An illusion of common descent

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One of the activities of evolutionary biologists is modeling 'trees of life'. Before the advent of molecular biology such trees were predominantly based on morphological characteristics and ontogenetic traits. Nowadays, most modeling is based on molecular biology data. One of the surprises is that the well-known 'Darwinian trees of descent' are often not recapitulated by the genetic data. A Google search using the terms 'comparative genomics' and 'unexpected' resulted in over 60,000 hits, indicating that we can learn something unforeseen about the nature of mutations from comparative genomics. Since many mutations have been found in DNA 'hot spots', evolutionary trees are actually a byproduct, or artifact; a result of common design and the non-random nature of mutations. This novel view is supported by recent observations and provides an explanation for two phenomena associated with molecular phylogeny: homoplasy and nested hierarchy.

Mutations that spontaneously and randomly appear in the germ line can be passed on from one generation to the next and can be followed in time. The current consensus is that mutations in a DNA sequence are introduced at random and occur only once—except in some 'hot spots'. This view is summarized by Futuyma in an evolutionary textbook as follows:

> "Mutation is random in two senses. First … we cannot predict which of a large number of gene copies will undergo the mutation … Second, and more importantly, mutation is random in the sense that the chance that a particular mutation will occur is not influenced by whether or not the organism is in an environment in which that mutation would be advantageous …

> "[That] Mutations occur at random … does not mean that all conceivable mutations are equally likely to occur, because, as we have noted, the developmental foundation for some imaginable transformations do not exist. It does not mean that all loci, or regions within a locus, are equally mutable, for geneticists have described differences in mutation rates, at both the phenotypic and molecular levels, among and within loci …

> "It does not mean that environmental factors cannot influence mutation rates: ultraviolet and other radiation, as well as various chemical mutagens and poor nutrition, do indeed increase rates of mutations."[1]

If this view is correct, alignment of nucleotides, or 'point mutations', in the DNA of different species would be the best evidence for common descent. Random mutations in ancestral DNA sequences would also be present in all descendants according to the laws of inheritance. Hence, any alignment of 'mutations' can be considered molecular evidence for common descent. On the other hand, mutations that do not line up in phylogenetic analyses are *de novo* mutations introduced after the organism supposedly split into separate species. As such, they are evidence for the random character of mutations.

Let's critically analyze whether Futuyma's view can stand in the light of current biology. To a certain extent Futuyma may be right. For instance, we may not be able to predict which gene will mutate. Or, whether advantageous mutations are deliberately induced as an adaptive response to the environment of the organism.[2]

There may be *another* aspect, however, that determines where a mutations is introduced—its DNA environment. As mentioned by Futuyma, some DNA sequences may be more likely to mutate than others because the site of mutation often depends on the molecular context. This fact is well-known in genetics and has been covered extensively.[3–6]

Non-random mutations in *Drosophila*

That mutation may not be an entirely random phenomenon first occurred to me when I read a paper by Schmid and Tautz that discussed the 1G5 gene of *Drosophila melanogaster* and *D. simulans*.[7] The gene, found in both species is a unique, single copy gene of unknown function, but is not a pseudogene. The 1G5 gene caught the authors' interest because it was the fastest changing gene in the study. The sequence of the 1G5 gene is 1,081 base pairs (bp) long and contains only one small intron of 61 bp. Figure 1 shows all 75 polymorphic sites in an 864 bp segment (including the intron) of 13 populations of *D. melanogaster* and 4 populations of *D. simulans*. The authors concluded that almost none of the amino acid positions are under strong selective constraint because the fraction of polymorphic sites in the intron is comparable to the fraction of polymorphic sites in the coding region. In other words, the IG5 gene is evolving /changing in a neutral way in which selection is not involved.

