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Human Disease-Associated Mitochondrial Mutations Fixed in Nonhuman Primates

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Abstract. A number of human disease-associated sequences have been reported in other species, such as rodents, but compensatory changes appear to prevent these deleterious mutations from being expressed. The aim of this work was to compare the mitochondrial DNA of multiple primates to ascertain whether mitochondrial disease-causing sequences in humans are fixed in nonhuman primates. Indeed, 46 sequences related to human pathology were identified in 1 or more of the 12 studied nonhuman primates, the majority of which were associated with late-onset diseases. Most of these sequences can be explained by the presence of secondary compensatory changes that render these mutations phenotypically inert. Nonetheless, and since humans not only are the longest-lived primate but feature the largest brain, one hypothesis is that a gradual optimization of the human mitochondrion occurred in the hominid lineage driven by the need to optimize the aerobic energy metabolism to delay neurodegeneration. Therefore, it is also proposed that some of these disease-associated sequences in nonhuman primates may be linked to the evolution of human longevity and intelligence, indicating a general pattern of selection on longevity in the course of evolution of the human mitochondrion.

Key words: Aging — Bioinformatics — Brain — Longevity — Mitochondrial genome — Neurodegeneration

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Introduction

A number of human disease-associated sequences have been reported in other species (Kondrashov et al. 2002; Waterston et al. 2002; Kern and Kondrashov 2004). For example, position 53 of the human α-synuclein is normally occupied by alanine and a substitution by threonine predisposes to Parkinson's disease. Healthy mice and rats carry threonine at the homologous position of their α-synuclein proteins, a phenomenon termed fixed differences of disease-associated mutations (FDDAMs). Since rodents do not appear to be affected, even in the case of early-onset mutations, it was concluded that compensatory changes prevented such deleterious mutations from being expressed (Kondrashov et al. 2002; Gao and Zhang 2003).

In contrast to the so far limited number of sequenced mammalian nuclear genomes, a number of mitochondrial genomes are available, such as primate genomes. In primates, the mitochondrial DNA (mtDNA) features 37 genes and encodes 13 proteins involved in the mitochondrion's energy production. Even though it encodes a small fraction of all mitochondrial proteins, a number of pathologies have been associated with the mtDNA. In fact, mitochondrial diseases are now recognized as one of the most important classes of inherited neurological diseases, and pathologies originating in the mtDNA are dominated by the involvement of the nervous system as well as the myocardial and skeletal muscles (DiMauro and Schon 2003). Since primates are biologically and phenotypically similar, the rationale of this work is that studying the evolution of human pathogenic mutations in the mitochondrial DNA of

Table 1. List of species used plus GenBank accession numbers

Symbol	Common name	Species name	GenBank accession	Longevity (yr)[a]
Cebus	White-fronted capuchin	*Cebus albifrons*	NC_002763	44
Gorilla	Gorilla	*Gorilla gorilla*	NC_001645	54
Homo	Man	*Homo sapiens*	NC_001807	122.5
Gibbon	Gibbon	*Hylobates lar*	NC_002082	44
Lemur	Ring-tailed lemur	*Lemur catta*	NC_004025	30
Ape	Barbary ape	*Macaca sylvanus*	NC_002764	31
Rhesus	Rhesus macaque	*Macaca mulatta*	NC_005943	36
Loris	Slow loris	*Nycticebus coucang*	NC_002765	26.5
Bonono	Pygmy chimpanzee	*Pan paniscus*	NC_001644	48
Chimp	Chimpanzee	*Pan troglodytes*	NC_001643	60
Baboon	Baboon	*Papio hamadryas*	NC_001992	45
Pongo	Orangutan	*Pongo pygmaeus*	NC_001646	59
Tarsier	Tarsier	*Tarsius bancanus*	NC_002811	12

[a]Longevity records obtained from the AnAge database, build 6 (http://genomics.senescence.info/species/).

other primates may allow an understanding of the evolutionary forces behind the emergence of FDDAMs and human mitochondrial diseases.

