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Accelerated Evolution of Nervous System Genes in the Origin of *Homo sapiens*

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Summary

Human evolution is characterized by a dramatic increase in brain size and complexity. To probe its genetic basis, we examined the evolution of genes involved in diverse aspects of nervous system biology. We found that these genes display significantly higher rates of protein evolution in primates than in rodents. Importantly, this trend is most pronounced for the subset of genes implicated in nervous system development. Moreover, within primates, the acceleration of protein evolution is most prominent in the lineage leading from ancestral primates to humans. Thus, the remarkable phenotypic evolution of the human nervous system has a salient molecular correlate, i.e., accelerated evolution of the underlying genes, particularly those linked to nervous system development. In addition to uncovering broad evolutionary trends, our study also identified many candidate genes—most of which are implicated in regulating brain size and behavior—that might have played important roles in the evolution of the human brain.

Introduction

Greatly expanded and highly complex brains are among the most defining attributes distinguishing primates, especially humans, from other mammals (Brodmann, 1912; Jerison, 1973; Finlay and Darlington, 1995). As a result of increased brain size and complexity, behavioral repertoires became much richer in primates, culminating in highly sophisticated cultural behaviors in humans such as language, tool use, and social learning (Spuhler, 1959; Matsuzawa, 2001).

In past decades, researchers have devoted significant efforts toward understanding the evolutionary processes that gave rise to the distinct features of the human brain. Traditionally, such efforts have focused on the anatomical and physiological differences between the human brain and that of the other taxa, as well as the behavioral manifestations of these differences (Jerison, 1973; Byrne and Whiten, 1988; Aiello and Dean, 1990; Matsuzawa, 2001). More recently, the genetic basis of brain evolution has emerged as a topic of considerable discussion. Of particular interest are questions regarding what genes underlie brain differences between humans and other species, and how changes in these genes led to specific alterations in brain biology. As yet, these important questions remain poorly explored. In this study, we probe these questions by comparative genomics studies utilizing both primates and nonprimate species.

It has long been noted that brains of various extant and extinct primates display remarkable variation in size, organization, and behavioral output (Noback and Montagna, 1970; Armstrong and Falk, 1982; Byrne and Whiten, 1988; Matsuzawa, 2001). This is particularly true for the evolutionary lineage leading from ancestral primates to humans, in which the increase in brain size and complexity was remarkably rapid and persistent throughout the lineage (Jerison, 1973; Walker et al., 1983). In contrast, for most nonprimate mammalian orders, the extent of intra-ordinal brain differences is much more limited (Brodmann, 1912; Pagel and Harvey, 1989). For example, the encephalization quotient, a rough measure of brain size scaled allometrically to body size, can differ by more than an order of magnitude between humans and nonhuman primates, but varies much less between species of any nonprimate order (Williams, 2002). Thus, the phenotype of the nervous system has apparently undergone far greater evolutionary changes in primates than most other mammals.

Extrapolating from these observations, we hypothesized that the intensified phenotypic evolution of the brain seen in primates might have a molecular correlate—that is, genes involved in nervous system biology might display more dynamic molecular evolutionary changes in primates relative to nonprimate mammals. We further surmised that within primates, the lineage leading from ancestral primates to humans might exhibit more dramatic evolutionary changes than other primate lineages, on the basis that the increase in brain size and complexity is most profound in the lineage leading to humans.

In this study, we compared the evolutionary rates of an extensive set of nervous system-related genes between primates and rodents. To obtain evolutionary rates in primates, we compared sequences between human and the Old World monkey, macaque. We note that even though much discussion of human evolution has focused on human-chimpanzee comparisons, the strong sequence similarities between these two species results in high stochastic uncertainty in the estimation of evolutionary rates. This is likely to reduce the statistical power in detecting interesting evolutionary signatures. Human-macaque comparisons, in contrast, offer much more accurate rate estimation because of the considerably greater sequence divergence. For the nonprimate mammalian order, we used rodents, with rat and mouse as the species chosen for comparison. The evolutionary time separating human and macaque (20–25 million

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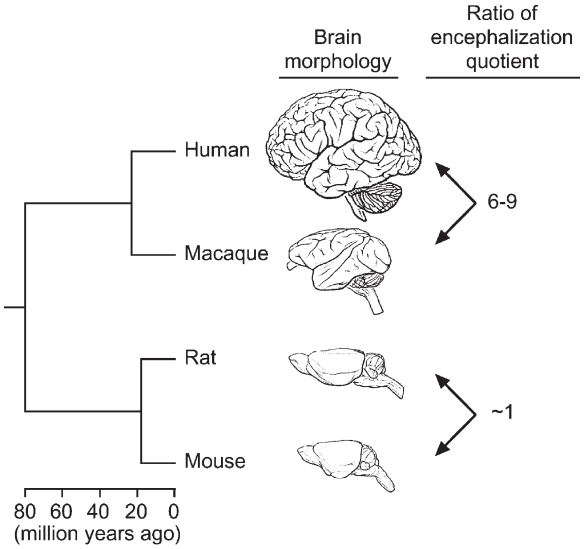

Figure 1. Phylogenetic Relationship of the Four Taxa Used in the Study

Ratios of encephalization quotient (brain size allometrically scaled to body size) between taxa are indicated following published data (Williams, 2002). Brains of different taxa are not drawn to scale of absolute size. Estimated evolutionary time separating these four taxa is depicted.

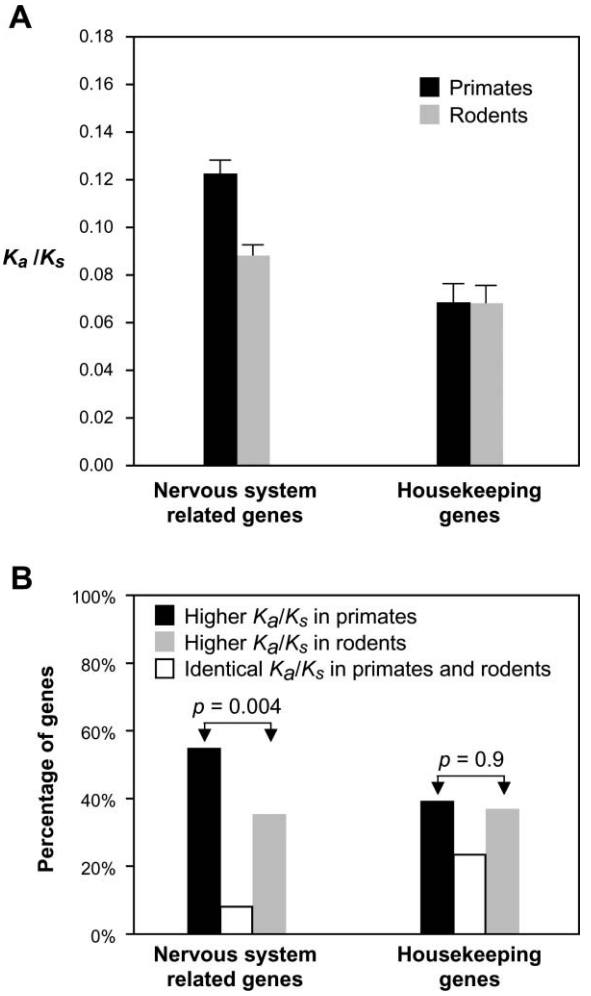

Figure 2. Evolution of Nervous System Genes and Housekeeping Genes in Primates and Rodents

(A) Evolutionary rates in primates and rodents.

(B) Percentage of genes that evolved with higher K_a/K_s in one or the other mammalian order.

The p values indicate the statistical significance of primate-rodent disparities.

years) is grossly comparable to that separating rat and mouse (16–23 million years) (Kumar and Hedges, 1998; Springer et al., 2003). However, point mutation rates are lower in primates than in rodents (Gibbs et al., 2004), which results in the synonymous sequence divergence between human and macaque being about half that between rat and mouse. Despite the fact that human-macaque sequence divergence is less, the size and complexity of the brain differ profoundly between these two primates while remaining grossly comparable between the two rodents (Figure 1). Comparisons of these four taxa should, therefore, allow us to interpret any molecular evolutionary differences of nervous system genes between primates and rodents within the meaningful context of contrasting evolutionary outcomes in brain phenotypes between these two mammalian orders.

By comparing nervous system genes across the four aforementioned taxa, we demonstrate that the average rate of protein evolution as scaled to neutral divergence is indeed considerably faster in primates than in rodents and that this trend is most pronounced for the subset of genes implicated in nervous system development. We further show that within primates, such evolutionary acceleration is much greater in the lineage leading from ancestral primates to humans relative to lineages leading to nonhuman species. Thus, the dramatic evolution of nervous system phenotype in primates, particularly humans, is indeed correlated with salient molecular evolutionary footprints in the underlying genes.

Results

Evolution of Nervous System Genes

We used multiple criteria to compile a list of genes as broadly representative of nervous system biology as possible. First, we performed extensive literature searches to obtain a set of genes demonstrated to play important roles in the nervous system. Second, we used databases of expressed sequence tags (ESTs) and SAGE tags (Velculescu et al., 1999) to identify a group of genes expressed exclusively or predominantly in the brain. Lastly, we included a set of genes implicated in various diseases of the nervous system, such as brain malformations, mental retardation, and neurodegeneration. Many of the genes appear to function exclusively in the nervous system whereas others may also play roles in additional tissues. In either case, the prominent involvement of these genes in the nervous system makes them good candidates for our study. By sequencing and bioinformatics, we obtained orthologous sequences for 214 such genes in all of the four taxa chosen for this study (Supplemental Table S1 at http://www.cell.com/cgi/content/full/119/7/1027/DC1/). We note that these genes are scattered randomly across the genome. Be-

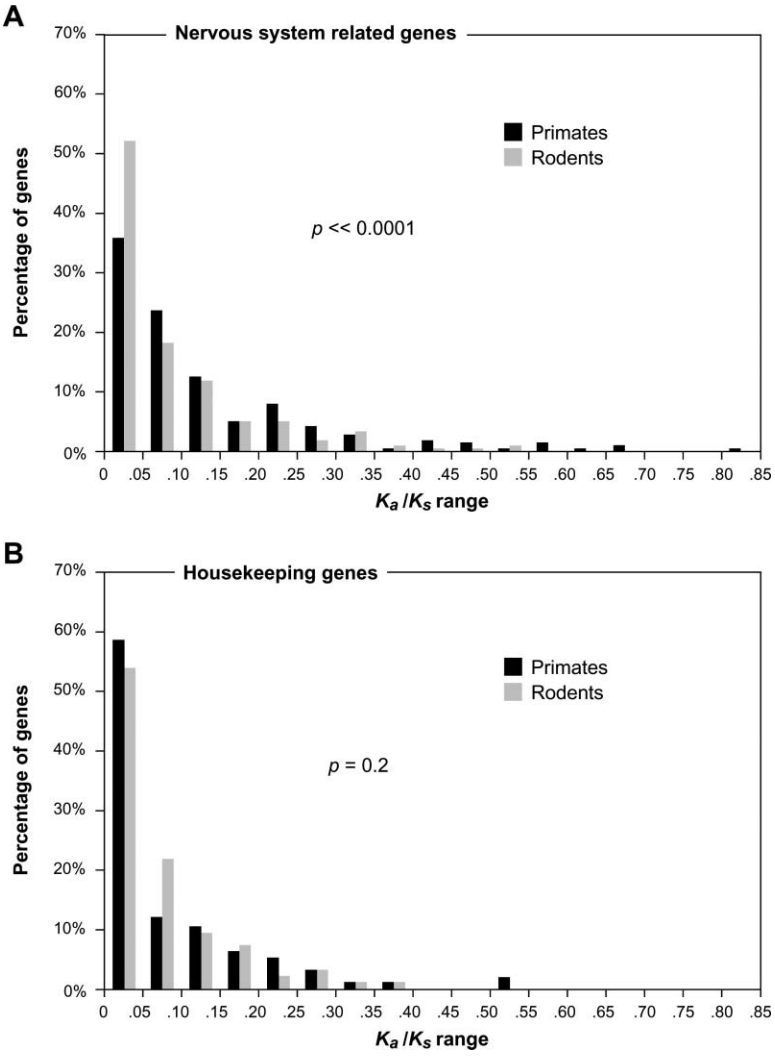

Figure 3. The K_a/K_s Distributions of Nervous System Genes and Housekeeping Genes in Primates and Rodents

(A) Nervous system-related genes.
(B) Housekeeping genes.
The p values indicate the statistical significance of primate-rodent disparities.

cause the acquisition of these genes was done without prior knowledge of their evolutionary properties, the findings discussed below are not due to selective sampling of genes with desirable evolutionary parameters.

The pace of protein evolution as scaled to neutral divergence is commonly approximated by the ratio between nonsynonymous (K_a) and synonymous (K_s) substitution rates (Li, 1997). To infer K_a/K_s ratios of genes in primates, we compared human and macaque orthologs. For rodent K_a/K_s, rat and mouse sequences were compared. The average K_s of these genes is 0.065 $\pm$ 0.028 (mean $\pm$ SD) for the primate comparison and 0.158 $\pm$ 0.063 for the rodents, in close agreement with previous reports (Yi et al., 2002; Gibbs et al., 2004). Notably, the average K_a/K_s of these genes is substantially higher (by 37%) in primates than in rodents (Figure 2A), and the disparity is statistically highly significant ($p << 0.0001$ by Fisher's exact test). As discussed below, additional statistical tests further corroborated the significance of this disparity. This result indicates that the average rate of protein evolution for these genes after scaling to neutral divergence is faster in primates than in rodents by a significant margin.

We next counted the number of genes that showed higher K_a/K_s in primates than rodents, or vice versa. We found that, not surprisingly, there were substantially more genes with higher K_a/K_s in primates than the other way around (118 versus 77; Figure 2B). Such a departure from parity is statistically significant ($p = 0.004$ by the binomial test). This observation argues that the higher average K_a/K_s in primates is contributed to by a large fraction of these nervous system genes beyond just a few outliers.

Finally, we compared the K_a/K_s distributions between primates and rodents. We found that primates have far fewer genes in the very low K_a/K_s range (i.e., $K_a/K_s \leq 0.05$) as compared to rodents, and more genes in the high K_a/K_s range (Figure 3A). Statistical tests confirmed that the primate distribution differed significantly from the rodent distribution ($p << 0.0001$ by the Wilcoxon signed-rank test).

Evolution of Housekeeping Genes

The significantly higher average K_a/K_s of nervous system genes in primates is suggestive of adaptive evolution. However, this observation in itself is by no means a definitive proof of adaptive evolution because it could also arise from relaxed functional constraint. The classi-

cal (and most stringent) test of adaptive evolution requires K_a/K_s greater than 1. Yet, none of the genes sampled here have K_a/K_s greater than 1. In fact, the observation of overall low K_a/K_s is consistent with previous reports that nervous system genes tend to experience strong evolutionary constraint (Duret and Mouchiroud, 2000). Such constraint, which curbs K_a/K_s to levels substantially lower than 1, would mask the effect of adaptive evolution. We therefore sought additional evidence of adaptive evolution by examining the evolution of a set of housekeeping genes. Given that housekeeping genes perform basic cellular functions that are likely conserved across different species, they should have evolved predominantly under constraint (and experiencing little positive selection). If housekeeping genes also show higher K_a/K_s in primates, then it would cast doubt on the interpretation that the elevated K_a/K_s of nervous system genes in primates is the consequence of positive selection. We compiled a list of housekeeping genes that satisfied two stringent criteria. First, they must be involved in the most basic cellular functions such as metabolism and protein synthesis. Second, they must exhibit ubiquitous expression based on EST and SAGE databases (Velculescu et al., 1999). By sequencing and bioinformatics, we obtained orthologs for 95 such genes across the four taxa, which are scattered randomly across the genome (Supplemental Table S2 at http://www.cell.com/cgi/content/full/119/7/1027/DC1/). The average K_s of these genes is 0.061 $\pm$ 0.032 (mean $\pm$ SD) for the primate comparison and 0.171 $\pm$ 0.067 for the rodents, which closely parallels the nervous system genes. But unlike the nervous system genes, the average K_a/K_s of the housekeeping genes in primates is very similar to—and statistically indistinguishable from—that in rodents (Figure 2A). Additionally, the fraction of genes with higher K_a/K_s in primates is comparable to that with higher K_a/K_s in rodents (37 versus 35; Figure 2B). Finally, the K_a/K_s distributions of these genes are not statistically distinct between primates and rodents (Figure 3B). This finding indicates comparable levels of selective constraint on housekeeping genes between primates and rodents. It therefore argues that the considerably higher average K_a/K_s of nervous system genes in primates is not a part of a nonspecific, genome-wide phenomenon.

Classification of Nervous System Genes

The above results still leave open two possible interpretations. One is stronger positive selection on nervous system genes in primates than rodents. The other is weaker functional constraint on these genes in primates. We argue that the possibility of weaker constraint seems unlikely, on the basis that the primate nervous system is far more complex (and therefore likely demanding greater precision in gene function) relative to the rodent nervous system. This consideration notwithstanding, we searched for additional evidence that might differentiate between positive selection and relaxation of constraint. To this end, we focused on two categories of genes that are particularly relevant to the understanding of nervous system evolution. One comprises genes whose functions are strongly biased toward nervous system development. The other consists of genes biased toward the routine physiological operations and maintenance of the nervous system.