Drosophila melanogaster originally stems from the African continent but has been present in Europe and Asia since early history. Until 1875, *Drosophila* did not exist in Canada or in the rest of the North American continent. In 1900 it was also not present in Mexico or Australia. Japan was colonized only in the 1960s. The current *Drosophila* populations in Latin-America, Australia and Japan are all due to recent migrations, mainly from European and Asian

populations. Based on the data, we can therefore make two interesting observations:

1. An Italian population invaded the Americas, first the USA (*D. mel III*) and then it migrated to Peru. In Peru it acquired the exact same mutation as the population in Japan (the A at position 835);

2. *Drosophila* populations from either Cyprus, Iraq or USSR invaded Canada and USA (*USA II*). The populations in Australia were not derived from the Italian (*D. mel 7*). Still the Australian population ended up with the exact same mutations the Italian population acquired in the USA (*USA III*). The Australian population (*D. mel III*) could have migrated from the USA (*D. mel 11*), and have acquired an A at position 637.

A fraction of the mutations in the IG5 gene is found on exactly the same location but is not the result of common descent! Because none of the positions may be under selective constraint, the observed 'shared mutations' in the gene may be the result of a non-random mechanism—a mechanism that produces *an illusion of common descent*. An important question that needs to be addressed is whether such non-random mutations are the rule rather than the exception. If the fraction of such non-random mutations is much greater than assumed, an alignment of the mutations would suddenly not be compelling molecular evidence of Darwin's common descent. Rather, the alignment may simply reflect the common biophysical properties of those organisms.

Non-random mitochondrial mutations

Mitochondria are the power plants of the cell. They convert sugars into biologically useful energy (ATP) and also generate heat. The more ATP generated, the less energy is left to produce heat. The efficiency of generating ATP and heat as a 'byproduct' appears to be a genetic trait. Genetic changes ('mutations') that result in an increase in the generation of heat automatically reduce the amount of ATP produced. People in the tropics will therefore tend to benefit from mitochondria that produce little heat and loads of ATP. In contrast, people in Arctic Regions benefit from mitochondria with a heat bias. A few years ago, an Australian team found that heat-generating mitochondria are indeed common in Arctic Regions.[8] They explained it as the result of natural selection, but there is also good evidence these adaptive mutations may have occurred several times as non-random mutations.

"An Italian study published in 2001, for example, showed that healthy centenarians in Italy have a high incidence of a certain mutation in the cytochrome B gene, which is part of the energy-production machinery. … Remarkably, Wallace's study has found that this lineage, and another found in Europe which also associated with longevity … have the same mutations. Yet the two mutations occurred independently of each other. Wallace's study goes against the traditional view that the spread of most mitochondrial mutations occur by chance, says Alan Cooper, head of the
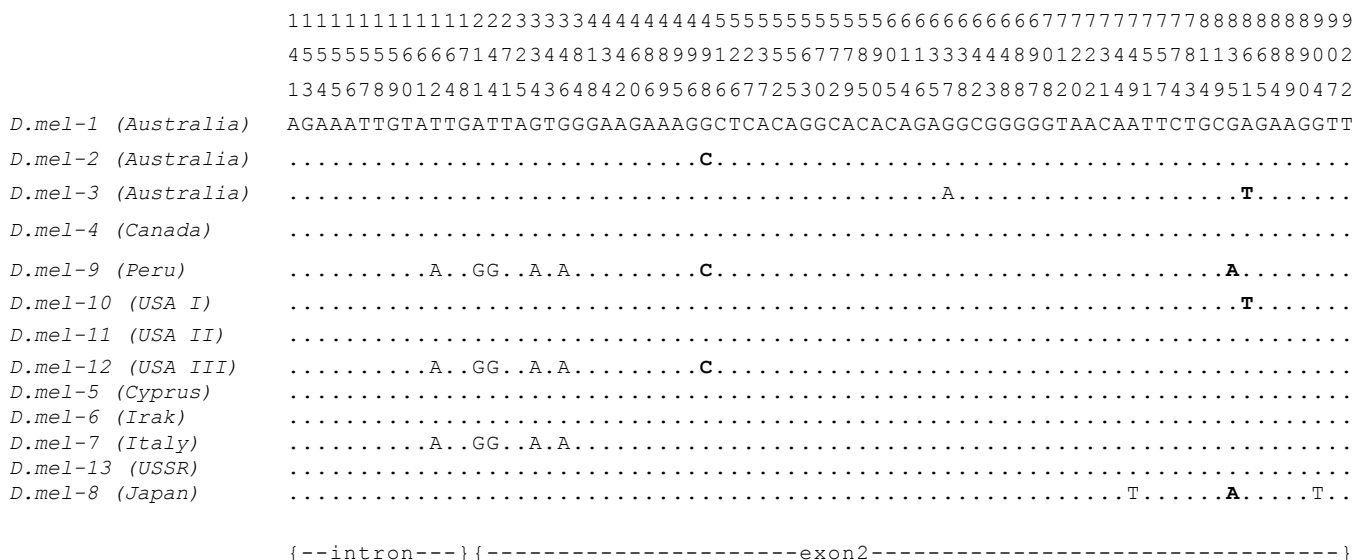
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D.mel-1 (Australia)   AGAAATTGTATTGATTAGTGGGAAGAAAGGCTCACAGGCACACAGAGGCGGGGGTAACAATTCTGCGAGAAGGTT
D.mel-2 (Australia)   ...........................................C.............................
D.mel-3 (Australia)   ...............................................A....................T.......
D.mel-4 (Canada)      .........................................................................
D.mel-9 (Peru)        ..........A..GG..A.A.........C..................................A.........
D.mel-10 (USA I)      .........................................................................T.......
D.mel-11 (USA II)     .........................................................................
D.mel-12 (USA III)    ..........A..GG..A.A.........C...........................................
D.mel-5 (Cyprus)      .........................................................................
D.mel-6 (Irak)        .........................................................................
D.mel-7 (Italy)       ..........A..GG..A.A.....................................................
D.mel-13 (USSR)       .........................................................................
D.mel-8 (Japan)       ..............................................................T......A.....T..