Humans are the longest-lived primate, and longevity has been progressively increasing in the lineage that leads to humans. Moreover, humans feature a slower progression of age-related diseases, including neurodegenerative diseases (Finch 1990, pp 150–202; Erwin and Hof 2002). Another striking feature of our species is the large human brain and the energy requirements associated with it (Parker 1990). Since humans have the largest brain and the longest life span among primates, it is possible that an optimization of the mitochondrion occurred during hominid evolution to delay neurodegeneration. Indeed, phylogenetic analyses have revealed adaptive changes in the evolution of the biochemical machinery responsible for aerobic energy metabolism in primates. For example, adaptive evolution has been reported in nuclear-encoded proteins of the mitochondrial cytochrome *c* and in subunits of complexes III and IV. Driving such changes could be the anthropoid neocortex, one of the most aerobic and energy-consuming tissues (Grossman et al. 2001; Goldberg et al. 2003). Intriguingly, the mtDNA has been implicated in human longevity inheritance (Korpelainen 1999) and mitochondria have been related to aging (Harman 1972). For instance, mice expressing a defective mitochondrial DNA polymerase displayed signs of accelerated aging (Trifunovic et al. 2004). Therefore, another objective of this work was to investigate whether a link exists between mitochondrial mutations, the optimization of the mitochondrion, and the evolution of human intelligence and longevity.

Methods

Human mtDNA mutations were obtained from Mitomap (http://www.mitomap.org). Mutations in coding sequences resulting from frameshift or nonsense mutations were not considered, resulting in a total of 172 mutations: 107 mutations in RNA genes and 65 in protein-coding genes. A complementary set of 152 protein variants associated with human mutations and polymorphisms was obtained from SWISS-PROT build 45 (Yip et al. 2004). FDDAMs were identified based on data from Mitomap, and the SWISS-PROT annotation was used to confirm and further analyze the results. Complete mtDNA sequences were obtained from GenBank for all available primate mitochondrial genomes. Accession numbers and the complete list of species used are available in Table 1.

Multiple sequence alignments were computed using the ClustalW 1.83 multiple alignment algorithm (Thompsons et al. 1994). Phylogenetic trees were calculated based on multiple sequence alignments of the entire mitochondrial genome. Procedures were performed by way of the Ageing Research Computational Tools 0.9 (de Magalhaes et al. 2005), which uses Bioperl 1.4 (http://bio.perl.org/) and is available online at http://genomics.senescence.info/software/. GeneDoc 2.6 (http://www.psc.edu/biomed/genedoc/) and TreeView 1.6.6 (http://taxonomy.zoology.gla.ac.uk/rod/treeview.html) were used to, respectively, display the multiple alignments and the phylogenetic trees.

Results

Mutation data from Mitomap were used to find sequences in the mitochondrial genome of nonhuman primates identical to human disease-associated sequences. Overall, I found 46 positions that can be considered FDDAMs in at least one nonhuman primate: 13 positions in protein-coding genes, 32 positions in RNA genes, and 1 position in the mitochondrial promoter. Of these, at least in 10 cases there is reasonable evidence of an association with human disease (Table 2). All these cases were confirmed by a review of the literature to minimize false positives; for instance, positions were excluded if considerable doubts existed of their association with human disease. Moreover, these FDDAMs probably do not represent sequencing errors since often different species carry the same mutation at the same position. While errors in Mitomap are unlikely (Kern and Kondrashov 2004), FDDAMs in protein-coding genes were further confirmed using data from SWISS-PROT. The complete list of FDDAMs is presented in the Supplementary Material available online.

Table 2. Human disease-associated mutations fixed in nonhuman primates[a]

Gene (OMIM)	np	b change	aa change	Disease[b]	Primates with a FDDAM	Phylogeny[c]	Late-onset
				RNA genes			
MTRNR1 (561000)	1555	A–G	—	DEAF	*Pongo*	Mammals	+/–
MTTC (590020)	5814	T–C	—	ME	*Gibbon*	Unclear	+/–
MTTS1 (590080)	7445	A–G	—	SNHL	*Pongo*	Hominidae	–
MTTK (590060)	8356	T–C	—	MERRF	*Ape*, *baboon*, *cebus*, *tarsier*, *loris*, *lemur*	Primates	+
MTTE (590025)	14709	T–C	—	MM + DM	*Gibbon, baboon*, *rhesus*	Conserved	+/–
				Protein-coding genes			
MTND1 (516000)	4216	T–C	Y–H	LHON	*Pongo*, *loris*, *tarsier*	Primates	+
MTND2 (516001)	4917	A–G	N–D	LHON	*Pongo*	Conserved	+
MTATP6 (516060)	9101	T–C	I–T	LHON	*Pongo*, *baboon*, *lemur*, *loris*, *tarsier*, *cebus*	Conserved	+
MTCO3 (516050)	9438	G–A	G–S	LHON	*Rhesus*, *baboon*	Conserved	+
MTCO3 (516050)	9804	G–A	A–T	LHON	*Pongo*, *ape*, *rhesus*	Conserved	+