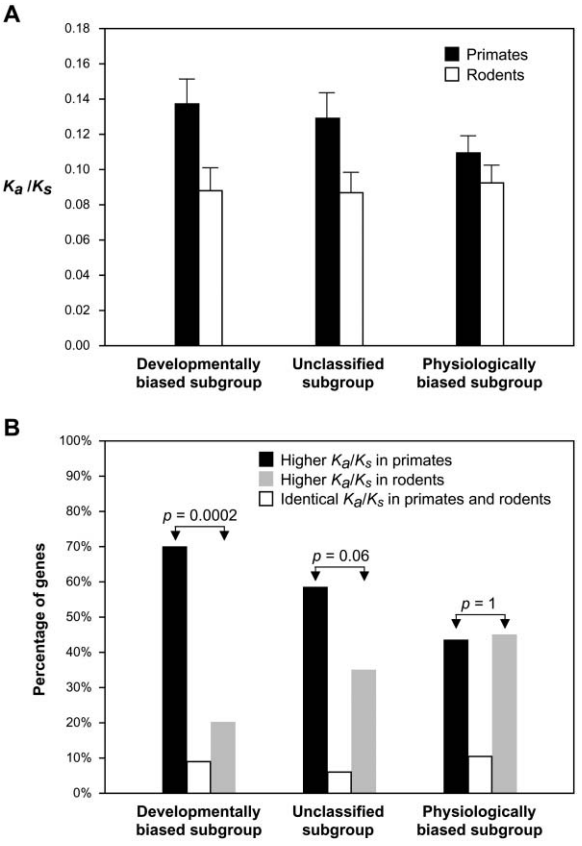

Figure 4. Evolution of Different Functional Subgroups of Nervous System Genes

(A) Evolutionary rates in primates and rodents.

(B) Percentage of genes that evolved with higher K_a/K_s in one or the other mammalian order.

The p values indicate the statistical significance of primate-rodent disparities.

The evolution of the primate brain is characterized by extensive structural modifications, which are necessarily achieved through changes in the molecular programs that underlie brain development. If the higher K_a/K_s of nervous system genes in primates is indeed the consequence of positive selection, then such selection is likely to have impinged more intensely on the developmentally biased genes. The result would be even greater primate-rodent K_a/K_s disparity (in the direction of higher primate K_a/K_s) for the developmental genes, and perhaps less K_a/K_s disparity for the physiological genes. To test this hypothesis, we classified our nervous system genes into subgroups whose functions are biased toward either nervous system development or physiology. We took several cautionary measures to minimize the inherent uncertainty in the functional classification of genes. First, we imposed stringent definitions on both subgroups. Genes were included in the developmentally biased subgroup only if a preponderance of evidence, particularly in vivo gain- or loss-of-function studies, had demonstrated unequivocal roles of these genes in nervous system development. On the other hand, genes were placed in the physiologically biased category only if a combination of biochemical, pharmacological, and

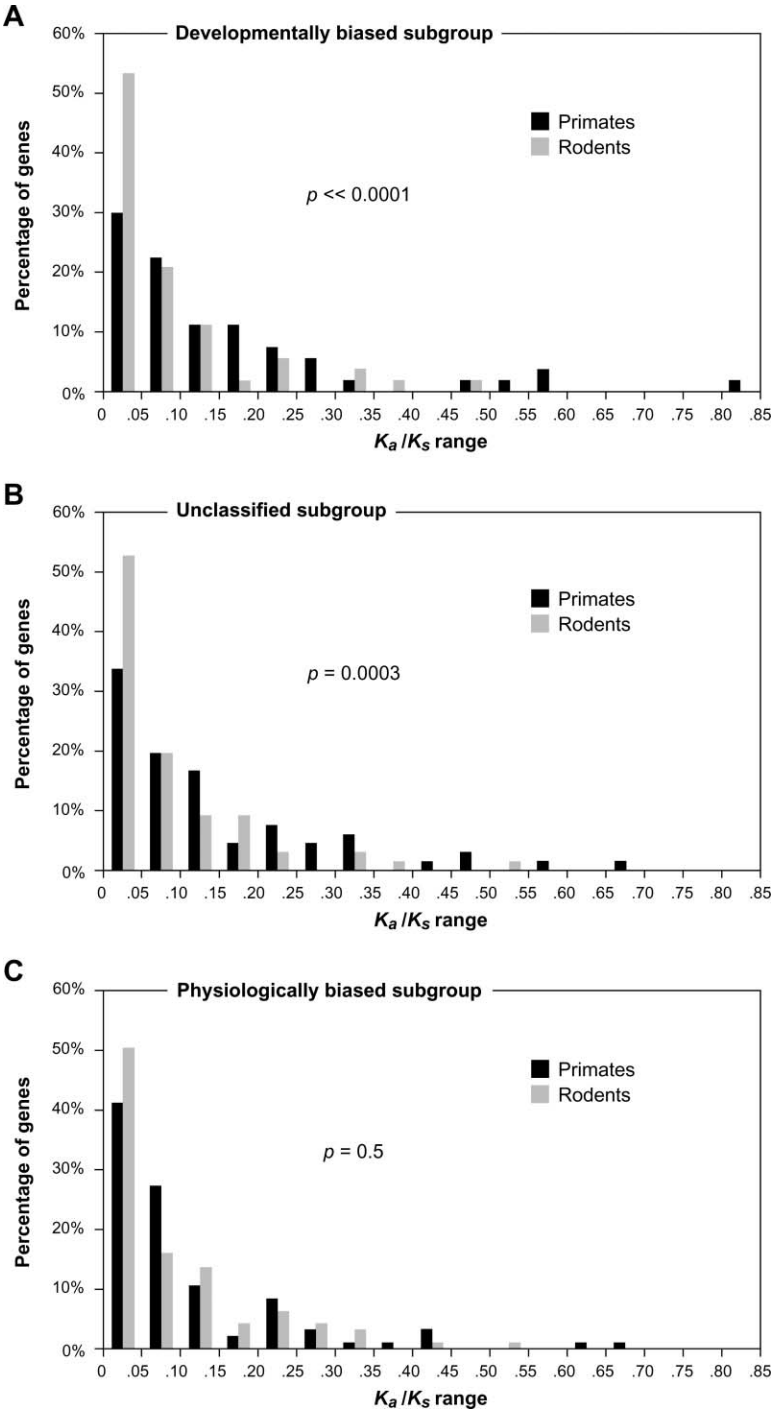

Figure 5. The K_a/K_s Distributions of Three Subgroups of Nervous System Genes in Primates and Rodents

(A) Developmentally biased subgroup.
(B) Unclassified subgroup.
(C) Physiologically biased subgroup.
The p values indicate the statistical significance of primate-rodent disparities.

genetic evidence had shown that their predominant functions lie in the routine operation and maintenance of the nervous system. Second, we created an "unclassified" subgroup to encompass all the genes that could not be clearly assigned to the first two categories, either because of insufficient functional data or because they appear to be prominently involved in both neural development and physiology. Third, classification of genes was performed blind to the evolutionary properties of these genes.

The nervous system genes were partitioned into these three subgroups without any overlap between categories. The developmentally biased subgroup contained 53 genes that included patterning signals of the developing nervous system, downstream components of such signals, transcription factors that specify neuronal phenotypes, and regulators of neural precursor proliferation, apoptosis, differentiation, migration, and morphogenesis. The physiologically biased subgroup had 95 genes, comprised predominantly of neurotransmitters, their synthesis enzymes and receptors, neurohormones, voltage-gated ion channels, synaptic vesicle compo-

nents, factors involved in synaptic vesicle release, metabolic enzymes specific to neurons or glia, and structural components of the nervous system. The unclassified subgroup contained the remaining 66 genes. Notably, the developmentally biased subgroup showed even greater K_a/K_s disparity between primates and rodents than did the entire set of nervous system genes. The average K_a/K_s of this subgroup is significantly higher (by 53%) in primates than in rodents ($p = 0.002$ by Fisher's exact test; Figure 4A). In addition, the great majority of developmental genes exhibited higher K_a/K_s in primates whereas only a small fraction displayed higher K_a/K_s in rodents (37 versus 11), which is a significant departure from parity ($p = 0.0002$ by the binomial test; Figure 4B). In contrast to the developmental genes, the physiologically biased subgroup exhibited much less primate-rodent K_a/K_s disparity (Figure 4A). Furthermore, the number of genes in this subgroup with higher K_a/K_s in primates is comparable to that with higher K_a/K_s in rodents (42 versus 43; Figure 4B). Indeed, the reason that the average K_a/K_s of the physiological subgroup is slightly higher in primates can be attributed to a subset of outliers with markedly higher K_a/K_s in primates than in rodents (these outliers are discussed later).

Interestingly, the unclassified subgroup shows evolutionary parameters that are intermediate between the developmental and the physiological subgroups. This is true when considering K_a/K_s values (Figure 4A) or the number of genes with higher K_a/K_s in either primates or rodents (39 versus 23; Figure 4B). We next compared K_a/K_s distributions between primates and rodents for each subgroup. For the developmental subgroup, primates showed a marked deficiency of genes in the lowest K_a/K_s range (i.e., $K_a/K_s \leq 0.05$) as compared to rodents, but a relative excess of genes in the higher K_a/K_s range (Figure 5A). In particular, the very top K_a/K_s ranges ($K_a/K_s > 0.5$) contain only primate, and no rodent genes. This notable primate-rodent disparity is statistically highly significant ($p << 0.0001$ by the Wilcoxon signed-rank test). In contrast, K_a/K_s distributions of the physiological genes are much more similar between primates and rodents and are not statistically distinct (Figure 5C). For the unclassified subgroup, the K_a/K_s distributions again exhibit an intermediate level of primate-rodent disparity (Figure 5B).

The higher K_a/K_s of nervous system genes in primates means that there is an overabundance of amino acid substitutions (after scaling to neutral divergence) in primates as compared to rodents. A rough estimate suggests an excess of 1–2 amino acid substitutions per nervous system gene in primates than would have occurred if the average K_a/K_s in primates was similar to (rather than significantly higher than) the average rodent K_a/K_s. The excess becomes 3–4 substitutions per gene in primates when considering only the developmental subgroup.

Genes with Marked Evolutionary Rate Disparities between Primates and Rodents

To identify candidate genes whose molecular evolutionary changes might bear particular relevance to brain evolution, we searched for genes with the most marked K_a/K_s disparities between primates and rodents. Using a p value of 0.05 as a cutoff, we obtained a set of 24 outlying genes with significantly higher K_a/K_s in primates than in rodents (hereon referred to as "primate-fast outliers") (Table 1A).

As expected, the developmental subgroup has the highest proportion of outliers (9 out of 53, or 17%). The physiological subgroup contains 9 outliers among 95 genes (9%), while the unclassified subgroup has 6 outliers among 66 genes (9%). Interestingly, a preponderance of these outliers appeared to be involved in controlling brain size or behavior. Mouse knockout of *CASP3* exhibits severe overgrowth of the brain; *LHX1* knockout shows absence of brain and other anterior structures; and *NRCAM* knockout leads to reduced cerebellum size. Perhaps even more interesting are the observations that mutations in human *ASPM*, *MCPH1*, *PAFAH1B1*, and *SHH* all result in severe reductions in brain size (microcephaly). Hence, 7 of the outliers are implicated in controlling brain size. Mouse knockout of *DVL1* displays defective social behavior; *PEG3* knockout shows impaired maternal behavior; *ADCYAP1* knockout exhibits altered anxiety state; knockouts of *GDI1*, *GRIN2A*, or *CSPG3* show deficits in learning or neural correlates of learning; knockouts of *CHRM5*, *DRD2*, or *OPRM1* exhibit defects in acquiring reward-mediated behavior; and mutation in *AANAT* alters circadian rhythm. Thus, 10 of the outliers are involved in regulating behavior.

It is remarkable that 17 out of the 24 primate-fast outliers are linked to the regulation of either brain size or behavior. This trend suggests that genes controlling brain size or behavior are preferential targets of positive selection during primate evolution. The functional specificity of these outliers adds additional credence to the notion that the higher K_a/K_s of nervous system genes in primates is likely the consequence of adaptive evolution.

For the developmental and unclassified subgroups, removal of the primate-fast outliers only moderately reduced the overall primate-rodent K_a/K_s disparities (data not shown). This suggests that for these two subgroups, the higher average K_a/K_s in primates is contributed to by many genes, and not just the primate-fast outliers. For the physiological subgroup, however, removal of the outlying genes actually led to higher average K_a/K_s in rodents than in primates (by nearly 10%). This hints at the possibility that, overall, physiological genes might actually be slightly more conserved in primates, except for a small subset of genes that underwent adaptive evolution (and hence exhibiting much higher K_a/K_s in primates).

Using the same statistical cutoff, we also obtained 3 rodent-fast outliers, considerably fewer than the primate-fast outliers (Table 1B). Such a dramatic disparity is consistent with the tendency of nervous system genes to have higher K_a/K_s in primates than in rodents. Among the 95 housekeeping genes, only two showed significant K_a/K_s disparities between primates and rodents, and both had higher K_a/K_s in rodents (Supplemental Table S2 online). This reinforces the notion that housekeeping genes evolved under levels of selective constraint that tended to remain steady across different mammalian lineages.

Comparison between Human Lineage and Macaque Lineage

Increases in brain size and complexity are evident in the evolution of many primate lineages (Jerison, 1973).

However, this increase is far more dramatic in the lineage leading to humans than in other primate lineages (Williams, 2002). If the higher average K_a/K_s of nervous system genes in primates (based on human-macaque comparison) is indeed the product of adaptive evolution, then one might expect this accelerated evolution to be more dramatic in the lineage leading from human-macaque ancestors to humans than the lineage leading to macaques. To address this possibility, we followed a phylogeny-based methodology as previously described (Messier and Stewart, 1997). Specifically, we chose squirrel monkey (*Saimiri boliviensis*), a New World monkey, as an outgroup to partition human-macaque sequence divergence into the two respective branches. (Squirrel monkey can serve as a highly reliable outgroup because it is closely related to the catarrhine clade containing human and macaque; rat and mouse are too distantly related to primates to be reliable outgroups.)

We first focused on the primate-fast outliers of the nervous system genes because they have the greatest likelihood of bearing relevance to primate brain evolution. Using squirrel monkey sequences as an outgroup, we found that they have much higher average K_a/K_s in the human lineage than the macaque lineage (Figure 6A) and that the difference is statistically significant ($p = 0.004$ by Fisher's exact test). Additionally, at the level of individual genes, the great majority (20 out of 24) evolved faster in the human lineage, which is a significant departure from parity ($p = 0.002$ by the binomial test).

As a control, we also examined a set of 25 nervous system genes with comparable evolutionary rates between primates and rodents and found that these genes do not show any statistically significant K_a/K_s disparities between the human and the macaque lineages (Figure 6A).

Thus, nervous system genes with higher K_a/K_s values in primates than in rodents also have a strong tendency to have higher K_a/K_s in the human branch than in the macaque branch. That the K_a/K_s of these genes is markedly and specifically elevated along the human branch—in which the increase in brain size and complexity is most dramatic—further argues that adaptive evolution rather than relaxed functional constraint is likely responsible.

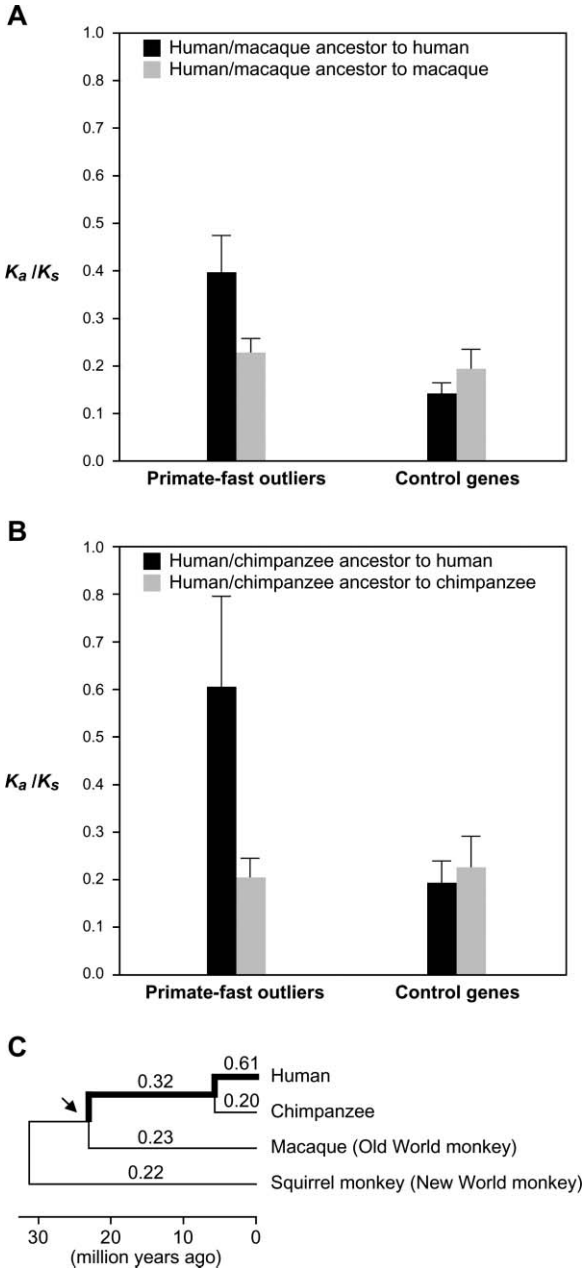

Figure 6. Evolutionary Rates of the Primate-Fast Outliers and the Control Group of Nervous System Genes in Different Primate Lineages

(A) Comparison between the lineage from human-macaque ancestor to human and the lineage to macaque.

