire greater food resources, and thus had greater opportunities to survive (with little disadvantage). These individuals would perform nonaggressive response because they would understand that the presence of humans was harmless, and thus would have a weakened fear reaction. We therefore propose a "selection for excitatory synaptic plasticity" hypothesis to account for the successful domestication of dogs from wolves. Following this hypothesis, affected learning and memory abilities would facilitate the behavioral shift, prolonged exposure to humans, and helped the dogs to understand the meaning of our gestures. Comparison of the genome of experimental foxes that have been tamed, and the unselected controls, may be an approach to test this hypothesis.

Materials and Methods

Reads of genome sequences were mapped onto the reference genome by using BWA-MEM (bio-bwa.sourceforge.net), and SNPs were calling by Genome Analysis Toolkit (McKenna et al. 2010) (GenomeAnalysisTK-2.6-4-g3e5ff60). The RNA-seq data from the frontal cortex of the wolf and the dog were from Albert et al. (2012). Tophat (Trapnell et al. 2009) and Cufflinks (Trapnell et al. 2010) were used to assemble transcripts and calculate the expression value of genes. GO analysis was performed using g:profiler (http://biit.cs.ut.ee/gprofiler/). Weighted gene coexpression networks were performed by WGCNA package implemented in R (Langfelder and Horvath 2008).

The full experimental methods are provided in supplementary material S1, Supplementary Material online.

Supplementary Material

Supplementary material, table S1, and figure S1 are available at *Genome Biology and Evolution* online (http://www.gbe.oxfordjournals.org/).

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