[a]Please refer to the Supplementary Material available online for the complete list of FDDAMs as well as bibliographical references.
[b]Pathology abbreviations (adapted from Mitomap): DEAF—maternally inherited deafness or aminoglycoside-induced deafness; ME—mitochondrial encephalomyopathy; SNHL—sensorineural hearing loss; MERRF—myoclonic epilepsy and ragged red muscle fibers; MM—mitochondrial myopathy; DM—diabetes mellitus; LHON—Leber hereditary optic neuropathy.
[c]Phylogeny was derived having the normal human sequence as reference: conserved means the normal human nucleotide is conserved across mammalian species except in the cases considered FDDAMs; unclear indicates that the sequence is not sufficiently conserved to determine divergence.

There was only one disease-associated substitution whose normal sequence is unique to humans: np 1438 on MTTRNR1. All studied nonhuman primates feature A1438, while humans feature G1438.

A strong mutational bias was witnessed in that more transitions than transversions were observed: approximately 5:1. There was also a roughly threefold higher number of fixed positions in nonhuman primates associated with human pathology than substitutions that are neither the normal nor the disease-associated sequence (available online as Supplementary Material), which appears to solely reflect this mutational bias (not shown).

Given the large variation in age of onset and pathology of mitochondrial disorders, often even within the same family, it is difficult to quantify the percentage of mitochondrial pathologies with a late onset. Even so, it is remarkable that roughly three of four of the total FDDAMs (available online as Supplementary Material) and nine of the ten FDDAMs likely pathogenic in humans (Table 2) have been associated with pathologies whose onset occurs after reproductive age. Though caution is advised when interpreting these results, they open the possibility that some of these FDDAMs could be a result of the rapid increase in longevity in the evolutionary history of humans (see Discussion).

Using protein variants obtained from SWISS-PROT, and according to the SWISS-PROT annotation, it was possible to analyze the distribution of changes in nonhuman primates at positions associated with human variants according to the type of human variant (Table 3). The number of positions in nonhuman primates different from the human sequence and associated with human polymorphisms was higher than expected by chance alone: in all species, there were 413 instances of sequence changes at positions associated with human polymorphisms, but the expected value was 268. This difference was statistically significant according to the chi-squared test ($p < 0.001$), suggesting that some human polymorphisms may be older than the differences between primates. In contrast, the number of changes at positions annotated as disease-causing in SWISS-PROT was lower than what would be expected by chance: 33 versus 60, respectively. Again, this difference was statistically significant ($p = 0.002$, χ^2 test). These results suggest that positions associated with human diseases, but not those associated with neutral human polymorphisms, are under evolutionary pressure in nonhuman primates, indicating that they have deleterious effects even in nonhuman primates.

The complete list of FDDAMs is presented in the Supplementary Material available online. Further datasets, including all the multiple alignments as well as additional materials, are available online at http://genomics.senescence.info/evolution/mtDNA.html.

Discussion

Secondary Compensatory Substitutions in Nonhuman Primates

Previously, FDDAMs have been considered as phenotypically inert and explained by the presence of secondary compensatory changes (Kondrashov et al.

Table 3. Conservation of the different types of SWISS-PROT variants in nonhuman primates

Variant type	*n* variants[a]	Nonconserved[b]	Ratio	Total[c]	Expected[d]	*p* value
Disease	35	13	37%	60	89	0.002
Polymorphism	105	75	71%	413	268	< 0.001
Unclassified	12	5	42%	39	31	0.129
Total	152	93	61%	512	388	< 0.001

[a]Number of SWISS-PROT variants found in human mitochondrial proteins.
[b]Number of positions associated with SWISS-PROT variants found to be different from the human sequence in at least one nonhuman primate.
[c]Sum of nonconserved positions with respect to the human sequence in all nonhuman primates at positions associated with SWISS-PROT variants.
[d]Number of changes in nonhuman primates at positions associated with SWISS-PROT variants expected to be found by chance alone. The value represents the sum of the average sequence divergence between each nonhuman primate and the human mitochondrial DNA versus the number of variants present in the human sequence.
[e]Calculated using the chi-squared test.