(B) Comparison between the lineage from human-chimpanzee ancestor to human and the lineage to chimpanzee.

(C) Phylogenetic tree depicting K_a/K_s values along the primate lineage leading to humans (bolded lines) and in nonhuman primate lineages (plain lines). Note that the K_a/K_s value shown next to the squirrel monkey branch applies to the entire lineage from the catarrhine ancestor node (indicated by arrow) to squirrel monkey.

Comparison between Human Lineage and Chimpanzee Lineage

Another important question is whether nervous system genes show different K_a/K_s between the human lineage and the chimpanzee lineage after the divergence of these two lineages. To address this question, we obtained chimpanzee sequences for both the primate-fast outliers and the control group. We then used macaque as an outgroup to partition human-chimpanzee divergence into separate human and chimpanzee branches. For the primate-fast outliers, the K_a/K_s of the human branch is considerably higher than the chimpanzee branch (Figure 6B). For the control genes, the two lineages show comparable and statistically indistinguishable K_a/K_s values (Figure 6B).

An important caveat in the above analysis is ascertainment bias. The primate-fast outliers were expected to show higher K_a/K_s in the human terminal branch (i.e., from human-chimpanzee ancestors to humans) than in the chimpanzee terminal branch, due to the fact that these genes were ascertained on the basis of elevated K_a/K_s in the human-to-macaque lineage (which subsumes the human terminal branch). We therefore performed computer simulations to evaluate the extent to

Table 1. Nervous System Genes Showing Significantly Faster Evolution in Either Primates or Rodents

A. Genes Showing Faster Evolution in Primates

Gene Class	Gene Symbol	Gene Name	Function in Nervous System	Nervous System Phenotype of Mutants	Primate			Rodent			References
					Ka	*Ks*	*Ka*/*Ks*	*Ka*	*Ks*	*Ka*/*Ks*	
Developmental	*ASPM*	Abnormal spindle-like microcephaly associated	A spindle-associated protein implicated in determining cerebral cortical size, presumably by regulating neural progenitor division and differentiation	Human homozygous mutations cause primary microcephaly, which is characterized by severely reduced brain size without other overt neuropathologies or dysmorphic features.	0.020	0.041	0.488	0.083	0.238	0.349	Bond et al., 2002
	CASP3	Caspase 3	A protease involved in the activation of the apoptosis pathway during neural precursor proliferation	Mouse homozygous mutants show marked brain ventricular zone expansion, exencephaly, and ectopic neuronal structures.	0.022	0.040	0.550	0.035	0.322	0.109	Kuida et al., 1996
	DVL1	Dishevelled 1	A PDZ-domain-containing protein involved in the Wnt signaling pathway	Dominant-negative mutation of *Dishevelled* in frog causes failure of neural axis formation. Mouse homozygous mutants show defects in social behavior, such as huddling, whisker trimming, and nest building, and in sensorimotor gating.	0.009	0.137	0.066	0.002	0.100	0.020	Sokol, 1996; Lijam et al., 1997
	LHX1	LIM homeo box 1	A transcription factor essential in organizing the anterior structures during development	Mouse homozygous mutants lack brain and other anterior head structures, but show normal development in the remaining body axis.	0.006	0.075	0.080	0.002	0.141	0.014	Shawlot et al., 1995
	MCPH1	Microcephalin	Implicated in the control of brain size, presumably by affecting the proliferation of neural progenitors	Human homozygous mutation leads to primary microcephaly.	0.040	0.048	0.833	0.070	0.146	0.479	Jackson et al., 2002
	NRCAM	Neuronal cell adhesion molecule	A cell adhesion molecule involved in developmental signaling of the nervous system	Mouse homozygous mutants show failure of cerebellar granule cells to extend neurites in vitro and reduced cerebellum size in vivo.	0.019	0.085	0.224	0.009	0.177	0.051	Sakurai et al., 2001
	NTRK3	Neurotrophic tyrosine kinase receptor, type 3	A tyrosine kinase receptor for neurotrophin 3	Mouse homozygous mutants fail to develop proprioceptive sensory neurons.	0.003	0.068	0.044	0.000	0.134	0.000	Klein et al., 1994
	PAFAH1B1	Platelet-activating factor acetylhydrolase, 1B, alpha subunit	An acetylhydrolase implicated in microtubule function during neuronal migration	Human heterozygous mutations cause severe defects in neuronal migration, leading to significantly reduced brain size (microcephaly) and lack of brain folding (lissencephaly). Mouse heterozygous mutants show impaired neuronal migration during development.	0.005	0.048	0.104	0.000	0.057	0.000	Reiner et al., 1993; Cahana et al., 2001
	SHH	Sonic hedgehog	A signaling molecule involved in specifying ventral structures of the central nervous system, and in driving the expansion of the developing brain	Human heterozygous mutations cause severely reduced brain size (microcephaly) and fusion of the two cerebral hemispheres (holoprosencephaly). Mouse homozygous mutants lack ventral structures of the central nervous system, display severe underdevelopment of the brain and holoprosencephaly.	0.029	0.091	0.319	0.021	0.163	0.129	Belloni et al., 1996; Roessler et al., 1996; Chiang et al., 1996
Physiological	*AANAT*	Arylalkylamine N-acetyltransferase	An enzyme that converts serotonin to N-acetylserotonin, the penultimate step in melatonin synthesis	Mouse homozygous mutants (found naturally in many inbred lines) have altered activity levels and circadian behavior.	0.032	0.079	0.405	0.023	0.266	0.086	Roseboom et al., 1998
	ADCYAP1	Adenylylcyclase-activating peptide1	An adenylylcyclase-stimulating hormone secreted from hypothalamus	Mouse homozygous mutants show remarkable behavioral changes including hyperactivity, explosive jumping, increased exploratory behavior, and less anxiety.	0.074	0.113	0.655	0.034	0.191	0.178	Hashimoto et al., 2001
	CHRM5	Acetylcholine receptor, muscarinic, 5	A member of the muscarinic subtype of acetylcholine receptors	Mouse homozygous mutants show defective reward/withdrawal response to morphine, and failure in acetylcholine-mediated dilation of cerebral blood vessels.	0.021	0.034	0.618	0.018	0.118	0.153	Yamada et al., 2001

Table 1. Continued.

Gene Class	Gene Symbol	Gene Name	Function in Nervous System	Nervous System Phenotype of Mutants	Primate			Rodent			References
					Ka	*Ks*	*Ka/Ks*	*Ka*	*Ks*	*Ka/Ks*	
	CHRNA2	Cholinergic receptor, neuronal nicotinic, a2	A member of the nicotinic subtype of acetylcholine-gated ion channels	Not available.	0.036	0.124	0.290	0.016	0.339	0.047	Elliott et al., 1996
	CHRNA5	Cholinergic receptor, neuronal nicotinic, a5	A member of the nicotinic subtype of acetylcholine-gated ion channels	Not available.	0.015	0.062	0.242	0.011	0.289	0.038	Boulter et al., 1990
	DRD2	Dopamine receptor D2	A member of the dopamine receptor family	Mouse homozygous mutants show suppression of morphine-mediated reward behavior and slow movement resembling Parkinson disease.	0.005	0.042	0.119	0.000	0.115	0.000	Maldonado et al., 1997; Baik et al., 1995
	GRIK4	Glutamate receptor, ionotropic kainate, 4	A member of the kainate subtype of glutamate-gated ion channels	Not available.	0.003	0.030	0.100	0.002	0.123	0.016	Szpirer et al., 1994
	GRIN2A	Glutamate receptor, ionotropic NMDA, 2A	A member of the NMDA subtype of glutamate-gated ion channels	Mouse homozygous mutants show deficits in spatial learning and synaptic plasticity.	0.008	0.063	0.127	0.007	0.164	0.043	Sakimura et al., 1995
	OPRM1	Oxytocin receptor	A G-protein-coupled receptor for opioid ligands	Mouse homozygous mutants show defect in morphine-mediated analgesia and reward response.	0.012	0.049	0.245	0.026	0.235	0.111	Matthes et al., 1996
Unclassified	*CSPG3*	Chondroitin sulfate proteoglycan 3	A chondroitin sulfate proteoglycan implicated in neuronal adhesion and migration	Mouse homozygous mutants are overtly normal, with mild deficits in synaptic plasticity.	0.029	0.065	0.446	0.059	0.188	0.314	Zhou et al., 2001
	DPPX	Dipeptidyl peptidase IV related	A dipeptidyl-peptidase-like protein expressed predominantly in the brain	Not available	0.008	0.076	0.105	0.006	0.181	0.033	Wada et al., 1992
	GDI1	GDP dissociation inhibitor 1	A protein that inhibits RAB-mediated GDP-GTP exchange by preventing dissociation of GDP from RAB	Human mutations cause several forms of X-linked nonspecific mental retardation. Mouse homozygous mutants show impaired short-term memory and social behavior.	0.002	0.057	0.035	0.000	0.142	0.000	D'Adamo et al., 1998, 2002
	LYNX1	Lynx1	A neuronal membrane molecule highly expressed in the brain and linked to the modulation of neuronal nicotinic acetylcholine receptors	Not available.	0.030	0.086	0.349	0.000	0.221	0.000	Miwa et al., 1999
	PEG3	Paternally expressed gene 3	A maternally imprinted zinc finger protein implicated in the TNF signaling pathway	Female mutant mice show impaired nurturing behavior and reduced milk ejection due to reduced hypothalamic oxytocin neurons.	0.024	0.077	0.312	0.032	0.170	0.188	Li et al., 1999
	TTR	Transthyretin	A thyroid hormone carrier highly expressed in choroid plexus and constituting a major protein component of cerebrospinal fluid	Mouse homozygous mutants have reduced thyroid hormone levels but are overtly normal.	0.035	0.060	0.583	0.041	0.273	0.150	Episkopou et al., 1993
B. Genes Showing Faster Evolution in Rodents											
Developmental	*ASCL1*	Achaete-scute complex like 1	A transcription factor involved in the development of olfactory, autonomic, and enteric neurons	Mouse homozygous mutants die at birth and lack olfactory and autonomic neurons.	0.000	0.111	0.000	0.024	0.189	0.127	Guillemot et al., 1993
	NEUROD2	Neurogenic differentiation 2	A transcription factor involved in inducing neural precursor cells to undergo neuronal differentiation	Mouse homozygous mutants die a few weeks after birth and show reduced cerebellar granular cell layer.	0.001	0.049	0.020	0.047	0.136	0.346	Olsen et al., 2001
Physiological	*PPT1*	Palmitoyl-protein thioesterase 1	An enzyme that removes palmitate groups from lipid-modified proteins	Mouse homozygous mutations develop motor defects such as spasticity and die by 10 months of age. Human homozygous mutations cause neuronal ceroid lipofuscinosis.	0.000	0.054	0.000	0.025	0.253	0.253	Vesa et al., 1995; Gupta et al., 2001

which this ascertainment bias would result in elevated K_a/K_s in the human terminal branch. They showed that for the primate-fast outliers, ascertainment bias would indeed lead to an average K_a/K_s of the human terminal branch being higher than that of the chimpanzee branch. However, the actual K_a/K_s disparity between the human and the chimpanzee terminal branches is greater than that expected from ascertainment bias alone ($p = 0.04$; see Experimental Procedures). This suggests that ascertainment bias is unlikely to fully account for—though it clearly contributes to—the observed disparity in K_a/K_s between the human and the chimpanzee terminal branches.

With sequences of the primate-fast outliers available in four primate taxa (human, chimpanzee, macaque, and squirrel monkey), we constructed a phylogenetic tree and calculated K_a/K_s for each segment of the tree (Figure 6C). Clearly, the segments that lie along the lineage leading to humans (bolded in Figure 6C) have notably higher K_a/K_s than segments that branch away from this lineage.

The above data reinforce the notion that K_a/K_s values of nervous system genes in primates are especially elevated in the lineage leading from ancestral primates to humans, and that this trend has likely continued through recent human evolution.

Discussion

In this study, we examined the molecular evolution of an extensive set of nervous system-related genes in primates. We demonstrated that their average rate of protein evolution as scaled to neutral divergence (i.e., the K_a/K_s ratio) is significantly higher in primates than in rodents. One possible interpretation is adaptive evolution of these genes in primates, but it could also be due to relaxed functional constraint. We note, however, that brain size and complexity are much greater in primates than in rodents, which likely places stiffer demands on the functional precision of genes. It is therefore difficult to envision the relaxation of functional constraint as a major force in the evolution of the primate nervous system. This argument notwithstanding, we sought additional evidence that might bolster the case of adaptive evolution.

First, we examined a large set of housekeeping genes and noted that there is no significant primate-rodent disparity in the K_a/K_s of these genes. This argues that the primate-rodent K_a/K_s disparity seen in nervous system genes is not a nonspecific, genome-wide phenomenon.

Second, we classified our nervous system genes into functional categories. We found that the subgroup of nervous system genes with developmentally biased functions displayed much greater primate-rodent K_a/K_s disparity than the entire set of genes. In contrast, the K_a/K_s of genes that function predominantly in the routine physiological operations and maintenance of the nervous system showed much less primate-rodent disparity. The latter observation argues against reduced functional constraint on the primate nervous system per se, and together, these results are more consistent with the notion of adaptive evolution.

Third, we found that the average K_a/K_s of primate-fast outliers (i.e., those nervous system genes exhibiting significantly higher K_a/K_s in primates than in rodents) is considerably higher in the lineage leading from human-macaque ancestors to humans than the lineage leading to macaques. Furthermore, these same genes were also found to have evolved with much higher K_a/K_s in the human terminal branch than the chimpanzee branch after human-chimpanzee divergence. This disparity was not seen in a control set of nervous system genes that evolved at comparable rates between primates and rodents.

Fourth, mutations in many nervous system genes, including those with significantly higher K_a/K_s in primates, have been shown to cause severe nervous system defects in humans (Table 1A). This obviously does not support the notion of functional relaxation in these genes during human evolution.

Fifth, there is no evidence of recent duplications involving any of the genes studied (data not shown), which rules out the possibility of increased genetic redundancy for these genes in primates.

Finally, concurrent with the present study, more detailed evolutionary analyses were performed on two genes included in this study, *ASPM* and *MCPH1*, which have since been published by us and other groups (Zhang, 2003; Evans et al., 2004b; Kouprina et al., 2004; Evans et al., 2004a; Wang and Su, 2004). These detailed analyses, motivated by the observation that these two genes are involved critically and specifically in regulating brain size during development (Bond et al., 2002; Jackson et al., 2002), indeed revealed multiple lines of evidence in support of their adaptive evolution in primates and particularly in the primate lineage leading to humans. These include (1) significantly higher K_a/K_s in primates than in nonprimate mammals in addition to rodents, (2) much higher K_a/K_s in the primate lineage leading to humans than in the other primate lineages, (3) a preponderance of evolutionary signatures supporting the presence of positive selection in the lineage leading to humans, such as $K_a/K_s > 1$ for portions of this lineage and highly significant departure from the neutral expectation of the McDonald-Kreitman test (McDonald and Kreitman, 1991), and (4) evidence that strong positive selection tends to be focused within specific domains of these genes. Other genes not included in this study, such as *FOXP2*, *AHI1*, and *GLUD2*, have also revealed a possible link between alterations in protein sequences and phenotypic evolution of the human brain (Enard et al., 2002b; Ferland et al., 2004; Burki and Kaessmann, 2004).

Collectively, the above results argue against the possibility of relaxed functional constraint on the primate nervous system. Instead, they are more consistent with the interpretation that higher K_a/K_s of nervous system genes in primates—especially along the lineage leading to humans—is a reflection of adaptive evolution.

Indeed, as first recognized by Charles Darwin, adaptive evolution must have played a key role in driving the acquisition of greater cognitive powers in humans (Darwin, 1871). It is therefore reasonable to suppose that positive selection on genes involved in nervous system biology should have operated more intensely during the descent of humans than in species showing less dramatic cognitive evolution. However, researchers

have not been able to make a priori predictions regarding how intensified selection on the nervous system might have molded the molecular evolution of the primate genome. For example, it has remained a matter of speculation as to whether brain evolution involved a small number of key mutations in a few genes or a very large number of mutations in many genes (Carroll, 2003). It was also not known whether evolutionarily important mutations have occurred predominantly in regulatory sequences or coding regions (King and Wilson, 1975; McConkey et al., 2000; McConkey, 2002; Olson and Varki, 2003; Carroll, 2003), though preliminary data suggest that gene expression patterns of the human brain might have evolved rapidly (Enard et al., 2002a; Caceres et al., 2003; Uddin et al., 2004). Whereas our study does not address all these important questions, it does argue that the evolution of the brain in primates and particularly humans is likely contributed to by a large number of mutations in the coding regions of many underlying genes, especially genes with developmentally biased functions.

Might genes involved in tissues other than the nervous system also display accelerated evolution in primates? We argue that this is a distinct possibility given the precedent found in nervous system genes. In particular, accelerated evolution of genes might be found in tissue systems that are especially relevant to the adaptation of primates, such as the immune system, the digestive system, the reproductive system, the integumentary system, and the skeletal system.

