1

Point Mutations, Their Transition Rates and Involvements in Human and Animal Disorders

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1. Introduction

Point mutation or single base substitution is the replacement of a single base nucleotide with another nucleotide of the genetic material. Point mutations can be divided into transitions, changes between the purines A and G, or changes between the pyrimidines C and T, and transversions, changes between purines and pyrimidines. A fundamental aspect of DNA point mutation is the observation that transitional nucleotide changes commonly occur with greater frequency than transversional changes. This bias is primarily due to the biochemical structure of the nucleotide bases and the similar chemical properties of complementary base pairing (Topal & Fresco, 1976). Estimates of the bias are important for understanding the mechanisms of nucleotide substitution, assessing mode and strength of natural selection, and the relative abundance of transitional and/or transversional mutations has important consequences in epidemiological research as each class is associated with different diseases (Wakeley, 1996; Martínez-Arias et al., 2001). This review addresses the issue to which extent transition bias is ubiquitous among living organisms and whether this is similar in different species, along with the screening of point mutations associated with diseases and disorders.

2. Point mutations and transitional bias

Within coding sequences, transitional changes are often synonymous whereas transversional changes are not. When both types of changes lead to a change in protein sequence, the transitional change is often less severe with respect to the chemical properties of the original and mutant amino acids (Zhang, 2000). In mammalian nuclear DNA, transition mutations appear to be approximately twice as frequent as transversions as is evident from the substitution patterns of mammalian pseudogenes (Gojobori et al., 1982), in synonymous and non-coding SNPs in humans (Cargill et al., 1999), and in SNPs in mice (Lindblad-Toh et al., 2000). On the other hand, transitions are about as common as transversions in synonymous and intron SNPs in *Drosophila* DNA (Moriyama and Powell, 1996). In contrast to the modest transition bias observed in mammalian nuclear DNA, transitions appear to be about 15 times as frequent as transversions in human mitochondrial (mt) DNA (Tamura & Nei, 1993). In a detailed analysis of mtDNA Belle et al. (2005)

investigated the transition bias by assessing polymorphism in the cytochrome *b* gene (*cyt-b*) in 70 species distributed amongst mammals, birds, reptiles, amphibians, and fish, considering a total of 1823 mutations. The authors found that the bias towards transitions is widespread and the ts / tv ratio was always greater or equal to 1, and it varied from an average ratio of 2.4 in amphibians to 7.8 in birds. This is in sharp contrast with plant mtDNA where a transversion bias has been recorded (Wolfe et al., 1987), suggesting that the mitochondrial genomes of plants and animals follow very different patterns of evolution. Data of Belle et al. (2005) indicated little evidence for variation within orders or genera and between closely related species such as the great apes. For these primates, an advantage was that complete mtDNA sequences for humans, chimpanzees, gorillas and orangutans are available. Though humans displayed the greatest ts / tv ratio among these species (humans 13.75, chimpanzees 11.00, orangutans 6.87, gorillas 5.67), there was no evidence of significant variation ($\chi^2 = 5.8$, $df = 3$, $p = 0.12$) between species, suggesting that the parameter has not changed much during the evolution of the great apes. Generally, the majority of the variation appeared to be at higher phylogenetic levels, between orders and classes. No evidence that the metabolic rate affects the ts / tv ratio was found in surveyed species.

Rosenberg et al. (2003) conducted a similarly designed analysis of 4,347 mammalian protein-coding genes from seven species (human, mouse, rat, cow, sheep, pig, macaque) as well as from the introns and multiple intergenic regions from human, chimpanzee and baboon primates. Estimates showed that genes and regions with widely varying base composition exhibit uniformity of transition mutation rate both within and among mammalian lineages, with no relationship to intrachromosomal or interchromosomal effects. This points to similarity in point mutation processes in genomic regions with substantially different GC-content biases. Knowledge of the mutational transition/transversion rate bias also allows a prediction of time to saturation of substitutions at fourfold-degenerate sites. From mutation parameters the above authors derived that transversions become more common than transition after 250 Myr, i.e. the time about which transitions become saturated (at ~25% of sites). Transversions become saturated much more slowly, beginning to reach 50% after about 750 Myr. In addition, the observed number of transitional substitutions accumulates approximately linearly for about 100 Myr, whereas the transversional substitutions accumulate linearly for about 250 Myr.