2002; Gao and Zhang 2003). Such may be the case for some, probably even most, of the FDDAMs reported herein. For example, nine of the FDDAMs may be related to pathologies in humans occurring prior to reproductive age (available online as Supplementary Material). Since these FDDAMs cause the fitness of an organism to be nearly zero, and clearly nonhuman primates cannot exhibit the phenotype associated with these mutations, complementary changes probably exist to suppress the deleterious effects of these substitutions in nonhuman primates. A number of FDDAMs should thus constitute what have been termed compensated pathogenic deviations (Kondrashov et al. 2002).

In fact, several compensatory mechanisms in tRNAs have been described (Kern and Kondrashov 2004), and these may explain the majority of FDDAMs in tRNA genes identified in this work. For instance, compensatory secondary substitutions appear to occur in the case of the T8356C mutation in MTTK since some, but not all, of the species with a T8356C mutation also feature a compensatory secondary mutation at A8301G. Similarly, the G8361A mutation appears to be compensated by C8297T, and in MTTC, the T5814C mutation in the gibbon could be compensated by a A5807G mutation. The mechanisms of compensatory changes are also well illustrated in the MTTF gene, where the A606G and T618C FDDAMs appear to be compensatory for each other (Fig. 1). These results are in line with previous models showing that a pathogenic mutation in a tRNA is unlikely to be faced without a compensatory change (Kern and Kondrashov 2004) and so are not discussed further.

In protein-coding genes, compensatory substitutions may occur within the same protein or, in the case of proteins whose activity depends of other molecules, within a different molecule (Kondrashov et al. 2002). Given the complexity of proteins and the fact that all FDDAMs in protein-coding sequences

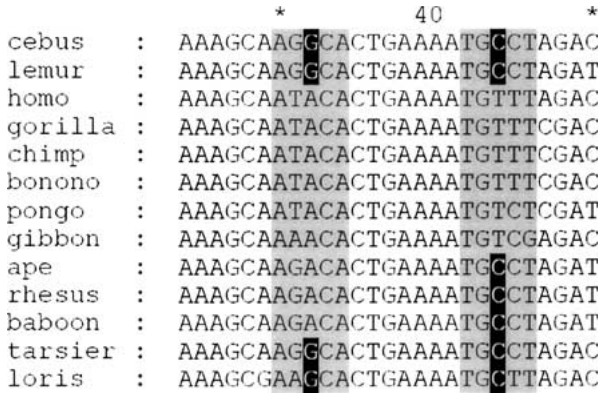

Fig. 1. Multiple alignment of the primate MTTF nucleotide sequence. Highlighted in black are the FDDAMs A606G and T618G. The tRNA anticodon stem is represented in gray. For the cebus, lemur, tarsier, and loris the FDDAMs are complementary to and compensatory for each other. That is not the case for the ape, rhesus, and baboon; presumably other compensatory changes occur in these organisms. Alignment generated with ClustalW and displayed using GeneDoc.

strongly associated with human disease have a late onset (Table 2), it is impossible to determine whether some FDDAMs feature compensatory substitutions, but this possibility clearly exists.

The mtDNA as Molecular Evidence for the Evolution of Human Longevity

The present study is unique in the high level of similarity between the species used and the possibility that some of the FDDAMs could be phenotypically expressed. Not all pathogenic mutations are lethal: molecules that fold into the same structure, such as the primate orthologs of a given protein, need not have the same fitness (Kondrashov et al. 2002). As mentioned previously, the majority of FDDAMs identified in nonhuman primates have been associated with pathologies occurring after sexual maturity and so are under a reduced natural