Recent discussions surrounding the genetic origin of humans have placed a great emphasis on human-chimpanzee comparative genomics. Undoubtedly, this approach has revealed—and will continue to reveal—genetic differences that might underlie the biological distinctions between these two sister species (Chou et al., 1998, 2002; Enard et al., 2002b; Clark et al., 2003; Stedman et al., 2004). Because of the exceedingly high degree of sequence identity between human and chimpanzee genomes, however, comparative studies often lack statistical power, and in many cases would overlook genetic differences that bear biological relevance. The issue of weak statistical power in human-chimpanzee sequence comparisons has been noted before (Shi et al., 2003) and is supported by our simulation studies showing that the average stochastic variance in K_s as a fraction of the true underlying mutation rate is about twice in human-chimpanzee comparison as it is in human-macaque comparison (our unpublished data). Relative to human-chimpanzee comparisons, our approach offers two important advantages. First, the use of a more distant primate species for comparison with humans provides the much needed statistical power for determining the evolutionary significance of sequence changes. Second, the use of nonprimate mammals as "controls" allows for the identification of primate-specific evolutionary signatures. We therefore propose that our methodology is a valuable complement to human-chimpanzee comparisons in probing the genetic basis of human origins.

In summary, our study revealed the following broad themes that characterize the molecular evolution of the nervous system in primates and particularly in humans. First, genes underlying nervous system biology exhibit higher average rate of protein evolution as scaled to neutral divergence in primates than in rodents. Second, such a trend is contributed to by a large number of genes. Third, this trend is most prominent for genes implicated in the development of the nervous system. Fourth, within primates, the evolution of these genes is especially accelerated in the lineage leading to humans. Based on these themes, we argue that accelerated protein evolution in a large cohort of nervous system genes, which is particularly pronounced for genes involved in nervous system development, represents a salient genetic correlate to the profound changes in brain size and complexity during primate evolution, especially along the lineage leading to *Homo sapiens*. Besides revealing broad evolutionary themes, our study also identified a set of genes whose molecular evolution might have contributed to the phenotypic evolution of the brain in primates. In-depth analyses of these genes might yield further insights into how changes in specific genes contribute to the emergence of primate- or human-specific traits.

Experimental Procedures

Sequence Acquisition

Standard RT-PCR protocols were employed to amplify coding sequences from the Old World monkey, crab-eating macaque (*Macaca fascicularis*), followed by sequencing of PCR product. Amplicons were designed to be 500–700 bp in length with a minimum of 50–75 bp of overlap between adjacent amplicons. Nervous system genes were amplified from cDNA combined from all major regions of the brain. Housekeeping genes were amplified from cDNA combined from the heart, lung, liver, kidney, and the pooled brain sample. Squirrel monkey (*Saimiri boliviensis*) sequences were obtained in a similar manner from brain tissue. For chimpanzee (*Pan troglodytes*), amplification was performed on genomic DNA. PCR primers to amplify nonhuman primate genes were designed based on orthologous human cDNA sequences. If a particular set of primers failed, new primers would be designed until successful primers were obtained. In rare cases of single-nucleotide polymorphisms, the derived allele was ignored because it did not represent fixed difference between species. Additional sequences, including human, chimpanzee, macaque, squirrel monkey, rat, and mouse, were obtained from public databases.

Inference of Ancestral Sequences

The human-macaque and the human-chimpanzee ancestral sequences were inferred using the PAMP program available in the PAML v.3.13 software package as previously described (Yang et al., 1995). Orthologous sequences from human, macaque, and squirrel monkey were used to infer the human-macaque ancestral sequences. Similarly, orthologous sequences from human, chimpanzee, and macaque were used to infer the human-chimpanzee ancestral sequences. In rare cases where there was ambiguity in inferring the ancestral nucleotide (i.e., the three taxa each had a different nucleotide at a given position), the corresponding codon was disregarded from the analysis. To obtain K_a/K_s of a terminal phylogenetic branch, inferred sequences at the ancestral node of the branch were compared with sequences at the terminal node. To obtain K_a/K_s of an internal branch, inferred sequences at one ancestral node were compared with inferred sequences at the other ancestral node.

Sequence Analysis and Tests of Statistical Significance

Orthologous coding sequences were aligned in frame using the Pileup and Framealign programs from the Wisconsin Package v10.2 (Accelrys Inc., San Diego, California). The Diverge program from the same package was employed to calculate evolutionary parameters by the Li method (Li, 1993), including the total numbers of nonsynonymous (A) and synonymous (S) substitutions corrected for multiple hits and transition/transversion bias, and K_a and K_s. The average

K_a/K_s for a group of genes was calculated as the ratio of average K_a and average K_s. The error bar of average K_a/K_s was generated by bootstrap simulation. To evaluate the statistical significance that the evolutionary rates of a group of genes differ between two lineages, a 2×2 contingency table was built, with the four entries being the total *A* and *S* values in either of the two lineages. Two-tailed Fisher's exact test was then applied to the table to obtain statistical significance that evolutionary rates differed between the two lineages. One-tailed Fisher's exact test was used to test the significance by which an individual gene had significantly higher K_a/K_s in one lineage versus the other. Given that this test utilizes the total numbers of nonsynonymous and synonymous changes, it is possible that a gene might have substantially higher K_a/K_s in one lineage than in the other, and yet the difference does not reach statistical significance because the total numbers of nonsynonymous and synonymous substitutions are low (as in short genes). Conversely, it is also possible that the K_a/K_s of a gene is only moderately higher in one lineage than in the other, and yet the difference is statistically significant because of the large number of substitutions involved (as in long genes). To evaluate the significance of the inequality in the number of genes with higher K_a/K_s in one lineage versus the number of genes with higher K_a/K_s in the other lineage, the two-tailed binomial test was used. To assess the significance that two sets of K_a/K_s values had distinct distributions, we used the nonparametric Wilcoxon signed-rank test, which evaluated the likelihood of the null hypothesis that two sets of paired data were drawn from the same underlying distribution (Hollander and Wolfe, 1999). We also used the nonparametric Kolmogorov-Smirnov test for the same purpose (Hollander and Wolfe, 1999), which in all cases confirmed the results of the Wilcoxon test.

Computer Simulations

Simulations were performed to assess the extent to which the ascertainment of the primate-fast outliers would elevate the K_a/K_s of these genes in the human terminal branch (i.e., from human-chimpanzee ancestors to humans) relative to the chimpanzee terminal branch. We considered a phylogenetic tree as depicted in Supplemental Figure S1 at http//www.cell.com/cgi/content/full/119/7/1027/DC1/. Four lineages in this tree were germane to the analysis: human-chimpanzee ancestor to human, human-chimpanzee ancestor to chimpanzee, human-chimpanzee ancestor to macaque, and rat to mouse. The levels of neutral divergence in these four lineages were set at a ratio of 6:6:62:174. This ratio was set according to published genome-typical K_s rates, which are 0.012 between human and chimpanzee (Chen et al., 2001), 0.068 between human and macaque (Yi et al., 2002), and 0.174 between rat and mouse (Gibbs et al., 2004). For each outlier gene, we performed simulations under the null assumption that the substitution rate (either nonsynonymous or synonymous) after scaling to neutral divergence is constant across all four lineages. By this assumption, any enrichment or deficit of substitutions in a given lineage (including situations that would produce significantly higher human-macaque K_a/K_s than rat-mouse K_a/K_s) is the result of stochastic fluctuation. As the first step of the simulation, the total numbers of nonsynonymous (*A*) and synonymous (*S*) substitutions of the gene observed for both the human-to-macaque and the rat-to-mouse lineages were summed. The resulting numbers were then scaled up by 6/242 to correct for the addition of the chimpanzee terminal branch in the phylogeny. These corrected *A* and *S* numbers were apportioned onto the four lineages based on the 6:6:62:174 ratio to obtain the number of substitutions on each lineage as expected under the null assumption of equal evolutionary rates across lineages. For an individual lineage, simulation was performed to generate the number of substitutions that followed the Poisson distribution and with a mean being the expected number of substitutions. The subset of repetitions for which the human-macaque *A* and *S* numbers match that observed for the gene was selected for further analysis. This procedure was performed for all the primate-fast outliers, which produced one aforementioned subset of simulated data per gene. One data point per subset was then randomly selected to create a simulated outlier data set. By generating 100,000 such simulated outlier data sets, we were able to obtain the probability by which a simulated outlier data set produced *A/S* ratio disparity between the human and the chimpanzee terminal branches that was as great as or greater than the observed disparity.

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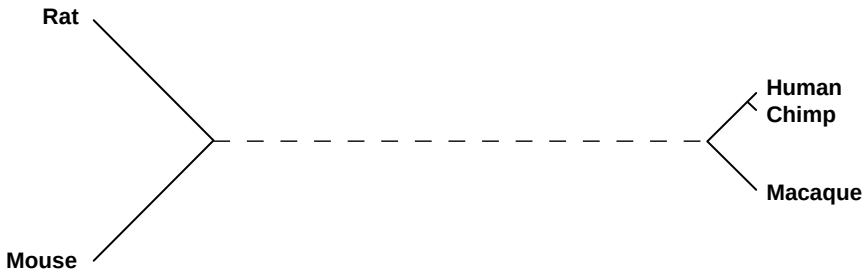
Supplemental Figure S1



Supplemental Figure S1: Phylogeny of the five taxa used in simulating the extent to which ascertainment bias in selecting primate-fast outliers would create K_a/K_s disparity between the human and the chimpanzee terminal branches. Lineages represented by solid lines are drawn to scale of genome-typical neutral sequence divergence (see Experimental Procedures for detail).

Supplemental Table S1. Nervous System Related Genes

Gene Class	Gene Symbol	Gene Name	Other Names	Primate Ka	Primate Ks	Primate Ka/Ks	Rodent Ka	Rodent Ks	Rodent Ka/Ks	Length compared	Accession Numbers Human	OWM	Mouse	Rat
Developmental	*ASCL1* **	ACHAETE-SCUTE COMPLEX, DROSOPHILA, HOMOLOG-LIKE 1	MAMMALIAN ACHAETE-SCUTE HOMOLOG-1 (MASH1)	0.000	0.111	0.000	0.024	0.189	0.127	651	NM_004316	AY650320	NM_008533	NM_022384
	ASPM *	ABNORMAL SPINDLE-LIKE, MICROCEPHALY-ASSOCIATED	ASP, DROSOPHILA, HOMOLOG OF; MCPH5	0.020	0.041	0.488	0.083	0.238	0.349	10434	NM_018136	AY485418	NM_009791	XM_213891
	ASTN	ASTROTACTIN		0.000	0.038	0.000	0.002	0.103	0.019	513	NM_004319	AY650334	NM_007495	XM_222785
	ATOH1	ATONAL, DROSOPHILA, HOMOLOG OF, 1	MATH1, MOUSE, HOMOLOG OF (MATH1)	0.011	0.063	0.175	0.021	0.142	0.148	945	NM_005172	AY650376	NM_007500	Genomic
	BDNF	BRAIN-DERIVED NEUROTROPHIC FACTOR		0.006	0.026	0.231	0.005	0.100	0.050	558	NM_001709	AY011478	NM_007540	NM_012513
	CASP3 *	CASPASE 3, APOPTOSIS-RELATED CYSTEINE PROTEASE	PARP CLEAVAGE PROTEASE; APOPAIN; CPP32	0.022	0.040	0.550	0.035	0.322	0.109	792	NM_004346	AY650318	NM_009810	NM_012922
	CASP9	CASPASE 9, APOPTOSIS-RELATED CYSTEINE PROTEASE	APOPTOTIC PROTEASE ACTIVATING FACTOR 3 (APAF3)	0.033	0.056	0.589	0.047	0.126	0.373	1182	NM_001229	AY650319	NM_015733	NM_031632
	CNTN1	CONTACTIN 1		0.006	0.074	0.081	0.003	0.343	0.009	465	NM_001843	AF424844	NM_007727	NM_057118
	CNTN2	CONTACTIN 2	TRANSIENTLY-EXPRESSED AXONAL GLYCOPROTEIN (TAX1); TAG1; AXONIN 1	0.004	0.067	0.060	0.027	0.208	0.130	645	NM_005076	AY775946	NM_011531	NM_012884
	CRMP1	COLLAPSIN RESPONSE MEDIATOR PROTEIN 1	DIHYDROPYRIMIDINASE-LIKE 1 (DPYSL1); DIHYDROPYRIMIDINASE-RELATED PROTEIN 1 (DRP1)	0.004	0.077	0.052	0.004	0.157	0.025	1644	NM_001313	AY650329	NM_007765	NM_012932
	CTNNA2	CATENIN, ALPHA-2	CADHERIN-ASSOCIATED PROTEIN, RELATED (CAPR)	0.000	0.057	0.000	0.006	0.139	0.043	1095	NM_004389	AY650344	NM_009819	XM_232077
	CTNNB1	CATENIN, BETA-1	CADHERIN-ASSOCIATED PROTEIN, BETA	0.001	0.040	0.025	0.001	0.170	0.006	2103	NM_001904	AY650367	NM_007614	NM_053357
	DAB1	DISABLED, DROSOPHILA, HOMOLOG OF, 1		0.005	0.018	0.278	0.007	0.083	0.084	1665	NM_021080	AB055282	NM_010014	NM_153621
	DLX2	DISTAL-LESS HOMEO BOX 2	TES1	0.023	0.041	0.561	0.007	0.150	0.047	138	NM_004405	AY650359	NM_010054	XM_230986
	DVL1 *	DISHEVELLED 1	DSH, DROSOPHILA, HOMOLOG OF, 1 (DVL)	0.009	0.137	0.066	0.002	0.100	0.020	1908	NM_004421	AY650369	NM_010091	NM_031820
	EN1	ENGRAILED 1		0.000	0.100	0.000	0.000	0.086	0.000	237	NM_001426	AY650360	NM_010133	Genomic
	EN2	ENGRAILED 2		0.005	0.053	0.094	0.006	0.313	0.019	558	NM_001427	AY650377	NM_010134	Genomic
	EPHA5	EPHRIN RECEPTOR EphA5	HEK7; EHK1; BSK; TYRO4	0.002	0.058	0.034	0.005	0.205	0.024	1107	NM_004439	AB066532	NM_007937	XM_341201
	FGF1	FIBROBLAST GROWTH FACTOR 1	ENDOTHELIAL CELL GROWTH FACTOR (ECGF); HEPARIN-BINDING GROWTH FACTOR 1 (HBGF1)	0.004	0.065	0.062	0.000	0.171	0.000	393	NM_000800	AY650348	NM_010197	NM_012846
	FGF2	FIBROBLAST GROWTH FACTOR 2	FIBROBLAST GROWTH FACTOR, BASIC (FGFB)	0.000	0.054	0.000	0.000	0.160	0.000	330	NM_002006	AF251270	NM_008006	NM_019305
	FOXG1B	FORKHEAD BOX G1B	FORKHEAD, DROSOPHILA, HOMOLOG-LIKE 1 (FKHL1); ONCOGENE QIN; BRAIN FACTOR 1 (BF1)	0.013	0.105	0.124	0.000	0.037	0.000	714	NM_005249	AY650321	NM_008241	NM_012560
	GAP43	GROWTH ASSOCIATED PROTEIN 43	NEUROMODULIN; NERVE GROWTH-RELATED PEPTIDE GAP43	0.008	0.058	0.138	0.004	0.066	0.061	714	NM_002045	AB063093	NM_008083	NM_017195
	GAS7	GROWTH ARREST-SPECIFIC 7		0.004	0.066	0.061	0.002	0.099	0.020	1221	NM_003644	AB093665	NM_008088	NM_053484
	GBX2	GASTRULATION BRAIN HOMEO BOX 2	GASTRULATION AND BRAIN-SPECIFIC 2	0.004	0.057	0.070	0.000	0.090	0.000	432	NM_001485	AY650361	NM_010262	XM_346072
	GDNF	GLIAL CELL LINE-DERIVED NEUROTROPHIC FACTOR		0.007	0.033	0.212	0.006	0.103	0.058	480	NM_000514	AF106678	NM_010275	NM_019139
	GLI3	GLI-KRUPPEL FAMILY MEMBER 3	ONCOGENE GLI3	0.010	0.060	0.167	0.028	0.120	0.233	1338	NM_000168	AY775947	NM_008130	XM_225411
	HOXB1	HOMEOBOX B1		0.010	0.077	0.130	0.023	0.108	0.213	888	NM_002144	AC146691	NM_008266	XM_220896
	ID2	INHIBITOR OF DNA BINDING 2	INHIBITOR OF DIFFERENTIATION 2	0.009	0.068	0.132	0.004	0.045	0.089	381	NM_002166	AY650362	NM_010496	NM_013060
	LHX1 *	LIM HOMEO BOX GENE 1	LIM1	0.006	0.075	0.080	0.002	0.141	0.014	1203	NM_005568	AY650378	NM_008498	NM_145880
	LHX2	LIM HOMEO BOX GENE 2	LIM HOX GENE 2 (LH2)	0.003	0.059	0.051	0.000	0.049	0.000	528	NM_004789	AY650352	NM_010710	XM_216050
	LRP8	LOW DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 8	APOLIPOPROTEIN E RECEPTOR 2 (APOER2)	0.017	0.060	0.283	0.025	0.156	0.160	468	NM_004631	AY650325	NM_053073	XM_342877
	MCPH1 *	MICROCEPHALIN		0.040	0.048	0.833	0.070	0.146	0.479	2223	NM_024596	AY742816	AY070216	XM_225006
	MFNG	MANIC FRINGE	FRINGE, DROSOPHILA, HOMOLOG OF, MANIC	0.016	0.073	0.219	0.031	0.129	0.240	801	NM_002405	AY650338	NM_008595	NM_199110
	NEUROD2 **	NEUROGENIC DIFFERENTIATION 2		0.001	0.049	0.020	0.047	0.136	0.346	1092	NM_006160	AY650353	NM_010895	NM_019207
	NKX2B	NK2, DROSOPHILA, HOMOLOG OF, B	NKX2.2, MOUSE, HOMOLOG OF	0.008	0.031	0.000	0.000	0.000	0.000	192	NM_020795	AY775948	NM_198862	NM_053992
	NLGN2	NEUROLIGIN 2		0.000	0.010	0.258	0.000	0.135	0.000	456	NM_018977	AF462607	NM_172932	NM_134336
	NLGN3	NEUROLIGIN 3		0.000	0.021	0.000	0.003	0.048	0.000	432	NM_005450	AF424850	NM_008711	XM_343954
	NOG	NOGGIN, MOUSE, HOMOLOG OF		0.000	0.032	0.000	0.000	0.032	0.063	379	NM_002509	AY650332	NM_010919	XM_345446
	NRCAM *	NEURONAL CELL ADHESION MOLECULE		0.019	0.085	0.224	0.009	0.177	0.051	555	NM_005010	AF462608	NM_176930	NM_013150
	NTF3	NEUROTROPHIN 3	NEUROTROPHIC FACTOR 3 (NT3)	0.008	0.069	0.116	0.004	0.111	0.036	723	NM_002527	AF222683	NM_008742	NM_031073
	NTRK2	NEUROTROPHIC TYROSINE KINASE, RECEPTOR, TYPE 2	TYROSINE KINASE RECEPTOR B (TRKB)	0.000	0.039	0.000	0.004	0.183	0.022	552	NM_006180	AY742817	NM_008745	NM_012731
	NTRK3 *	NEUROTROPHIC TYROSINE KINASE, RECEPTOR, TYPE 3	TYROSINE KINASE RECEPTOR C (TRKC); NEUROTROPHIN 3 RECEPTOR	0.003	0.068	0.044	0.000	0.134	0.000	1584	NM_002530	AY742818	NM_182809	NM_019248
	OTX1	ORTHODENTICLE, DROSOPHILA, HOMOLOG OF, 1		0.005	0.107	0.047	0.009	0.167	0.054	648	NM_014562	AY650364	NM_011023	NM_013109
	OTX2	ORTHODENTICLE, DROSOPHILA, HOMOLOG OF, 2		0.000	0.021	0.000	0.000	0.035	0.000	198	NM_021728	AY650365	NM_144841	XM_224009
	PAFAH1B1 *	PLATELET-ACTIVATING FACTOR ACETYLHYDROLASE, ISOFORM 1B, ALPHA SUBUNIT	LISSENCEPHALY 1 (LIS1)	0.005	0.048	0.104	0.000	0.057	0.000	1122	NM_000430	AB083321	NM_013625	NM_031763
	RELN	REELIN	RL	0.004	0.062	0.065	0.015	0.253	0.059	9699	NM_005045	AY650356	NM_011261	NM_080394