The accumulation of base substitutions not subject to natural selection is the neutral mutation rate. Most CpGs (regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide, separated by one phosphate) in mammals are uniquely hypermutable (e.g., Hwang & Green, 2004). The Cs of most CpGs are methylated (Ehrlich & Wang, 1981; Miranda & Jones, 2007), which enhances the deamination of C that produce in this case a T:G mismatch. The net result is that methyl-CpGs mutate at 10–50 times the rate of C in any other context (Sved & Bird, 1990), or of any other base (Hwang & Green 2004). Consequently, CpGs not under selection are replaced over time by TpG/CpAs. Mammals thus exhibit two dramatically different neutral mutation rates: the CpG mutation rate and the non-CpG rate. Walser et al. (2011) determined the neutral non-CpG mutation rate as a function of CpG content by comparing sequence divergence of thousands of pairs of neutrally evolving chimpanzee and human orthologs that differ primarily in CpG content. Both the mutation rate and the mutational spectrum (transition/transversion ratio) of non-CpG residues changed in parallel as sigmoidal function of CpG content. As different

mechanisms generate transitions and transversions, these results indicate that both mutation rate and mutational processes are contingent on the local CpG content. Authors assessed that a threshold CpG content of ~0.53% must be attained before the non-CpG mutation rate is markedly affected, and the CpG effect reaches saturation at levels above ~0.63% CpG. Methyl-CpG may mediate the recruitment of various DNA- or histone-binding proteins and other factors (Cedar & Bergman, 2009), which could conceivably affect the susceptibility of the DNA to mutation. In this case the correlation between non-CpG mutations and CpG content would mean that chromatin states promoted by CpG methylation, or that result in it, render DNA more susceptible to mutation than DNA not in such states. There is some evidence that the mutation rate of compact heterochromatin (closed, inactive formation of chromosome) is higher than euchromatin (opened, transcribed chromosome portion) (Prendergast et al., 2007).

In attempting to quantify the context dependence of nucleotide substitution rates, Zhang et al. (2007) generated sequence data in baboon, chimpanzee and human by the NISC Comparative Sequencing Program. The study confirmed that C→T substitutions are enhanced at CpG sites compared with other transitions, and are relatively independent of the identity of the preceding nucleotide. While, as expected, transitions in general occurred more frequently than transversions, the most frequent transversions involved the C at CpG sites, with their rate comparable to the rate of transitions at non-CpG sites. A four-class model of the rates of context-dependent evolution in primate DNA sequences, CpG transitions > non-CpG transitions ≈ CpG transversions > non-CpG transversions, was consequently inferred from the observed mutation spectrum.

To relate establishment of mitochondrial mutations to environmental stress, Khrapko et al. (1997) investigated whether point mutations accumulated during a human lifetime were different from those that arise in human cell cultures in the absence of added xenobiotic chemicals. They found that human organs such as colon, lung, muscle and their derived tumors share nearly all mitochondrial hotspot point mutations that indicate that they are primarily spontaneous in nature and arise either from DNA replication error or reactions of DNA with endogenous metabolites. The hypothesis that environmental mutagens are important contributors to mitochondrial point mutagenesis thus no longer seems tenable. Assessments of the types of point mutations observed as polymorphisms have shown that both G→A and A→G transitions occur more frequently than transversions that was consistent with previous observations in human mtDNA (Aquadro & Greenberg, 1983; Horai & Hayasaka, 1990). In TK6 cells (human lymphoblast cells with normal P53 function) and in human tissues the mitochondrial point mutation rate appeared to be more than two orders of magnitude higher than the nuclear point mutation rate.