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Figure 1. Non-random mutations in the fruitfly *Drosophila melanogaster*. Before 1875, there were no populations of *D. melanogaster* in Canada and the rest of the American continent, and none in Australia before the 1900s. Current populations of *D. melanogaster* in the Americas and Australian continent are modern invaders. They originated mainly from Eurasian populations (which are relatively homogeneous), although there is a small proportion that stem from African populations. An Australian population could not have taken over a Russian niche, because there was no Australian population at that time (or Japanese or Mexican population; there was also no *Drosophila* in Japan before the 1960s, and none in Mexico before around the 1900s). *Drosophila* evolved/mutated in Africa, and then invaded Eurasia. From there, humans took *Drosophila* to the Americas and Australasia in their ships and aircrafts. The mutations and presented in bold font (positions 498, 835 and 861) can only be understood as *non-random 'hot spot' mutations*.

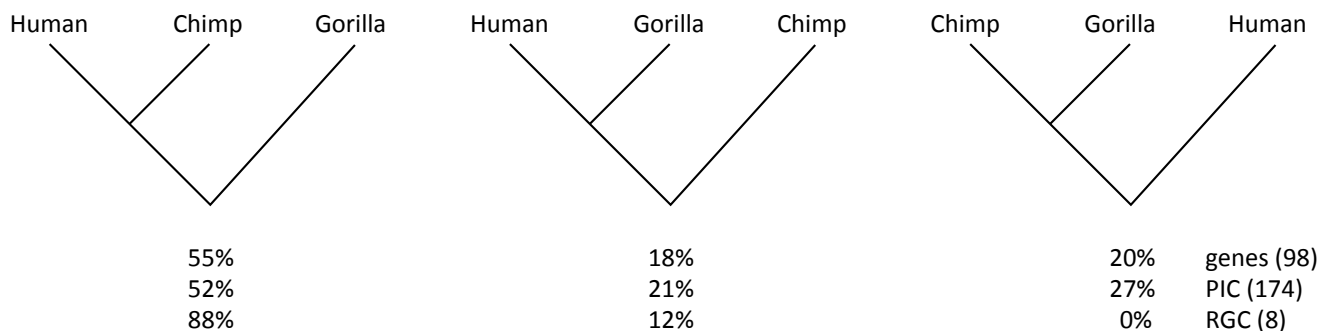| Human	Chimp	Gorilla		Human	Gorilla	Chimp		Chimp	Gorilla	Human	
	55%				18%				20%		genes (98)
	52%				21%				27%		PIC (174)
	88%				12%				0%		RGC (8)