	SEMA4F	SEMAPHORIN 4F	SEMAPHORIN W (SEMAW); SEMAPHORIN M (SEMAM)	0.010	0.065	0.154	0.004	0.120	0.033	444	NM_004263	AB047604	NM_011350	NM_019272
	SHH *	SONIC HEDGEHOG		0.029	0.091	0.319	0.021	0.163	0.129	795	NM_000193	AY650323	NM_009170	NM_017221
	SLC25A19	SOLUTE CARRIER FAMILY 25, MEMBER 19	AMISH MICROCEPHALY, MCPHA; MITOCHONDRIAL DEOXYNUCLEOTIDE CARRIER, DNC; MITOCHONDRIAL UNCOUPLING PROTEIN 1, MUP1	0.015	0.089	0.169	0.020	0.249	0.080	963	NM_021734	AY665293	NM_026071	XM_221118
	SLIT1	SLIT, DROSOPHILA, HOMOLOG OF, 1	SLIL1; MULTIPLE EPIDERMAL GROWTH FACTOR-LIKE DOMAINS 4 (MEGF4)	0.008	0.080	0.100	0.012	0.179	0.067	3102	NM_003061	AY650311	NM_015748	NM_022953
	TGIF	TRANSFORMING GROWTH FACTOR-BETA-INDUCED FACTOR		0.013	0.082	0.159	0.023	0.200	0.115	735	NM_170695	AY650366	NM_009372	XM_237524
	TWIST	TWIST, DROSOPHILA, HOMOLOG OF	TRANSCRIPTION FACTOR TWIST	0.003	0.068	0.044	0.002	0.082	0.024	603	NM_000474	AY369851	NM_011658	NM_053530
	ZIC5	ZIC FAMILY MEMBER 5		0.007	0.036	0.194	0.006	0.113	0.027	423	NM_033132	BV208923	NM_022987	XM_341380
Physiological	*AANAT* *	ARYLALKYLAMINE N-ACETYLTRANSFERASE	SEROTONIN N-ACETYLTRANSFERASE (SNAT)	0.032	0.079	0.405	0.023	0.266	0.086	606	NM_001088	U46661	NM_009591	NM_012818
	ADCYAP1 *	ADENYLYLCYCLASE-ACTIVATING PEPTIDE 1		0.074	0.113	0.655	0.034	0.191	0.178	483	NM_001117	AY775945	NM_009625	NM_016989
	ADORA1	ADENOSINE A1 RECEPTOR	RDC7	0.003	0.081	0.037	0.007	0.140	0.050	888	NM_000674	AY650342	NM_009629	NM_017155
	ALDP	ADRENOLEUKODYSTROPHY PROTEIN, INCLUDED	ATP-BINDING CASSETTE, SUBFAMILY D, MEMBER 1 (ABCD1); ADRENOMYELONEUROPATHY (AMN)	0.005	0.079	0.063	0.007	0.080	0.088	1206	NM_000033	AY650324	NM_007435	XM_343840
	APP	AMYLOID BETA A4 PRECURSOR PROTEIN	AMYLOID OF AGING AND ALZHEIMER DISEASE (AAA); CEREBRAL VASCULAR AMYLOID PEPTIDE (CVAP)	0.001	0.066	0.015	0.005	0.209	0.024	2085	NM_000484	M58727	NM_007471	NM_019288
	ATP1A3	ATPase, Na+/K+ TRANSPORTING, ALPHA-3 POLYPEPTIDE	SODIUM-POTASSIUM-ATPase, ALPHA-3 POLYPEPTIDE	0.000	0.099	0.000	0.000	0.180	0.000	609	NM_152296	BQ807995	NM_144921	NM_012506
	BCHE	BUTYRYLCHOLINESTERASE	PSEUDOCHOLINESTERASE E1 (CHE1)	0.000	0.044	0.000	0.027	0.231	0.117	423	NM_000055	M62777	NM_009738	NM_022942
	CADPS	CALCIUM-DEPENDENT ACTIVATOR PROTEIN FOR SECRETION	CAPS	0.000	0.059	0.000	0.006	0.240	0.025	606	NM_003716	AY650343	NM_012061	NM_013219
	CHRM1	CHOLINERGIC RECEPTOR, MUSCARINIC, 1	ACETYLCHOLINE RECEPTOR, MUSCARINIC, 1	0.003	0.053	0.057	0.008	0.136	0.059	1380	NM_000738	AF026262	NM_007698	NM_080773
	CHRM2	CHOLINERGIC RECEPTOR, MUSCARINIC, 2	ACETYLCHOLINE RECEPTOR, MUSCARINIC, 2	0.004	0.058	0.069	0.015	0.224	0.067	600	NM_000739	AF512348	NM_203491	NM_031016
	CHRM3	CHOLINERGIC RECEPTOR, MUSCARINIC, 3	ACETYLCHOLINE RECEPTOR, MUSCARINIC, 3	0.000	0.047	0.000	0.004	0.101	0.040	363	NM_000740	AF512351	NM_033269	NM_012527
	CHRM4	CHOLINERGIC RECEPTOR, MUSCARINIC, 4	ACETYLCHOLINE RECEPTOR, MUSCARINIC, 4	0.000	0.040	0.000	0.000	0.083	0.000	232	NM_000741	AF148140	NM_007699	XM_345403
	CHRM5 *	CHOLINERGIC RECEPTOR, MUSCARINIC, 5	ACETYLCHOLINE RECEPTOR, MUSCARINIC, 5	0.021	0.034	0.618	0.018	0.118	0.153	1596	NM_012125	AF026264	NM_205783	NM_017362
	CHRNA2 *	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, ALPHA POLYPEPTIDE 2	ACETYLCHOLINE RECEPTOR, NEURONAL NICOTINIC, ALPHA-2 SUBUNIT	0.036	0.124	0.290	0.016	0.339	0.047	279	NM_000742	AJ245971	NM_144803	NM_133420
	CHRNA3	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, ALPHA POLYPEPTIDE 3	ACETYLCHOLINE RECEPTOR, NEURONAL NICOTINIC, ALPHA-3 SUBUNIT	0.006	0.068	0.088	0.028	0.231	0.121	369	NM_000743	AJ245972	NM_145129	NM_052805
	CHRNA4	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, ALPHA POLYPEPTIDE 4	ACETYLCHOLINE RECEPTOR, NEURONAL NICOTINIC, ALPHA-4 SUBUNIT	0.034	0.113	0.301	0.037	0.175	0.211	558	NM_000744	AJ245973	NM_015730	NM_024354
	CHRNA5 *	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, ALPHA POLYPEPTIDE 5	ACETYLCHOLINE RECEPTOR, NEURONAL NICOTINIC, ALPHA-5 SUBUNIT	0.015	0.062	0.242	0.011	0.289	0.038	552	NM_000745	AJ245974	NM_176844	NM_017078
	CHRNA6	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, ALPHA POLYPEPTIDE 6	ACETYLCHOLINE RECEPTOR, NEURONAL NICOTINIC, ALPHA-6 SUBUNIT	0.024	0.096	0.250	0.057	0.188	0.303	588	NM_004198	AJ245975	NM_021369	NM_057184
	CHRNA7	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, ALPHA POLYPEPTIDE 7	ACETYLCHOLINE RECEPTOR, NEURONAL NICOTINIC, ALPHA-7 SUBUNIT	0.016	0.145	0.110	0.003	0.108	0.028	468	NM_000746	AF486623	NM_007390	NM_012832
	CHRNB2	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, BETA POLYPEPTIDE 2	ACETYLCHOLINE RECEPTOR, NEURONAL NICOTINIC, BETA-2 SUBUNIT	0.013	0.158	0.082	0.035	0.255	0.137	330	NM_000748	AJ245977	NM_009602	NM_019297
	CHRNB3	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, BETA POLYPEPTIDE 3	ACETYLCHOLINE RECEPTOR, NEURONAL NICOTINIC, BETA-3 SUBUNIT	0.033	0.086	0.384	0.082	0.193	0.425	231	NM_000749	AJ245978	NM_173212	NM_133597
	CHRNB4	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, BETA POLYPEPTIDE 4	ACETYLCHOLINE RECEPTOR, NEURONAL NICOTINIC, BETA-4 SUBUNIT	0.035	0.083	0.422	0.030	0.118	0.254	573	NM_000750	AJ245979	NM_148944	NM_052806
	CLN2	CEROID LIPOFUSCINOSIS, NEURONAL 2, LATE INFANTILE TYPE		0.011	0.051	0.216	0.026	0.128	0.203	1689	NM_000391	AB083308	NM_009906	NM_031357
	CNR1	CANNABINOID RECEPTOR 1	CB1 RECEPTOR (CB1)	0.000	0.037	0.000	0.001	0.190	0.005	1416	NM_001840	AF286025	NM_007726	NM_012784
	CPLX1	COMPLEXIN 1	SYNAPHIN 2	0.004	0.104	0.038	0.000	0.136	0.000	402	NM_006651	BQ807469	NM_007756	NM_022864
	CRHR1	CORTICOTROPIN-RELEASING HORMONE RECEPTOR 1	CORTICOTROPIN-RELEASING FACTOR RECEPTOR (CRFR1)	0.001	0.044	0.023	0.003	0.156	0.019	840	NM_004382	AB078141	NM_007762	NM_030999
	DBH	DOPAMINE BETA-HYDROXYLASE	DOPAMINE BETA-MONOOXYGENASE	0.025	0.117	0.214	0.068	0.233	0.292	261	NM_000787	AF070919	NM_138942	NM_013158
	DNCI1	DYNEIN, CYTOPLASMIC, INTERMEDIATE CHAIN 1		0.002	0.056	0.036	0.007	0.165	0.042	1692	NM_004411	AY369807	NM_010063	NM_019234
	DRD1	DOPAMINE RECEPTOR D1		0.001	0.082	0.012	0.009	0.253	0.036	1236	NM_000794	AF077862	NM_010076	NM_012546
	DRD2 *	DOPAMINE RECEPTOR D2		0.005	0.042	0.119	0.000	0.115	0.000	1221	NM_000795	U13757	NM_010077	NM_012547
	DRD3	DOPAMINE RECEPTOR D3		0.004	0.083	0.048	0.021	0.162	0.130	660	NM_000796	AF027358	NM_007877	NM_017140
	DRD4	DOPAMINE RECEPTOR D4	D4DR	0.020	0.073	0.274	0.027	0.132	0.205	273	NM_000797	AF125666	NM_007878	NM_012944
	ENO2	ENOLASE 2	ENOLASE, GAMMA; ENOLASE, NEURON-SPECIFIC (NSE)	0.004	0.052	0.077	0.007	0.155	0.045	1251	NM_001975	AY650330	NM_013509	NM_139325
	GABRA1	GAMMA-AMINOBUTYRIC ACID RECEPTOR, ALPHA-1	GABA-A RECEPTOR, ALPHA-1 POLYPEPTIDE	0.000	0.049	0.000	0.000	0.032	0.000	294	NM_000806	AF512350	NM_010250	NM_183326
	GABRA2	GAMMA-AMINOBUTYRIC ACID RECEPTOR, ALPHA-2	GABA-A RECEPTOR, ALPHA-2 POLYPEPTIDE	0.002	0.070	0.029	0.000	0.246	0.000	630	NM_000807	CN643273	NM_008066	XM_223378
	GABRA3	GAMMA-AMINOBUTYRIC ACID RECEPTOR, ALPHA-3	GABA-A RECEPTOR, ALPHA-3 POLYPEPTIDE	0.000	0.080	0.000	0.000	0.083	0.000	168	NM_000808	AFY394495	NM_008067	NM_017069
	GABRA4	GAMMA-AMINOBUTYRIC ACID RECEPTOR, ALPHA-4	GABA-A RECEPTOR, ALPHA-4 POLYPEPTIDE	0.013	0.057	0.228	0.039	0.189	0.206	222	NM_000809	AY394496	NM_010251	NM_080587