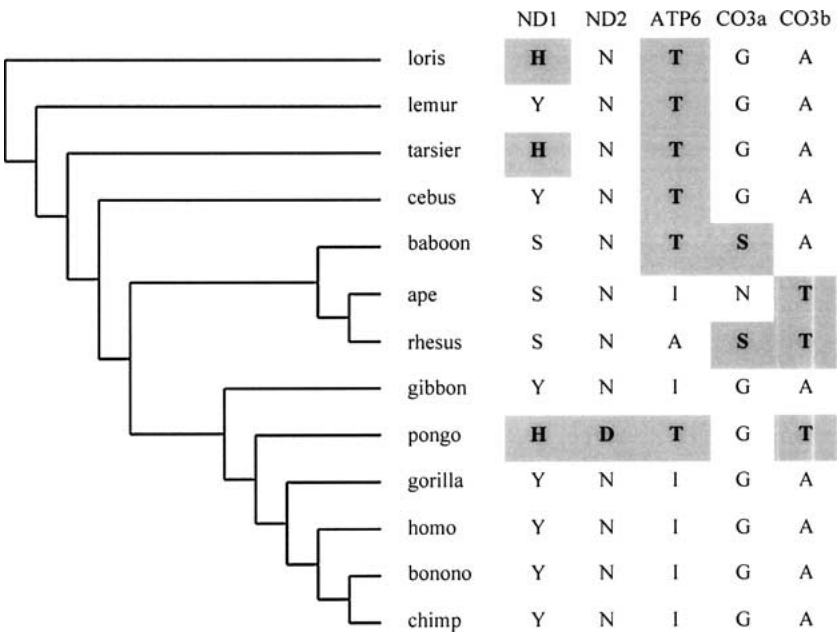

Fig. 2. Phylogenetic distribution in primates of FDDAMs associated with LHON in protein-coding genes. Residues are shown at each position associated with LHON in humans (see Table 2 for nucleotide positions and base changes). FDDAMs are in boldface on a gray background. Figure derived from TreeView based on the phylogeny calculated with ClustalW using the mtDNA of all primates employed in this study.

selection (Hamilton 1966). Contrary to previous studies, which mostly involved mutations that are unconditionally pathogenic and lethal under natural conditions (Kondrashov et al. 2002; Gao and Zhang 2003), many of these substitutions in humans increase the risk of developing diseases rather than being a sole factor in pathology. The major question, then, is whether some of the FDDAMs reported herein could be linked to the evolution of human longevity.

The need to optimize mitochondria to prevent neurodegeneration is clear (Nicholls 2002), particularly in humans who have the most energy-demanding brain of all primates and live longer. As such, the reported results, as a whole, could indicate an optimization of the human mitochondrion similar to that previously reported in the nuclear-encoded mitochondrial proteins of primates (Grossman et al. 2001; Goldberg et al. 2003). Given the evolutionary and biological proximity of primates, the large human brain, and the rapid and recent evolution of hominid longevity, it is possible that some of the reported FDDAMs are biologically significant. The way human disease-associated mutations appear to be selected against in nonhuman primates supports this view (Table 3). For instance, humans feature G1438, while all other studied nonhuman primates feature A1438. The mutation G1438A in humans is likely to be associated with type 2 diabetes (Yu et al. 2001). Interestingly, age-related diabetes has been reported in nonhuman primates at frequently younger ages than in humans (Bodkin et al. 1995). Therefore, one possibility is that the substitution of A by G in human evolution was selected by natural selection to delay the onset of type 2 diabetes.

A number of FDDAMs in protein-coding genes have been associated with Leber's hereditary optic neuropathy (LHON). Although LHON can occur in infants, it is normally an adult-onset vision disease. Visual ability has been shown to decline with age in nonhuman primates (Erwin and Hof 2002, pp. 15, 16, 141, 142, 144). For example, aging of the vision system has been reported in rhesus monkeys at considerably earlier ages (25–28 years) than witnessed in humans (Spear et al. 1994), probably due to neuronal changes (Schmolesky et al. 2000). A phylogenetic analysis reveals that only a few lineages are affected by these FDDAMs (Fig. 2). Even though, as expected, lineages further from humans are more affected, the orangutan (*Pongo* genus) is particularly prone to FDDAMs linked to LHON. Six of the FDDAMs considerably supported by experimental evidence to be pathogenic were present in the orangutan, including four of five of those associated with LHON (Table 2). Interestingly, age-related changes in the lenses of orangutans have been described, and these occur faster than in humans (Rathbun and Holleschau 1992). Furthermore, some indirect evidence suggests that age-related changes in the lenses of orangutans occur differently than in other primates (Holleschau and Rathbun 1994). The link between FDDAMs in orangutans and these results is appealing but more data are necessary regarding the age-related degeneration of visual function in these animals.