Figure 2. Small, three-branched cladograms showing the relationship between man, chimpanzee and gorilla. The similarities displayed in these trees are highly dependent on the traits being considered. The Darwinian idea that the chimpanzee is man's closest relative is 'supported' by only 55% of the tested genes and in only 52% of the parsimony-informative characters (PICs). These unexpected results can easily be explained as the result of homoplasy, i.e. unexpected shared gene rearrangement which are now challenging current evolutionary trees. Indeed, 18% of the genes, 21% of the PICs and 12% of the rare genomic changes (RGC) found in humans are more similar to those observed in gorilla. A fraction of the tested genes (6/98) is unbiguous. A parsimonious explanation is that homoplasy is simply a result of *interspecies (or transbaraminic) hot spots*. (Figure adapted from ref. 15).

Ancient Biomolecules Centre at the University of Oxford."[9]

The non-random nature of mutations in mitochondrial DNA can be illustrated by a small deletion of nine nucleotides.[10] The deletion is located between two genes in the mitochondrial control region, and is present at varying frequencies in Asia, Southeast Asia, Polynesia, and the New World, but also in sub-Saharan Africa. Comparing mitochondrial DNA sequences of sub-Saharan Africans with those of Asians revealed that both populations had independently acquired the deletion. The deletion also independently occurred in South-East Asia, Polynesia and the New World. Hence, the exact same mutations can be found in genomes independent of common descent. Natural selection and common descent are not required to explain the distribution of shared mutations. Rather, a common genetic mechanism explains such findings.

Non-random mutations experimentally visualized

Although non-random mutations are acknowledged as occurring in hot spots, it has been tacitly assumed that such mutations are most likely exceptions. This assumption, however, may be wrong. Experiments on mutation sites in the DNA of the common gut bacterium *Escherichia coli* have provided some remarkable results.

"Of 293 independent mutations identified within the *lacI*[−d] sequence on the F plasmid, 63% are located at 19 medium-level hotspot sites. Of 120 base substitutions identified within the *rpsL* sequence on a multicopy plasmid, 63% are located at 9 hotspot sites. Recently, the *rpsL* mutation assay was adapted to analyze mutations in the same target sequence that had become integrated into the chromosome of *E. coli* (K. Yoshiyama, M. Kawano, A. Isogawa and H. Maki, unpublished results). In this case, 70% of 1555 base substitutions examined are confined

to only two strong hotspot sites. The remaining 475 mutations are almost evenly distributed at 91 sites within the target sequence."[11]

In bacteria, the non-random character of mutations can only be resolved after the analysis of hundreds of DNA sequences. If sufficient numbers of sequences are included, the majority of mutations are in hot spots. Base substitutions and single-base frame shifts, two major classes of spontaneous mutations, occur non-randomly throughout the genome. Within target DNA sequences there are hot spots for particular types of spontaneous mutations. Outside of these hot spots, spontaneous mutations occur more randomly and much less frequently. Hot-spot mutations can therefore be attributed to endogenous DNA lesions rather than to replication errors.[11]

Radiation-induced non-random mutations

Direct evidence for environment-driven non-random mutations comes from studies carried out in areas with a high natural background of radioactivity. When unstable atoms drop or convert to a more stable energy state, they send out energy waves (beta and gamma radiation) and/ or emit a hydrogen particle (alpha radiation). The emitted radiation is better known as radioactivity. Radioactivity is highly mutagenic: it destroys the information in the DNA molecule. It has always been assumed that radiation is a random mutagen, i.e. the position at which mutations are introduced cannot be predicted. This is also the case for ultraviolet radiation and oxidative stress. Surprisingly, however, radioactivity has now been shown not to be a random mutagen.

Kerala, at the southern tip of India, is a densely populated peninsula with the world's highest level of natural occurring radioactivity: the beaches contain radioactive elements such as thorium and monazite. Generations of fishermen have made a living here, as well as on nearby low-radiation islands. In 2002, mutations in the mitochondrial DNA were analyzed and compared to a control group. Twenty-two mutations

were identified in the DNA sequence of families living in the *Kerala* area, whereas the control population had only one mutation in the same sequence. The increased mutation rate in the *Kerala* area wasn't unexpected, but the surprise was to find that the mutations were located at positions referred to by geneticists as 'evolutionary hot spots'. The investigators reported that

> "Strikingly, the radioactive conditions accelerate mutations at nucleotide positions that have been evolutionary hot spots for at least 60,000 years."[12]

Apparently, high energy radiation does not induce random mutation. In an environment with high levels of radiation, some positions are more likely to mutate than others. Over and over, radiation-induced mutations fall on the exact same hot spots. Therefore, positions where mutations occur in a DNA sequence may largely be (pre)determined.