GABRA6	GAMMA-AMINOBUTYRIC ACID RECEPTOR, ALPHA-6	GABA-A RECEPTOR, ALPHA-6 POLYPEPTIDE	0.010	0.096	0.104	0.015	0.229	0.066	267	NM_000811	AY644396	NM_008068	NM_021841
GABRB2	GAMMA-AMINOBUTYRIC ACID RECEPTOR, BETA-2	GABA-A RECEPTOR, BETA-2 POLYPEPTIDE	0.000	0.059	0.000	0.000	0.100	0.000	312	NM_000813	BV208520	NM_008070	NM_012957
GABRG2	GAMMA-AMINOBUTYRIC ACID RECEPTOR, GAMMA-2	GABA-A RECEPTOR, GAMMA-2 POLYPEPTIDE	0.005	0.069	0.072	0.000	0.149	0.000	645	NM_000816	BQ807441	NM_008073	NM_183327
GAD1	GLUTAMATE DECARBOXYLASE 1	GLUTAMATE DECARBOXYLASE, BRAIN, 67-KD (GAD67);	0.004	0.059	0.068	0.006	0.128	0.047	1671	NM_000817	AY122607	NM_008077	NM_017007
GFAP	GLIAL FIBRILLARY ACIDIC PROTEIN		0.003	0.073	0.041	0.017	0.159	0.107	1224	NM_002055	AY650314	NM_010277	NM_017009
GPR51	G PROTEIN-COUPLED RECEPTOR 51	GAMMA-AMINOBUTYRIC ACID B RECEPTOR 2 (GABBR2)	0.000	0.064	0.000	0.001	0.131	0.008	2328	NM_005458	AB048961	XM_143750	NM_031802
GRIA2	GLUTAMATE RECEPTOR, IONOTROPIC, AMPA 2	GLUTAMATE RECEPTOR 2 (GLUR2); GLURB	0.000	0.030	0.000	0.000	0.172	0.000	561	NM_000826	AY650386	NM_013540	NM_017261
GRIK4 *	GLUTAMATE RECEPTOR, IONOTROPIC, KAINATE 4		0.003	0.030	0.100	0.002	0.123	0.016	1983	NM_014619	AY650374	NM_175481	NM_012572
GRIN2A *	GLUTAMATE RECEPTOR, IONOTROPIC, N-METHYL-D-ASPARTATE, SUBUNIT 2A	N-METHYL-D-ASPARTATE RECEPTOR CHANNEL, SUBUNIT EPSILON-1 (NMDAR2A); NR2A	0.008	0.063	0.127	0.007	0.164	0.043	2910	NM_000833	AY650349	NM_008170	NM_012573
GRM1	GLUTAMATE RECEPTOR, METABOTROPIC, 1	MGLUR1	0.019	0.086	0.221	0.024	0.200	0.120	543	NM_000838	AY122610	NM_016976	NM_017011
GRM3	GLUTAMATE RECEPTOR, METABOTROPIC, 3		0.011	0.086	0.128	0.013	0.187	0.070	921	NM_000840	CN803563	NM_181850	XM_342626
GRM5	GLUTAMATE RECEPTOR, METABOTROPIC, 5		0.000	0.060	0.000	0.000	0.137	0.000	1384	NM_000842	AY122608	AK032422	NM_017012
HOMER-1B	HOMER, NEURONAL IMMEDIATE EARLY GENE, 1B		0.000	0.011	0.000	0.000	0.108	0.000	273	NM_004272	AY742813	NM_152134	NM_031707
HOMER-2B	HOMER, NEURONAL IMMEDIATE EARLY GENE, 2B		0.000	0.011	0.000	0.004	0.180	0.022	273	NM_199330	AY742814	XM_133550	NM_053309
HOMER-3	HOMER, NEURONAL IMMEDIATE EARLY GENE, 3		0.011	0.192	0.057	0.010	0.196	0.051	273	NM_004838	AY742815	NM_011984	NM_053310
HRH3	HISTAMINE RECEPTOR H3	G PROTEIN-COUPLED RECEPTOR 97 (GPCR97)	0.009	0.109	0.083	0.006	0.109	0.055	1335	NM_007232	AY231164	NM_133849	NM_053506
HTR1A	5-HYDROXYTRYPTAMINE RECEPTOR 1A	SEROTONIN 5-HT-1A RECEPTOR, BETA-2-ADRENERGIC RECEPTOR-LIKE PROTEIN G-21	0.009	0.091	0.099	0.040	0.162	0.247	459	NM_000524	AF489847	NM_008308	NM_012585
HTR1B	5-HYDROXYTRYPTAMINE RECEPTOR 1B	SEROTONIN 5-HT-1B RECEPTOR	0.006	0.077	0.078	0.009	0.083	0.108	630	NM_000863	BV166342	NM_010482	NM_022225
HTR1D	5-HYDROXYTRYPTAMINE RECEPTOR 1D	SEROTONIN 5-HT-1D RECEPTOR	0.008	0.128	0.063	0.004	0.142	0.028	879	NM_000864	AF512359	NM_008309	NM_012852
HTR2A	5-HYDROXYTRYPTAMINE RECEPTOR 2A	SEROTONIN 5-HT-2A RECEPTOR	0.002	0.067	0.030	0.010	0.113	0.088	1317	NM_000621	AY650372	NM_172812	NM_017254
HTR2B	5-HYDROXYTRYPTAMINE RECEPTOR 2B	SEROTONIN 5-HT-2B RECEPTOR	0.008	0.057	0.140	0.050	0.175	0.286	369	NM_000867	BV166345	NM_008311	NM_017250
HTR2C	5-HYDROXYTRYPTAMINE RECEPTOR 2C	SEROTONIN 5-HT-2C RECEPTOR	0.007	0.054	0.130	0.013	0.102	0.127	1008	NM_000868	AY650375	NM_008312	NM_012765
HTR4	5-HYDROXYTRYPTAMINE RECEPTOR 4	SEROTONIN 5-HT-4 RECEPTOR	0.002	0.052	0.038	0.007	0.071	0.099	534	NM_000870	AY650373	NM_008313	NM_012853
HTR6	5-HYDROXYTRYPTAMINE RECEPTOR 6	SEROTONIN 5-HT-6 RECEPTOR	0.011	0.071	0.155	0.012	0.133	0.090	570	NM_000871	AY650371	NM_021358	NM_024365
KCNQ2	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 2	POTASSIUM CHANNEL, VOLTAGE-GATED, SUBFAMILY Q, MEMBER 2	0.001	0.075	0.013	0.006	0.125	0.048	2016	NM_004518	AY650350	NM_010611	NM_133322
KCNS1	POTASSIUM CHANNEL, VOLTAGE-GATED, DELAYED-RECTIFIER, SUBFAMILY S, MEMBER 1	VOLTAGE-GATED POTASSIUM CHANNEL 9.1 (KV9.1)	0.007	0.031	0.226	0.024	0.325	0.074	381	NM_002251	AY650351	NM_008435	NM_053954
KCNV1	POTASSIUM CHANNEL, SUBFAMILY V, MEMBER 1	HNKA; KCNB3; KV2.3; KV8.1	0.000	0.057	0.000	0.004	0.146	0.027	1500	NM_014379	AB051133	NM_026200	NM_021697
MBP	MYELIN BASIC PROTEIN		0.011	0.093	0.118	0.000	0.168	0.000	285	NM_002385	CO048868	M15060	NM_017026
MOG	MYELIN-OLIGODENDROCYTE GLYCOPROTEIN		0.010	0.090	0.111	0.034	0.215	0.158	741	NM_002433	AB056396	NM_010814	NM_022668
NEFL	NEUROFILAMENT PROTEIN, LIGHT POLYPEPTIDE		0.015	0.106	0.142	0.006	0.154	0.039	891	NM_006158	CN643186	NM_010910	NM_031783
NPY	NEUROPEPTIDE Y	Y NEUROPEPTIDE	0.010	0.107	0.093	0.006	0.048	0.125	291	NM_000905	AF162280	NM_023456	NM_012614
NPY1R	NEUROPEPTIDE Y RECEPTOR Y1	NPYR	0.001	0.047	0.021	0.010	0.210	0.048	1149	NM_000909	AF303089	NM_010934	XM_344502
NPY2R	NEUROPEPTIDE Y RECEPTOR Y2		0.005	0.090	0.056	0.013	0.190	0.068	1143	NM_000910	AF303090	NM_008731	NM_023968
NPY5R	NEUROPEPTIDE Y RECEPTOR Y5		0.003	0.044	0.068	0.040	0.222	0.180	1335	NM_006174	AF303091	NM_016708	NM_012869
NRXN1	NEUREXIN 1		0.000	0.078	0.000	0.004	0.238	0.017	357	NM_004801	AF424835	NM_020252	NM_021767
OPRM1 *	OPIOID RECEPTOR, MU-1		0.012	0.049	0.245	0.026	0.235	0.111	1200	NM_000914	AF286024	NM_011013	NM_013071
PDYN	PRODYNORPHIN	ENKEPHALIN B; PREPROENKEPHALIN B	0.021	0.074	0.284	0.074	0.138	0.536	693	NM_024411	AY650313	NM_018863	NM_019374
PENK	PROENKEPHALIN	ENKEPHALIN A, PREPROENKEPHALIN A	0.005	0.053	0.094	0.005	0.291	0.017	285	NM_006211	AF512368	XM_131313	NM_017139
PLP1	PROTEOLIPID PROTEIN 1	PROTEOLIPID PROTEIN, MYELIN (PLP); LIPOPHILIN	0.002	0.013	0.154	0.004	0.030	0.133	660	NM_000533	AB083324	NM_011123	NM_030990
PNOC	PREPRONOCICEPTIN	PPNOC	0.000	0.075	0.000	0.067	0.220	0.305	285	NM_006228	AY011842	NM_010932	NM_013007
PPT1 **	PALMITOYL-PROTEIN THIOESTERASE 1		0.000	0.054	0.000	0.025	0.099	0.253	573	NM_000310	AB083325	NM_008917	NM_022502
PTGDS	PROSTAGLANDIN D2 SYNTHASE, BRAIN	PGD2 SYNTHASE (PGDS2); BETA-TRACE	0.026	0.063	0.413	0.060	0.195	0.308	570	NM_000954	AB032480	NM_008963	NM_013015
RAB3A	RAS-ASSOCIATED PROTEIN RAB3A		0.000	0.091	0.000	0.003	0.246	0.012	582	NM_002866	AY650355	NM_009001	NM_013018
RTN4R	RETICULON 4 RECEPTOR	NOGO RECEPTOR (NGR)	0.012	0.145	0.083	0.023	0.192	0.120	1419	NM_023004	AB045987	NM_022982	NM_053613
SH3GL2	SH3 DOMAIN, GRB2-LIKE, 2	ENDOPHILIN 1	0.001	0.042	0.024	0.008	0.153	0.052	870	NM_003026	BQ807336	NM_019535	XM_342857
SLC18A3	SOLUTE CARRIER FAMILY 18, MEMBER 3	VESICULAR ACETYLCHOLINE TRANSPORTER (VACHT)	0.000	0.123	0.000	0.003	0.179	0.017	411	NM_003055	D83487	NM_021712	NM_031663
SLC1A2	SOLUTE CARRIER FAMILY 1 (GLIAL HIGH AFFINITY GLUTAMATE TRANSPORTER), MEMBER 2	EXCITATORY AMINO ACID TRANSPORTER 2, EAAT2; GLUTAMATE TRANSPORTER 1, GLT1	0.000	0.035	0.000	0.006	0.130	0.046	669	NM_004171	AB056372	NM_011393	NM_017215
SLC6A1	SOLUTE CARRIER FAMILY 6 (NEUROTRANSMITTER TRANSPORTER, GABA),	GABA TRANSPORTER (GABATR); GABATHG	0.001	0.090	0.011	0.000	0.107	0.000	1563	NM_003042	AY650357	NM_017870 3	NM_024371
SLC6A2	SOLUTE CARRIER FAMILY 6 (NEUROTRANSMITTER TRANSPORTER, NORADRENALINE), MEMBER 2	NEUROTRANSMITTER TRANSPORTER, NORADRENALINE, NAT1; NOREPINEPHRINE TRANSPORTER PROTEIN 1, NET1	0.005	0.067	0.075	0.013	0.222	0.059	1800	NM_001043	AF286026	NM_009209	NM_031343
SLC6A3	SOLUTE CARRIER FAMILY 6 (NEUROTRANSMITTER TRANSPORTER,	DOPAMINE TRANSPORTER (DAT)	0.006	0.110	0.055	0.005	0.125	0.040	1860	NM_001044	AF286447	NM_010020	NM_012694
SLC6A4	SOLUTE CARRIER FAMILY 6 (NEUROTRANSMITTER TRANSPORTER,	SEROTONIN TRANSPORTER (SERT); 5-HYDROXYTRYPTAMINE TRANSPORTER (HTT)	0.007	0.076	0.092	0.029	0.251	0.116	1890	NM_001045	AF285761	NM_010484	NM_013034
SNAP25	SYNAPTOSOMAL-ASSOCIATED PROTEIN, 25-KD		0.000	0.010	0.000	0.000	0.226	0.000	570	NM_003081	AF240770	NM_011428	NM_030991
STX1A	SYNTAXIN 1A		0.009	0.070	0.129	0.002	0.114	0.018	618	NM_004603	AF240771	NM_016801	NM_053788
STXBP1	SYNTAXIN-BINDING PROTEIN 1	UNC18, C. ELEGANS, HOMOLOG OF, 1	0.000	0.076	0.000	0.005	0.175	0.029	1641	NM_003165	AY650333	NM_009295	NM_013038

	SYT5	SYNAPTOTAGMIN 5		0.006	0.066	0.091	0.005	0.138	0.036	732	NM_003180	AY650317	NM_016908	NM_019350
	TUBA3	TUBULIN, ALPHA, BRAIN-SPECIFIC	B-ALPHA-1; TUBULIN, ALPHA-3 (TUBA3)	0.000	0.080	0.000	0.000	0.105	0.000	1329	NM_006009	AF141923	NM_009446	XM_345263
	USP11	UBIQUITIN-SPECIFIC PROTEASE 11	UBIQUITIN CARBOXYL-TERMINAL HYDROLASE, X-LINKED (UHX1)	0.004	0.044	0.091	0.023	0.092	0.250	411	NM_004651	AY650379	NM_145628	BN000322
	VAMP2	VESICLE-ASSOCIATED MEMBRANE PROTEIN 2	SYNAPTOBREVIN 2 (SYB2)	0.003	0.045	0.067	0.000	0.082	0.000	348	NM_014232	AF240769	NM_009497	NM_012663
Unclassified	*ADAM23*	A DISINTEGRIN AND METALLOPROTEINASE DOMAIN 23	METALLOPROTEINASE-LIKE, DISINTEGRIN-LIKE, AND CYSTEINE-RICH PROTEIN 3 (MDC3)	0.009	0.051	0.176	0.028	0.114	0.246	462	NM_003812	AY650341	NM_011780	XM_244124
	API5	APOPTOSIS INHIBITOR 5	FIBROBLAST GROWTH FACTOR 2-INTERACTING FACTOR 2	0.000	0.015	0.000	0.003	0.176	0.017	1455	NM_006595	AY650380	XM_123850	XM_342470
	APLP1	AMYLOID BETA A4 PRECURSOR-LIKE PROTEIN 1	AMYLOID PRECURSOR-LIKE PROTEIN (APLP)	0.012	0.039	0.308	0.010	0.104	0.096	456	NM_005166	AY650326	NM_007467	NM_017211
	APTX	APRATAXIN		0.005	0.043	0.116	0.003	0.179	0.017	504	NM_017692	AB056422	NM_025545	NM_148889
	ATP1B2	ATPase, Na+/K+ TRANSPORTING, BETA-2 POLYPEPTIDE	Na,K-ATPase BETA-2 POLYPEPTIDE; ADHESION MOLECULE ON GLIA (AMOG)	0.005	0.062	0.081	0.013	0.189	0.069	786	NM_001678	AY650327	NM_013415	NM_012505
	BAI3	BRAIN-SPECIFIC ANGIOGENESIS INHIBITOR 3		0.005	0.037	0.135	0.010	0.162	0.062	663	NM_001704	AY775949	NM_175642	XM_217367
	CDH6	CADHERIN 6	K-CADHERIN	0.000	0.064	0.000	0.009	0.241	0.037	825	NM_004932	AY650358	NM_007666	NM_012927
	CDH8	CADHERIN 8		0.002	0.085	0.024	0.013	0.117	0.111	795	NM_001796	AY650345	NM_007667	NM_053393
	CHN1	CHIMERIN 1	N-CHIMERIN (CHN); CHIMERIN, ALPHA-1; GTPase-ACTIVATING PROTEIN, RHO, 2 (ARHGAP2); RHO-GTPase-ACTIVATING PROTEIN 2 (RHOGAP2)	0.000	0.031	0.000	0.004	0.204	0.020	429	NM_001822	AB049856	NM_029716	NM_032083
	CKB	CREATINE KINASE, BRAIN TYPE	CKBB	0.013	0.053	0.245	0.013	0.161	0.081	831	NM_001823	CN802981	NM_021273	NM_012529
	CLU	CLUSTERIN	APOLIPOPROTEIN J (APOJ); SULFATED GLYCOPROTEIN 2 (SGP2); COMPLEMENT-ASSOCIATED PROTEIN SP-40,40; COMPLEMENT LYSIS INHIBITOR (CLI); TESTOSTERONE-REPRESSED PROSTATE MESSAGE 2 (TRPM2)	0.022	0.079	0.278	0.034	0.191	0.178	1251	NM_001831	AY650328	NM_001823	NM_012679
	CNTNAP1	CONTACTIN-ASSOCIATED PROTEIN 1	CONTACTIN-ASSOCIATED PROTEIN, CASPR; p190	0.004	0.095	0.042	0.010	0.128	0.078	432	NM_003632	AF480426	NM_016782	NM_032061
	*CSPG3 **	CHONDROITIN SULFATE PROTEOGLYCAN 3	NEUROCAN (NCAN)	0.029	0.065	0.446	0.059	0.188	0.314	3150	NM_004386	AY650346	NM_007789	NM_031653
	CX3CR1	CHEMOKINE, CX3C MOTIF, RECEPTOR 1	G PROTEIN-COUPLED RECEPTOR 13 (GPR13); G PROTEIN-COUPLED RECEPTOR V28 (V28)	0.018	0.064	0.281	0.016	0.129	0.124	660	NM_001337	AY185884	NM_009987	NM_133534
	DLL1	DELTA-LIKE 1	DELTA, DROSOPHILA, HOMOLOG OF, 1 (DELTA1)	0.011	0.098	0.112	0.032	0.153	0.209	1347	NM_005618	AY650368	NM_007865	NM_032063
	*DPPX **	DIPEPTIDYL PEPTIDASE IV-RELATED PROTEIN	DIPEPTIDYL PEPTIDASE VI (DPP6)	0.008	0.076	0.105	0.006	0.181	0.033	1851	NM_001936	AY650347	NM_010075	NM_022850
	DPYSL3	DIHYDROPYRIMIDINASE-LIKE 3	UNC-33-LIKE PHOSPHOPROTEIN (ULIP); DIHYDROPYRIMIDINASE-RELATED PROTEIN 3 (DRP3)	0.002	0.068	0.029	0.004	0.103	0.039	690	NM_001387	AY650381	NM_009468	NM_012934
	DRPLA	DENTATORUBRAL-PALLIDOLUYSIAN ATROPHY	ATROPHIN 1 (ATN1), NOD, B37	0.012	0.056	0.214	0.044	0.251	0.175	858	NM_001940	AJ133274	NM_007881	NM_017228
	ETV5	ETS VARIANT GENE 5	ETS-RELATED MOLECULE (ERM)	0.003	0.023	0.130	0.000	0.183	0.000	408	NM_004454	AY650337	NM_023794	XM_221387
	*GDI1 **	GDP DISSOCIATION INHIBITOR 1	RAB GDP-DISSOCIATION INHIBITOR, ALPHA (RABGDIA);	0.002	0.057	0.035	0.000	0.142	0.000	1332	NM_001493	AB083312	NM_010273	NM_017088
	GNAZ	GUANINE NUCLEOTIDE-BINDING PROTEIN, ALPHA Z POLYPEPTIDE		0.000	0.063	0.000	0.002	0.237	0.008	666	NM_002073	AY650382	NM_010311	NM_013189
	GPM6A	GLYCOPROTEIN M6A	NEURONAL MEMBRANE GLYCOPROTEIN M6A	0.000	0.046	0.000	0.004	0.188	0.021	756	NM_005277	AB093668	NM_153581	NM_178105
	GPR24	G PROTEIN-COUPLED RECEPTOR 24	MELANIN-CONCENTRATING HORMONE RECEPTOR 1 (MCHR1); SLC1	0.006	0.075	0.080	0.008	0.191	0.042	1059	NM_005297	AF513988	NM_145132	NM_031758
	GRCA1	GENE RICH CLUSTER, A1		0.005	0.040	0.125	0.015	0.258	0.058	510	NM_014449	AY650388	NM_013533	XM_342757
	HAPIP	HUNTINGTIN-ASSOCIATED PROTEIN-INTERACTING PROTEIN	DUO	0.001	0.083	0.012	0.006	0.106	0.057	2028	NM_003947	AY650383	XM_358803	NM_032062
	HIP1R	HUNTINGTIN-INTERACTING PROTEIN 1-RELATED PROTEIN	HUNTINGTIN-INTERACTING PROTEIN 12, HIP12	0.006	0.103	0.058	0.006	0.190	0.032	1035	XM_290592	AB093666	NM_145070	XM_213777
	HPCA	HIPPOCALCIN		0.006	0.055	0.000	0.000	0.158	0.000	552	NM_002143	AY650336	NM_010471	NM_017122
	ITM2B	INTEGRAL MEMBRANE PROTEIN 2B		0.001	0.046	0.022	0.009	0.205	0.044	798	NM_021999	AB083306	NM_008410	XM_214228
	LY6H	LYMPHOCYTE ANTIGEN 6 COMPLEX, LOCUS H		0.004	0.070	0.057	0.004	0.103	0.039	354	NM_002347	AY650310	NM_011837	XM_235426
	*LYNX1 **	LYNX1, MOUSE, HOMOLOG OF		0.030	0.086	0.349	0.000	0.221	0.000	348	NM_023946	AY422956	NM_011838	Genomic
	MAP1B	MICROTUBULE-ASSOCIATED PROTEIN 1B	FUTSCH, DROSOPHILA, HOMOLOG OF, FUTSCH	0.006	0.046	0.130	0.016	0.177	0.090	858	NM_005909	AY369829	NM_008634	XM_215469
	MAPK10	MITOGEN-ACTIVATED PROTEIN KINASE 10	PROTEIN KINASE, MITOGEN-ACTIVATED, 10 (PRKM10); C-JUN KINASE 3 (JNK3)	0.000	0.039	0.000	0.007	0.169	0.041	435	NM_002753	AY650363	NM_009158	NM_012806
	MAPT	MICROTUBULE-ASSOCIATED PROTEIN TAU	MTBT1	0.002	0.077	0.026	0.006	0.227	0.026	834	NM_005910	AY369831	NM_010838	NM_017212
	MOBP	MYELIN-ASSOCIATED OLIGODENDROCYTE BASIC PROTEIN		0.008	0.032	0.250	0.000	0.085	0.000	186	NM_006501	AY650315	NM_008614	NM_012720
	NCAM1	CELL ADHESION MOLECULE, NEURAL, 1	CD56	0.004	0.047	0.085	0.026	0.208	0.125	2067	NM_000615	AY650370	NM_010875	NM_031521
	NES	NESTIN		0.040	0.060	0.667	0.089	0.166	0.536	1898	NM_006617	AY650322	NM_016701	NM_012987
	NGFB	NERVE GROWTH FACTOR, BETA SUBUNIT		0.009	0.075	0.120	0.020	0.122	0.164	648	NM_002506	AF222682	NM_013609	XM_227525
	NP25	NEURONAL PROTEIN, 25-kD, RAT, HOMOLOG OF		0.000	0.085	0.000	0.003	0.097	0.031	585	NM_013259	CO725279	NM_031676	NM_019754
	NPAS3	NEURONAL PAS DOMAIN PROTEIN 3		0.004	0.040	0.100	0.004	0.118	0.034	438	NM_022123	BV166543	NM_013780	XM_234124
	OLFM1	OLFACTOMEDIN 1	NEUROBLASTOMA PROTEIN (NOE1)	0.011	0.061	0.180	0.004	0.086	0.047	1125	NM_006334	AY650384	NM_019498	NM_053573
	OPCML	OPIOID-BINDING PROTEIN/CELL ADHESION MOLECULE-LIKE	OPIOID-BINDING CELL ADHESION MOLECULE (OBCAM)	0.005	0.053	0.094	0.012	0.107	0.112	954	NM_002545	AY650354	NM_177906	NM_053848
	PBP	PHOSPHATIDYLETHANOLAMINE-BINDING PROTEIN	RAF KINASE INHIBITOR PROTEIN; RKIP HIPPOCAMPAL CHOLINERGIC NEUROSTIMULATING PEPTIDE PRECURSOR PROTEIN; HCNP PRECURSOR PROTEIN	0.009	0.037	0.243	0.036	0.289	0.125	561	NM_002567	X73137	NM_018858	NM_017236