Although speculative, one possibility is that the long-term maintenance of vision in humans could come at a cost. It has been reported that, unlike human infants, monkey infants exhibit relatively little astigmatism (Kee et al. 2002). The antagonistic plei-

otropy theory states that alleles beneficial earlier in life are harmful late in life (Williams 1957). It could be that a trade-off between vision defects in infancy and long-term maintenance occurred in hominid evolution. Some FDDAMs that are not pathogenic in nonhuman primates could then derive not from secondary compensatory changes but from antagonistic pleiotropy in humans.

On the other hand, it is possible that some FDDAMs represent late-acting harmful mutations that appeared at specific primate lineages because nonhuman primates do not live long enough for these pathologies to express themselves. For example, the base substitution A1555G in MTTRNR1 has been linked to deafness, particularly in an age-related fashion (Zhao et al. 2004). Age-related changes in the auditory functions of nonhuman primates have been reported to occur faster than in humans (Erwin and Hof 2002, pp. 15, 16). For instance, one study found an age-related decline in the auditory function of rhesus monkeys by a mean age of 25 years (Torre and Fowler 2000). Position 1555 is well-conserved among mammals except in the *Pongo* genus and so the substitution of A by G is likely a recent event (not shown). Given that position 1555 is well-conserved among mammals, maybe this substitution occurred in the *Pongo* genus due to the diminishing force of natural selection at later ages, as proposed by the evolutionary theory of aging (Medawar 1952). Similarly, np 4917 is intriguing since asparagine is well-conserved from amphibians to primates. The substitution of asparagine by aspartic acid is unique to the *Pongo* genus and could represent a late-acting harmful gene. Of course it is premature to assume that some FDDAMs are pathogenic in nonhuman primates, but if that is shown to be the case, then they could result from late-acting harmful mutations evolving in individual primate lineages.

It is also noteworthy to mention that mutations at np 10006 and 12246 have been associated with aging in humans (Munscher et al. 1993), and even though an association with age-related pathology has not been confirmed, these aging-associated sequences are fixed in several nonhuman primate species (not shown). An association with successful aging has also been made with the A9055T polymorphism in MTATP6 (Ross et al. 2001). Intriguingly, even though alanine is well-conserved among mammals, its substitution by threonine, apart from a few primates, occurs only in whales, such as the bowhead whale, the longest-lived mammal (not shown).

Concluding Remarks

While the most likely explanation for the FDDAMs found in nonhuman primates remains secondary compensatory changes, one thought-provoking hypothesis is the possibility that some of these FDDAMs result from the gradual optimization of the mtDNA in primates and hominids. This link between mutation data and evolutionary events could indicate a general pattern of selection on longevity in the course of evolution of the human mitochondrion, in line with a number of previous observations (Parker 1990; Grossman et al. 2001; Goldberg et al. 2003).

If indeed subhuman primates do not suffer from the diseases associated with, at least, some of these FDDAMs, which surely happens for early-onset fatal diseases, then understanding the mechanisms of compensatory changes may prove valuable in the study of these diseases. On the other hand, if some of these FDDAMs are biologically relevant in nonhuman primates, then such animals could become useful models of human disease.

In conclusion, this work demonstrates that FDDAMs exist in the mitochondrial genome of several nonhuman primates. Neutral polymorphisms older than primate differences may account for some modern human polymorphisms. In contrast, human disease-associated sequences appear to be selected against in nonhuman primates, suggesting that these decrease fitness even in other species. Some FDDAMs could then be biologically significant. Although the nuclear background is of course relevant for the pathological aspects of mitochondrial diseases, it is possible that some FDDAMs are due to the evolution of human longevity. When other primate nuclear genomes become available, it will be exciting to investigate whether more FDDAMs are present, such as in nuclear-encoded mitochondrial proteins, and if these relate to the evolution of human longevity.

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