Homoplasy

A comparison of human, chimpanzee and Rhesus Macaque genes revealed that many mutations are shared between the Rhesus Macaque and humans but do not appear in chimpanzees.[13] In other studies which compared human, chimpanzee and gorilla sequences this peculiar phenomenon was also observed, i.e. human genes often resemble those of gorillas, not chimpanzees.[14] So whether humans are more 'closely related' to chimpanzees than to gorillas then appears to depend on which genes are compared. Only 55% of the human genes resulted in the expected Darwinian tree.

The sharing of unexpected sequence arrangement is a common observation and is known as *homoplasy*. Scientists speak of homoplasy when DNA sequences are identical in organisms that are not closely related in an evolutionary tree. (Mutations in) DNA sequences often conflict with 'known' evolutionary trees.

> "Homoplasy has long been appreciated in theoretical phylogenetics, with much effort invested into understanding its causes and providing corrections for them. However, the observed patterns … give cause for concern that the extent of homoplasy is much greater than expected under widely accepted models of sequence evolution and that the attendant consequences for the limits to phylogenetic resolution are not sufficiently appreciated."[14]

Apparently, homoplasy is fairly common (10–15% according to reference 14) and, in my opinion, simply reflects the non-random nature of mutations. Homoplasy is, in fact, nothing but part of the illusion of common descent caused by *inter-species hot spots* recognized and acknowledged by evolutionists. How do evolutionists discriminate between random and non-random mutations when they are modelling the tree of life? In other words, how do they differentiate between homoplasy and real common descent mutations? The answer is they don't. It appears their trees are nothing but common design plus a handful of non-random mutations.

Nested hierarchy

Phylogenetic analyses often display *nested hierarchy*. This means that the genes of distinct organisms appear to us as groups within groups. For instance, the genes of humans usually group with primates. Primates group with mammals, which then group with vertebrates. The nested hierarchy is a reflection of DNA sequences that are more dissimilar in organisms that are more distantly related. This is what one might expect from common descent with modification; the longer the time since two organisms supposedly split from a common ancestor, the more differences should be observed. Nested hierarchy is therefore believed to present compelling evidence for evolution and meant to imply common descent. However, according to Francis S. Collins, the director of the Human Genome Project:

> "If these genomes were created by individual acts of special creation, why would this particular feature [nested hierarchy] appear?"[15]

Collins considers *nested hierarchy* a problem for special creation and it his main reason for accepting Darwin's common descent. But the nested hierarchy observed among species that cannot reproduce may just be a result of the functional restrictions (between separate designs) and non-random mutations.

Functional domains of proteins include sites for *phosphorylation, glycosylation, ubiquitinilation, sumoylation* and *glutathionylation*, as well as sites that interact with other proteins. The function of such domains is determined by specific sequences of amino acids that must be coded in the DNA. All functional domains and sites will contribute to the sequence identity of homologous genes in separate species. Phylogenetic analyses are therefore in effect a genetic mirage—the result of artificial constraints imposed by analysing functional domains together with non-random mutations—largely determined by the physico-chemical properties of the DNA sequence and its environment.

The pseudogene argument revisited

A pseudogene is a gene that has lost its function, usually due to the accumulation of debilitating mutations. A well-known example is the GULO gene, which is inactive in humans. Hence, man cannot make vitamin C. In fact, all the families tested from one primate suborder, the *Catarrhini*, also lack the ability to make their own vitamin C, whereas those from the suborder *Platyrrhini* make this vitamin in the liver. Degenerative loss of vitamin C biosynthesis has evidently occurred quite frequently. A deletion mutation in humans is also present in chimpanzees, orangutans and macaques.[16] This deletion is usually hailed as the ultimate evidence for the existence of a common ancestor for both humans and apes. Based on the occurrence of non-random mutations, could this shared deletion in primate genes simply be the result of an *inter-species hot spot*?