PDE1B	PHOSPHODIESTERASE 1B	PDE1B1	0.009	0.065	0.138	0.006	0.099	0.061	1608	NM_000924	AB060237	NM_008800	NM_022710
PEG3 *	PATERNALLY EXPRESSED GENE 3		0.024	0.077	0.312	0.032	0.170	0.188	3789	NM_006210	AB051112	NM_008817	XM_218226
PHYHIP	PHYTANOYL-CoA HYDOXYLASE INTERACTING PROTEIN	PAHX-AP	0.000	0.070	0.000	0.000	0.149	0.000	713	NM_014759	AY650335	NM_145981	XM_224336
PI12	PROTEASE INHIBITOR 12	SERINE PROTEASE INHIBITOR, CLADE I, MEMBER 1 (SERPINI1); NEUROSERPIN	0.021	0.042	0.500	0.066	0.212	0.311	549	NM_005025	BQ807367	NM_009250	NM_053779
POU3F2	POU DOMAIN, CLASS 3, TRANSCRIPTION FACTOR 2	BRN2, MOUSE, HOMOLOG OF (BRN2); OCTAMER BINDING TRANSCRIPTION FACTOR 7 (OCT7); N-OCT-3 GENE	0.003	0.029	0.103	0.000	0.056	0.000	375	NM_005604	AY650385	NM_008899	NM_031576
PPP2R2B	PROTEIN PHOSPHATASE 2, REGULATORY SUBUNIT B, BETA	PP2APR55-BETA; PP2AB55-BETA; PP2AB-BETA; PR55-BETA	0.000	0.035	0.000	0.002	0.103	0.019	1296	NM_004576	AB071066	NM_028392	NM_022209
PRNP	PRION PROTEIN	PRION-RELATED PROTEIN (PRIP); PRP	0.015	0.112	0.134	0.014	0.163	0.086	759	NM_000311	AY382293	NM_011170	NM_012631
PSEN1	PRESENILIN 1		0.003	0.054	0.056	0.019	0.187	0.102	1401	NM_000021	AB083326	NM_008943	NM_019163
PTPRZ1	PROTEIN-TYROSINE PHOSPHATASE, RECEPTOR-TYPE, ZETA-1	HPTP-ZETA (HPTPZ); RPTP-BETA (RPTPB)	0.016	0.033	0.485	0.053	0.136	0.390	3489	NM_002851	AF424845	NM_011219	NM_013080
RGS4	REGULATOR OF G PROTEIN SIGNALING 4		0.000	0.056	0.000	0.009	0.147	0.061	426	NM_005613	AY650340	NM_009062	NM_017214
RPH3A	RABPHILIN 3A		0.005	0.070	0.071	0.010	0.201	0.050	2019	NM_014954	AY650339	NM_011286	NM_133518
RTN1	RETICULON 1	NEUROENDOCRINE-SPECIFIC PROTEIN (NSP)	0.003	0.059	0.051	0.000	0.068	0.000	594	NM_021136	CN646452	NM_153457	NM_053865
SHC3	SHC-LIKE PROTEIN, NEURONAL	NSHC	0.018	0.078	0.231	0.021	0.139	0.151	645	NM_016848	AY369841	NM_009167	AB001453
SIAT8B	SIALYLTRANSFERASE 8B	SIALYLTRANSFERASE X (STX)	0.004	0.058	0.069	0.004	0.097	0.041	1125	NM_006011	AY742821	NM_009181	NM_057156
SNCB	SYNUCLEIN, BETA		0.000	0.070	0.000	0.007	0.182	0.038	393	NM_003085	AY650316	NM_033610	NM_080777
SST	SOMATOSTATIN	SMST	0.000	0.057	0.000	0.000	0.093	0.000	351	NM_001048	M19318	NM_009215	NM_012659
STMN1	STATHMIN 1	LEUKEMIA-ASSOCIATED PHOSPHOPROTEIN p18 (LAP18); METABLASTIN	0.000	0.053	0.000	0.003	0.188	0.016	378	NM_005563	AY650331	NM_019641	NM_013101
STMN2	STATHMIN-LIKE 2	SUPERIOR CERVICAL GANGLIA, NEURAL SPECIFIC, 10 (SCGN10)	0.003	0.011	0.273	0.003	0.237	0.013	486	NM_007029	AY650387	NM_025285	NM_053440
SYNPO	SYNAPTOPODIN		0.006	0.068	0.088	0.015	0.169	0.089	762	NM_007286	AY650312	XM_129030	NM_021695
TM4SF2	TRANSMEMBRANE 4 SUPERFAMILY, MEMBER 2	MEMBRANE COMPONENT, X CHROMOSOME, SURFACE MARKER 1 (MXS1); TRANSMEMBRANE PROTEIN A15	0.004	0.023	0.174	0.007	0.148	0.047	636	NM_004615	AB047628	NM_019634	XM_343768
TMOD2	TROPOMODULIN 2	N-TROPOMODULIN (NTMOD)	0.011	0.033	0.333	0.005	0.124	0.040	333	NM_014548	CO725760	NM_016711	NM_031613
TTR *	TRANSTHYRETIN	PREALBUMIN, THYROXINE-BINDING (TBPA); PALB;	0.035	0.060	0.583	0.041	0.273	0.150	411	NM_000371	AY012016	NM_013697	NM_012680
UCHL1	UBIQUITIN CARBOXYL-TERMINAL ESTERASE L1	UBIQUITIN C-TERMINAL HYDROLASE, NEURON-SPECIFIC; PGP9.5	0.005	0.066	0.076	0.012	0.194	0.062	609	NM_004181	AB056429	NM_011670	NM_017237
WWP2	WW DOMAIN-CONTAINING PROTEIN 2		0.000	0.055	0.000	0.000	0.170	0.000	234	NM_007014	AY775950	NM_025830	XM_214669

* Primate-fast outlier; ** Rodent-fast outlier

Supplemental Table S2. Housekeeping Genes

Gene Symbol	Gene Name	Other Names	Primate Ka	Primate Ks	Primate Ka/Ks	Rodent Ka	Rodent Ks	Rodent Ka/Ks	LengthS compared	Accession Numbers Human	OWM	Mouse	Rat
ACADSB	ACYL-CoA DEHYDROGENASE, SHORT/BRANCHED CHAIN		0.022	0.042	0.524	0.044	0.242	0.182	1074	NM_001609	AY742811	NM_025826	NM_013084
ACTB	ACTIN, BETA		0.005	0.104	0.048	0.000	0.094	0.000	792	NM_001101	AF209434	NM_007393	NM_031143
ADPRT	ADP-RIBOSYLTRANSFERASE	POLY(ADP-RIBOSE) POLYMERASE (PPOL); PARP1	0.015	0.115	0.130	0.023	0.252	0.091	651	NM_001618	BQ807575	NM_007415	NM_013063
ALDOA	ALDOLASE A, FRUCTOSE-BISPHOSPHATE	FRUCTOSE 1,6-BISPHOSPHATE ALDOLASE A; ALDOLASE A (ALDA); ALDOLASE 1; FRUCTOALDOLASE A	0.003	0.089	0.034	0.003	0.131	0.023	1092	NM_000034	AB066558	NM_007438	NM_012495
ALDOC	ALDOLASE C, FRUCTOSE-BISPHOSPHATE	FRUCTOALDOLASE C (ALDC)	0.001	0.079	0.013	0.008	0.151	0.053	1092	NM_005165	AB051116	XM_126120	NM_012497
AMD1	S-ADENOSYLMETHIONINE DECARBOXYLASE		0.002	0.012	0.167	0.010	0.057	0.175	498	NM_001634	BQ807702	NM_009665	NM_031011
AP2M1	ADAPTOR-RELATED PROTEIN COMPLEX 2, MU-1 SUBUNIT	CLATHRIN-ASSOCIATED/ASSEMBLY/ADAPTOR PROTEIN, MEDIUM 1 (CLAPM1); CLATHRIN ADAPTOR PROTEIN 50 (AP50)	0.000	0.029	0.000	0.000	0.132	0.000	514	NM_004068	BQ807661	NM_009679	NM_053837
APEX	APEX NUCLEASE	APURINIC ENDONUCLEASE (APE); HUMAN APURINIC ENDONUCLEASE 1 (HAP1); REDOX FACTOR 1 (REF1)	0.000	0.056	0.000	0.004	0.165	0.024	285	NM_080649	AF455796	NM_009687	NM_024148
ARF1	ADP-RIBOSYLATION FACTOR 1		0.000	0.062	0.000	0.000	0.041	0.000	516	NM_001658	AY650309	NM_007476	NM_022518
ARHB	RAS HOMOLOG GENE FAMILY, MEMBER B	APLYSIA RAS-RELATED HOMOLOG 6 (ARH6); ONCOGENE RHO H6 (RHOH6)	0.000	0.113	0.000	0.000	0.052	0.000	480	NM_004040	BQ807624	NM_007483	NM_022542
ATP1A1	ATPase, Na+/K+ TRANSPORTING, ALPHA-1 POLYPEPTIDE	SODIUM-POTASSIUM-ATPase, ALPHA-1 POLYPEPTIDE; Na,K-ATPase, ALPHA-A CATALYTIC POLYPEPTIDE	0.000	0.096	0.000	0.000	0.163	0.000	135	NM_000701	AY742812	NM_144900	NM_012504
ATP5A1	ATP SYNTHASE, H+ TRANSPORTING, MITOCHONDRIAL F1 COMPLEX, ALPHA SUBUNIT, ISOFORM 1	MITOCHONDRIAL ATP SYNTHETASE (ATPM); MITOCHONDRIAL ATP SYNTHETASE, OLIGOMYCIN-RESISTANT (OMR)	0.008	0.038	0.211	0.017	0.311	0.055	588	NM_004046	BQ807752	NM_007505	NM_023093
BCKDK	BRANCHED CHAIN ALPHA-KETOACID DEHYDROGENASE KINASE		0.010	0.071	0.141	0.027	0.160	0.169	1236	NM_005881	AB071122	NM_009739	NM_019244
CALM1	CALMODULIN 1	PHOSPHORYLASE KINASE, DELTA SUBUNIT (PHKD)	0.000	0.043	0.000	0.003	0.309	0.010	423	NM_006888	AY650306	NM_009790	NM_031969
CAPN1	CALPAIN 1	CALPAIN, LARGE POLYPEPTIDE L1	0.007	0.091	0.077	0.009	0.193	0.047	2142	NM_005186	AF284440	NM_007600	NM_019152
CAPN2	CALPAIN 2	CALPAIN, LARGE POLYPEPTIDE L2	0.005	0.081	0.062	0.011	0.176	0.063	2100	NM_001748	AF284441	NM_009794	NM_017116
CBR1	CARBONYL REDUCTASE 1		0.030	0.087	0.345	0.064	0.161	0.398	831	NM_001757	AFB059654	NM_007620	NM_019170
CHD4	CHROMODOMAIN HELICASE DNA-BINDING PROTEIN 4	Mi2-BETA	0.003	0.047	0.064	0.008	0.108	0.074	1401	NM_001273	AY650307	NM_145979	XM_232354
COG7	COMPONENT OF OLIGOMERIC GOLGI COMPLEX 7		0.009	0.059	0.153	0.011	0.150	0.073	1758	NM_153603	AB070114	XM_133861	XM_215051
DNCL1	DYNEIN, CYTOPLASMIC, LIGHT CHAIN	PROTEIN INHIBITOR OF NEURONAL NOS (PIN)	0.000	0.035	0.000	0.000	0.140	0.000	270	NM_003746	AB056397	NM_019682	NM_053319
E1BAP5	ADENOVIRUS E1B 55-KD PROTEIN-ASSOCIATED PROTEIN 5	E1B55-ASSOCIATED PROTEIN 5	0.006	0.076	0.079	0.008	0.164	0.049	876	NM_007040	AY650289	NM_144922	XM_341807
EEF1A1	EUKARYOTIC TRANSLATION ELONGATION FACTOR 1, ALPHA-1		0.000	0.046	0.000	0.002	0.191	0.010	1269	NM_001402	AY650290	XM_203909	NM_175838
EIF2S1	EUKARYOTIC TRANSLATION INITIATION FACTOR 2, SUBUNIT 1	EUKARYOTIC TRANSLATION INITIATION FACTOR 2-ALPHA	0.000	0.024	0.000	0.000	0.152	0.000	677	NM_004094	AY650291	NM_026114	NM_019356
EIF5	EUKARYOTIC TRANSLATION INITIATION FACTOR 5		0.004	0.097	0.041	0.000	0.188	0.000	402	NM_001969	BQ807923	NM_173363	NM_020075
ENO1 **	ENOLASE 1	ENOLASE, ALPHA; PHOSPHOPYRUVATE HYDRATASE (PPH)	0.000	0.058	0.000	0.019	0.163	0.117	1209	NM_001428	AB072753	NM_023119	NM_012554
G6PD	GLUCOSE-6-PHOSPHATE DEHYDROGENASE		0.003	0.099	0.030	0.012	0.100	0.120	612	NM_000402	AF208984	NM_008062	NM_017006
GAPD	GLYCERALDEHYDE-3-PHOSPHATE DEHYDROGENASE	G3PD	0.011	0.060	0.183	0.011	0.147	0.075	942	NM_002046	CN806311	NM_008084	NM_017008
GLUL	GLUTAMATE-AMMONIA LIGASE	GLUTAMINE SYNTHETASE (GLNS)	0.000	0.051	0.000	0.018	0.304	0.059	621	NM_002065	BQ807681	NM_008131	NM_017073
GOSR1	GOLGI SNAP RECEPTOR COMPLEX MEMBER 1	GOLGI SNARE, 28-KD, GS28	0.000	0.025	0.000	0.003	0.160	0.019	537	NM_004871	AY369815	NM_016810	NM_053584
GSTM4	GLUTATHIONE S-TRANSFERASE, MU-4		0.013	0.035	0.371	0.127	0.432	0.294	558	NM_000850	AF200709	NM_008184	NM_031154
HNRPAB	HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN A/B	APOLIPOPROTEIN B mRNA EDITING ENZYME, CATALYTIC POLYPEPTIDE 1-BINDING PROTEIN 1 (ABBP1)	0.010	0.045	0.222	0.043	0.158	0.272	549	NM_004499	AB063020	NM_010448	NM_031330
HNRPC	HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN C		0.001	0.018	0.056	0.000	0.104	0.000	792	NM_004500	AY650292	NM_016884	XM_214160
HNRPU	HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN U	SCAFFOLD ATTACHMENT FACTOR A, SAFA	0.001	0.054	0.019	0.000	0.159	0.000	1596	NM_004501	AB049840	NM_016805	NM_057139
HPRT1	HYPOXANTHINE GUANINE PHOSPHORIBOSYLTRANSFERASE 1	HPRT; HGPRT	0.000	0.029	0.000	0.011	0.091	0.121	654	NM_000194	S43335	NM_013556	XM_343829
HSPA5	HEAT-SHOCK 70-KD PROTEIN 5	GLUCOSE-REGULATED PROTEIN, 78-KD (GRP78); IMMUNOGLOBULIN HEAVY CHAIN-BINDING PROTEIN (BIP)	0.002	0.056	0.036	0.005	0.190	0.026	1797	NM_005347	AY650293	NM_022310	NM_023952
HSPA8	HEAT-SHOCK 70-KD PROTEIN 8	HEAT-SHOCK COGNATE PROTEIN, 71-KD (HSC71); LIPOPOLYSACCHARIDE-ASSOCIATED PROTEIN 1 (LAP1)	0.000	0.088	0.000	0.001	0.145	0.007	1815	NM_006597	AB072749	NM_031165	NM_024351
IARS	ISOLEUCYL-tRNA SYNTHETASE	ILRS	0.014	0.049	0.286	0.018	0.200	0.090	711	NM_013417	AY650302	NM_172015	XM_225196
IDH3A	ISOCITRATE DEHYDROGENASE 3, ALPHA SUBUNIT	ISOCITRATE DEHYDROGENASE, NAD(+)-SPECIFIC, MITOCHONDRIAL, ALPHA SUBUNIT	0.003	0.095	0.032	0.004	0.190	0.021	1017	NM_005530	X87172	NM_029573	NM_053638
IDH3B	ISOCITRATE DEHYDROGENASE 3, BETA SUBUNIT	ISOCITRATE DEHYDROGENASE, NAD(+)-SPECIFIC, MITOCHONDRIAL, BETA SUBUNIT	0.005	0.075	0.067	0.009	0.176	0.051	1089	NM_006899	X82632	NM_130884	XM_342518