Figure 3 shows the relevant part of *exon X* of the GULO gene in 11 organisms, including humans and primates. The deletion in nucleotide 97 is indicated by an asterisk. It is immediately obvious from the other sequences that position 97 is in fact a mutational hot spot. Reading position 97 from bottom to top, i.e. from rat to guinea pig, gives us the sequence A-C-G-A-C-A-G. Compare, for instance, the neighbouring nucleotides on positions 96 and 98. Both 96 and 98 read G-G-G-G-G-G-G and are therefore very secure, very stable positions. In contrast, the nucleotide on position 97 is highly unstable. Position 97 appears to be an inter-species hot spot, a highly unstable region that easily mutates. In man, chimpanzee, orangutan and macaque the deletion in this unstable position gives us an illusion of common descent.[17]

Discussion and outlook

Two elementary and distinct classes of mutations occur in DNA sequences: 1) *random mutations*, and 2) *non-random mutations*. Here, *random* has been defined as genetic changes that are entirely the result of chance;

where and *when* random mutations are introduced in a DNA sequence can neither be predicted nor foreseen. Random mutations are purely the physical outcome of the all-pervading frictional damage that accompanies all molecular machinery.[18] On the other hand, non-random mutations are the result of physico-chemical mechanisms; their position in a DNA strand reflects their non-random nature.

There are two distinct types of non-random mutations:
1. '*Veri*' ('true') non-random mutations, that occur in exactly the same location in all DNA sequence. These are non-random with respect to the position in the DNA sequence and it is very hard to distinguish them from shared mutations resulting from common descent;
2. '*Quasi*' ('almost') non-random positional mutations. A quasi mutation is non-random in the sense that it occurs in a determined DNA sequence, although the nucleotide affected is random (either A, T, C or G). In genetic analyses, quasi non-random mutations help to discriminate between non-random mutations and common descent.

We may not be able to predict *when* non-random mutations occur (except for radiation induced mutations),

	1	2	10	12	13	15	16	19	22	28	29	31	34	35	36	37	38	39	40	46	47	48	49	50	55	56	58	59	61	62	63	64	65
Orangutan	A	A	C	C	G	A	G	C	G	G	C	G	G	G	C	C	A	T	G	G	G	C	C	C	T	G	G	G	G	G	T	G	T
Man	A	A	C	C	G	A	G	C	G	G	C	G	G	G	C	C	G	T	G	G	G	C	C	C	T	G	G	G	G	G	T	G	T
Chimp	A	A	C	C	G	A	G	C	G	G	C	G	G	G	C	C	A	T	G	G	G	C	C	C	C	G	G	G	G	G	T	G	T
Macaque	A	A	C	C	A	G	G	C	G	G	A	G	G	G	C	C	A	T	G	G	G	C	C	C	T	G	G	G	G	G	T	G	T
Guinea Pig	A	G	C	A	G	A	G	C	G	G	C	G	G	A	G	C	A	T	G	A	G	C	T	C	C	A	G	G	G	G	C	A	G
Mouse	G	G	C	A	G	A	G	C	G	G	C	A	G	G	C	C	A	T	G	G	G	C	C	C	C	A	G	G	G	G	T	A	G
Cow	A	G	C	A	A	A	G	C	G	G	C	G	G	G	C	C	A	T	G	G	G	C	G	A	C	A	G	G	A	G	T	G	G
Chicken	T	G	A	A	G	A	A	A	G	G	C	G	G	G	C	T	G	C	C	G	A	A	C	A	C	A	G	A	G	G	T	G	G
Pig	A	G	C	A	G	A	G	C	C	G	C	G	G	G	C	C	A	T	G	G	G	C	C	C	C	A	G	G	G	G	T	G	G
Dog	A	G	C	A	G	A	G	C	G	A	C	G	A	G	C	C	A	T	G	G	G	C	C	C	C	A	G	A	G	G	T	G	G
Rat	G	G	C	A	G	A	G	C	A	G	C	A	G	G	C	C	A	T	G	G	G	C	C	C	C	A	A	G	G	G	T	A	G