IDH3G	ISOCITRATE DEHYDROGENASE 3, GAMMA SUBUNIT	ISOCITRATE DEHYDROGENASE, NAD(+)-SPECIFIC, MITOCHONDRIAL, GAMMA SUBUNIT	0.004	0.101	0.040	0.003	0.091	0.033	1065	NM_004135	X74124	NM_008323	XM_215224
KCNK1	POTASSIUM CHANNEL, SUBFAMILY K, MEMBER 1	POTASSIUM CHANNEL, WEAKLY INWARD-RECTIFYING, WITH TWIN P DOMAINS, 1 (TWIK1)	0.000	0.110	0.000	0.004	0.081	0.049	636	NM_002245	BQ807331	NM_008430	NM_021688
KNSL6	KINESIN-LIKE 6	MITOTIC CENTROMERE-ASSOCIATED KINESIN (MCAK)	0.011	0.058	0.190	0.050	0.233	0.215	2013	NM_006845	AB072747	NM_134471	NM_134472
MECP2	METHYL-CpG-BINDING PROTEIN 2		0.001	0.026	0.038	0.010	0.145	0.069	1458	NM_004992	AF295597	NM_010788	NM_022673
NOL5A	NUCLEOLAR PROTEIN 5A	NOP56; NOP56P	0.006	0.043	0.140	0.014	0.163	0.086	1782	NM_006392	AB066543	NM_024193	XM_342517
OGDH	OXOGLUTARATE DEHYDROGENASE	ALPHA-KETOGLUTARATE DEHYDROGENASE; E1K	0.000	0.085	0.000	0.019	0.093	0.204	387	NM_002541	AY650308	NM_010956	Genomic
P47	p47, RAT, HOMOLOG OF		0.000	0.007	0.000	0.000	0.128	0.000	411	NM_016143	AB049861	NM_198326	NM_031981
PCLY	PRENYLCYSTEINE LYASE		0.010	0.072	0.139	0.025	0.262	0.095	1515	NM_016297	AB062961	NM_025823	NM_145085
PCNA	PROLIFERATING CELL NUCLEAR ANTIGEN	DNA POLYMERASE DELTA AUXILIARY PROTEIN	0.000	0.088	0.000	0.010	0.198	0.051	783	NM_002592	AF347680	NM_011045	NM_022381
PDHB	PYRUVATE DEHYDROGENASE, BETA POLYPEPTIDE	E1, BETA POLYPEPTIDE, PHE1B	0.003	0.031	0.097	0.005	0.177	0.028	582	NM_000925	AF457193	NM_024221	XM_214142
POMT1	PROTEIN O-MANNOSYLTRANSFERASE 1	ROTATED ABDOMEN, DROSOPHILA, HOMOLOG OF (RT)	0.017	0.077	0.221	0.026	0.206	0.126	648	NM_007171	BQ807533	NM_145145	NM_053406
POT1 **	PROTECTION OF TELOMERES 1		0.007	0.057	0.123	0.082	0.281	0.292	1902	NM_015450	AB066545	NM_133931	XM_236822
PPIA	PEPTIDYL-PROLYL ISOMERASE A	CYCLOPHILIN A (CYPA)	0.000	0.039	0.000	0.012	0.078	0.154	495	NM_021130	AF023861	NM_008907	NM_017099
PRDX1	PEROXIREDOXIN 1	PROLIFERATION-ASSOCIATED GENE A (PAGA); NATURAL KILLER-ENHANCING FACTOR A (NKEFA)	0.003	0.050	0.060	0.016	0.118	0.136	564	NM_002574	AY650294	NM_011034	NM_057114
PRDX3	PEROXIREDOXIN 3	ANTIOXIDANT PROTEIN 1 (AOP1)	0.014	0.056	0.250	0.026	0.131	0.198	618	NM_006793	BQ807861	NM_007452	NM_022540
PRIM2A	PRIMASE POLYPEPTIDE 2A	PRIMASE, p58 SUBUNIT	0.007	0.040	0.175	0.022	0.185	0.119	657	NM_000947	AB056423	NM_008922	XM_217375
PSMA5	PROTEASOME SUBUNIT, ALPHA-TYPE, 5	PROTEASOME COMPONENT 5 (PSC5); PROTEASOME SUBUNIT ZETA	0.006	0.047	0.128	0.008	0.151	0.053	627	NM_002790	AY650295	NM_011967	NM_017282
PSMB4	PROTEASOME SUBUNIT, BETA-TYPE, 4		0.007	0.080	0.088	0.031	0.248	0.125	669	NM_002796	AY650296	NM_008945	NM_031629
PSMC1	PROTEASOME 26S SUBUNIT, ATPase, 1		0.003	0.029	0.103	0.000	0.182	0.000	606	NM_002802	BQ807494	NM_008947	NM_057123
PSMD1	PROTEASOME 26S SUBUNIT, NON-ATPase, 1		0.000	0.054	0.000	0.003	0.124	0.024	609	NM_002807	BQ807960	AK087947	NM_031978
PSMD12	PROTEASOME 26S SUBUNIT, NON-ATPase, 12	P55	0.000	0.062	0.000	0.002	0.150	0.013	735	NM_002816	CB310251	NM_025894	XM_213502
PSMD5	PROTEASOME 26S SUBUNIT, NON-ATPase, 5	PROTEASE 26S, SUBUNIT 5B, S5B	0.008	0.046	0.174	0.019	0.235	0.081	1512	NM_005047	AY742819	NM_080554	XM_216041
RAC1	RAS-RELATED C3 BOTULINUM TOXIN SUBSTRATE 1	RHO FAMILY, SMALL GTP-BINDING PROTEIN RAC1	0.000	0.042	0.000	0.000	0.181	0.000	521	NM_006908	AY775951	NM_009007	AY491395
RPL10	RIBOSOMAL PROTEIN L10	QM GENE	0.000	0.036	0.000	0.000	0.213	0.000	576	NM_006013	AY650303	NM_052835	NM_031100
RPL13A	RIBOSOMAL PROTEIN L13A		0.003	0.105	0.029	0.009	0.174	0.052	459	NM_012423	AY650304	NM_009438	NM_173340
RPL17	RIBOSOMAL PROTEIN L17		0.000	0.117	0.000	0.000	0.179	0.000	530	NM_000985	AY650298	XM_284068	NM_201415
RPL19	RIBOSOMAL PROTEIN L19		0.000	0.082	0.000	0.002	0.202	0.010	588	NM_000981	AB093677	NM_009078	NM_031103
RPL23A	RIBOSOMAL PROTEIN L23A		0.003	0.086	0.035	0.000	0.239	0.000	396	NM_000984	AC148698	NM_207523	XM_340850
RPL24	RIBOSOMAL PROTEIN L24		0.000	0.050	0.000	0.000	0.208	0.000	474	NM_000986	AB093678	NM_024218	NM_022515
RPL26	RIBOSOMAL PROTEIN L26		0.000	0.087	0.000	0.000	0.195	0.000	438	NM_000987	AB093679	NM_009080	XM_213346
RPL27A	RIBOSOMAL PROTEIN L27a		0.006	0.021	0.286	0.004	0.236	0.017	276	NM_000990	AY650297	NM_011975	XM_215041
RPL29	RIBOSOMAL PROTEIN L29		0.024	0.045	0.533	0.033	0.165	0.200	471	NM_000992	AB093681	XM_354376	NM_017150
RPL30	RIBOSOMAL PROTEIN L30		0.000	0.045	0.000	0.000	0.138	0.000	348	NM_000989	AB093680	NM_009083	NM_022699
RPL31	RIBOSOMAL PROTEIN L31		0.000	0.083	0.000	0.000	0.147	0.000	375	NM_000993	CB310491	NM_053257	NM_022506
RPL38	RIBOSOMAL PROTEIN L38		0.008	0.039	0.205	0.017	0.233	0.073	210	NM_000999	AB093674	NM_023372	XM_221081
RPL9	RIBOSOMAL PROTEIN L9		0.003	0.020	0.150	0.004	0.276	0.014	576	NM_000661	AY742820	NM_011292	XM_341213
RPLP1	RIBOSOMAL PHOSPHOPROTEIN, LARGE, P1	RIBOSOMAL PHOSPHOPROTEIN, ACIDIC, P1	0.000	0.034	0.000	0.016	0.285	0.056	276	NM_001003	AY347935	NM_018853	XM_343403
RPS10	RIBOSOMAL PROTEIN S10		0.000	0.024	0.000	0.000	0.276	0.000	495	NM_001014	CN645527	NM_025963	NM_031109
RPS11	RIBOSOMAL PROTEIN S11		0.000	0.109	0.000	0.000	0.249	0.000	408	NM_001015	AB093675	NM_013725	NM_031110
RPS3	RIBOSOMAL PROTEIN S3		0.004	0.046	0.087	0.002	0.153	0.013	681	NM_001005	AB047899	NM_012052	XM_341888
RPS4X	RIBOSOMAL PROTEIN S4, X-LINKED	SINGLE-COPY ABUNDANT mRNA (SCAR); CELL CYCLE GENE 2 (CCG2)	0.000	0.025	0.000	0.000	0.186	0.000	792	NM_001007	AB024285	NM_009094	XM_343803
RPS5	RIBOSOMAL PROTEIN S5		0.007	0.146	0.048	0.012	0.127	0.094	501	NM_001009	AY650305	NM_009095	XM_341788
RPS6	RIBOSOMAL PROTEIN S6		0.000	0.056	0.000	0.000	0.219	0.000	747	NM_001010	CN648337	NM_009096	NM_017160
SEPW1	SELENOPROTEIN W, 1		0.000	0.060	0.000	0.000	0.106	0.000	264	NM_003009	U67450	NM_009156	NM_013027
SFRS10	SPLICING FACTOR, ARGININE/SERINE-RICH, 10	TRANSFORMER 2, DROSOPHILA, HOMOLOG OF, BETA (TRA2B)	0.000	0.024	0.000	0.000	0.151	0.000	438	NM_004593	AY072879	NM_009186	NM_057119
SFRS5	SPLICING FACTOR, ARGININE/SERINE-RICH, 5	SPLICING FACTOR, ARGININE/SERINE-RICH, 40-KD (SRP40)	0.000	0.015	0.000	0.007	0.048	0.146	615	NM_006925	AY650299	NM_009159	NM_019257
SNX1	SORTING NEXIN 1		0.007	0.055	0.127	0.009	0.121	0.074	1422	NM_003099	AB056808	NM_019727	NM_053411
SOAT	STEROL O-ACYLTRANSFERASE	ACYL-CoA:CHOLESTEROL ACYLTRANSFERASE	0.011	0.038	0.289	0.039	0.222	0.176	1632	NM_003101	AF053337	NM_009230	NM_031118
SRP14	SIGNAL RECOGNITION PARTICLE, 14-KD	Alu RNA-BINDING PROTEIN, 14-KD SUBUNIT (ALURBP)	0.000	0.178	0.000	0.000	0.124	0.000	225	NM_003134	AF027404	NM_009273	XM_215815
SRP9	SIGNAL RECOGNITION PARTICLE, 9-KD	Alu RNA BINDING PROTEIN, 9-KD SUBUNIT, ALURBP	0.006	0.051	0.118	0.000	0.254	0.000	189	NM_003133	CB312006	NM_012058	Genomic
TKT	TRANSKETOLASE		0.009	0.130	0.069	0.000	0.107	0.000	456	NM_001064	BQ807596	NM_009388	NM_022592
TOP1	TOPOISOMERASE, DNA, I		0.001	0.073	0.014	0.005	0.142	0.035	1683	NM_003286	AY742822	NM_009408	NM_022615
UBB	UBIQUITIN B	POLYUBIQUITIN B	0.000	0.061	0.000	0.000	0.102	0.000	690	NM_018955	AB071067	NM_011664	NM_133895
WEE1	WEE 1 TYROSINE KINASE		0.002	0.047	0.043	0.011	0.109	0.101	1233	NM_003390	AB070176	NM_009516	XM_219264
YWHAE	TYROSINE 3-MONOOXYGENASE/TRYPTOPHAN 5-MONOOXYGENASE ACTIVATION PROTEIN, EPSILON ISOFORM	14-3-3 PROTEIN, EPSILON ISOFORM	0.000	0.019	0.000	0.009	0.029	0.310	591	NM_006761	AY650300	NM_009536	NM_031603
YWHAT	TYROSINE 3-MONOOXYGENASE/TRYPTOPHAN 5-MONOOXYGENASE ACTIVATION PROTEIN, THETA POLYPEPTIDE	14-3-3 PROTEIN, THETA ISOFORM	0.000	0.028	0.000	0.000	0.157	0.000	708	NM_006826	AY650301	NM_011739	NM_013053

** Rodent-fast outlier