	72	73	75	76	79	81	83	85	91	92	94	95	96	97	98	99	100	101	103	109	111	112	114	115	118	121	127	128	130	131	133	134	135
Orangutan	A	C	C	G	G	G	G	G	C	A	C	C	A	*	G	A	G	G	T	C	T	A	T	G	C	C	C	C	G	C	G	G	A
Man	A	C	T	G	G	G	G	A	C	A	C	T	G	*	G	A	G	G	T	C	T	A	T	G	C	C	C	C	G	T	G	G	A
Chimp	A	C	T	G	G	G	C	A	C	A	C	T	G	*	G	A	G	G	T	C	T	A	T	G	C	C	C	C	G	C	G	G	A
Macaque	A	A	C	G	G	G	G	G	C	A	C	C	A	*	A	G	G	G	T	C	T	A	T	G	C	C	C	C	G	C	G	G	A
Guinea Pig	A	C	C	T	G	G	G	G	C	A	C	C	G	**G**	G	G	G	G	C	C	T	G	T	G	C	C	C	C	G	A	G	G	A
Mouse	A	C	C	C	G	A	G	G	C	A	C	C	G	**A**	G	G	T	G	T	C	T	G	T	G	C	G	C	C	G	A	G	G	A
Cow	A	C	C	C	G	A	G	A	C	A	T	C	G	**C**	G	G	G	G	C	C	T	G	T	G	C	C	C	C	G	A	C	G	A
Chicken	A	C	C	T	G	A	G	G	T	G	T	C	G	**A**	G	C	G	G	T	C	G	G	T	G	C	C	C	C	G	C	G	G	A
Pig	A	C	C	C	G	A	G	G	C	A	T	C	G	**G**	G	C	G	G	C	C	T	G	T	G	C	C	C	C	G	A	G	G	A
Dog	T	C	C	T	G	A	G	C	C	A	C	C	G	**C**	G	G	G	G	T	C	T	G	T	G	C	C	C	C	G	A	G	G	A
Rat	A	C	C	C	A	A	G	G	C	A	C	C	G	**A**	G	G	C	G	T	T	T	G	T	G	C	C	C	C	G	A	G	G	A

Figure 3. Aligned nucleotide sequences of *exon X* (ten) from GULO genes and pseudogenes from a number of species. Positions with identical nucleotides in all organisms are not shown. The deletion mutation in position 97 (indicated by *) in this pseudogene is usually hailed as the ultimate evidence for the common descent shared between humans and the great apes. At first glance, this may appear to be a very strong case for common descent. However, after examining a large number of organisms, enabling the excluding non-random mutations, it becomes obvious that position 97 is in fact a hot spot for non-random mutations. (From the Truman-Terborg dataset in ref. 17).

Non-random mutations

Non-random mutations can be defined as 'hot-spot' mutations. It is becoming increasingly evident that mutations do not occur at random. Rather, the biophysico-chemical properties of the DNA strands and/or the environment of the DNA determines where mutations will be introduced.

There are two types of non-random mutations:

1) 'Veri' (or 'true') non-random mutations. These mutations are non-random with respect to nucleotide and position,
2) 'Quasi' (or 'almost') non-random mutations. These mutations are non-random with respect to position only.

Non-random mutations, then, help to explain:

• The alignment of mutations in 'trans-baraminic' (across kinds) genetic analyses,
• Homoplasy, the occurrence of the same sequence or gene rearrangements independent of common descent.

Together, common design and non-random mutational input create an illusion of common descent.

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but we can predict the position *where* they will appear. The incidence of veri and quasi non-random mutations is much higher than assumed—homoplasy is omnipresent—and there appears to be mutational cold spots, warm spots, hot spots and super hot spots.

Because non-random mutations have only been observed/discovered in studies analysing a sufficiently large number of individuals, they were not know until recently. From large-scale genetic comparisons, that include hundreds of sequences of the same species, the position of non-random mutations can be estimated with a high level of accuracy. In addition, sequence analyses from many different species may help to localize *interspecies hot spots*.

Upon close-up scrutiny, molecular biology has revealed that mutations are not just a random, chance-driven phenomenon. Although we do not yet know the 'whys and hows' of non-random mutations, what we do know is they create an illusion of common descent when they appear in organisms that cannot mate.

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