2.1 Mitochondrial and nuclear DNA mutations related to disorders

Although much smaller than the nuclear genome, mitochondrial DNA is equally important as it has been hypothesized to play a crucial role in ageing and carcinogenesis. This is mainly due to the fact that mitochondria represent the major site for the generation of cellular oxidative stress and play a key role in mediating programmed cell death (Birch-Machin, 2006). The first primary pathological mutations in mtDNA were discovered over 20 years ago (Holt et al., 1988; Wallace et al., 1988), and since then more than 100 mutations of mtDNA have been linked to human disease. The vast majority of these mutations fall into

two classes: point mutations and large-scale rearrangements. The latter can be partial deletions (D) or duplications involving 1–10 kb of DNA (Holt et al., 2010). Nevertheless, the rearranged mtDNA invariably coexists with wild type molecules, a situation termed heteroplasmy, which is also frequently (Saada et al., 2001), but not universally (Van Goethem et al., 2001) found among pathological point mutations of mtDNA. Cellular dysfunction usually occurs when the ratio of mutated to wild-type mtDNA exceeds a threshold level (Birch-Machin, 2000). Mitochondrial DNA is wholly dependent on the nucleus for its maintenance and replication, and so mutations in nuclear DNA can also produce defects in mtDNA, or mtDNA loss (Zeviani et al., 1989; Moraes et al., 1991).

Incomplete oxygen reduction within the mitochondrial respiratory chain can lead to the formation of the superoxide radical, the first molecule in the pathway responsible for the production of reactive oxygen species (ROS), often inducing DNA strand breaks (Kang & Hamasaki, 2003). Growing evidence suggests that cancer cells exhibit increased intrinsic ROS stress, due in part to oncogenic stimulation, increased metabolic activity and mitochondrial malfunction (e.g., Pelicano et al., 2004; Sedelnikova et al., 2010). As the mitochondrial respiratory chain is a major source of ROS generation and the exposed mtDNA molecule is in close proximity to the source of ROS, the vulnerability of the mtDNA to ROS-mediated damage appears to be a mechanism to amplify ROS-stressing cancer cells. Coupled with this phenomenon is free-radical theory of Harman (2001) who attributed ageing in a wide range of species by postulating that the production of intracellular ROS is the major determinant of life span. Intracellular ROS are primarily generated by the mitochondrial respiratory chain and thus constitute a prime target for oxidative damage. According to this theory, mtDNA mutations caused by ROS accumulate within the cell, leading to impaired respiratory chain proteins, thereby generating more ROS, which in turn causes higher mtDNA mutation rates. Although there are data supporting a direct functional role of mtDNA in ageing and photoageing (Trifunovic et al., 2004; Birch-Machin & Swalwell, 2010), there is still considerable debate about the type of mtDNA associated with ageing. For example, the most frequently reported DNA region under assumption presents 4977-bp common deletion, but its significance is under debate (Thayer et al., 2003; Meissner et al., 2010). In addition, there are single somatic mtDNA control region mutations associated with ageing in tissues including skin, but their functional significance is still unclear (Liu et al., 1998; Wallace, 2005). This process of chronological ageing can be accelerated in skin by chronic exposure to ultraviolet radiation, which has been shown to be associated with a further increase in mtDNA damage. Mitochondria have further been implicated in the carcinogenic process because of their role in apoptosis and other aspects of tumour biology, alongside ROS generation (Jakupciak et al., 2005). In many types of human malignancy such as colorectal, liver, breast, pancreatic, lung, prostate, bladder and skin cancer somatic mtDNA mutations have been detected (Durham et al., 2003; Dasgupta et al., 2008; Fry et al., 2008; Yin et al., 2010; Choi et al., 2011; Namslauer et al., 2011; Potenza et al., 2011). Furthermore, sequence variations of mtDNA have been observed in preneoplastic lesions, which suggest generation of mutations early in tumour progression (Parr et al., 2006).

Human cells lacking mtDNA, so-called ρ^0 (rho zero) cells, can be repopulated with mitochondria derived from healthy subjects or patients with suspected mtDNA defects, to produce cytoplasmic hybrids, or cybrids. If the respiratory capacity of the cybrid cell is impaired then the deficiency can be ascribed to the mitochondrial, as opposed to the nuclear, genome (Chomyn et al., 1991). The cybrid cell culture system has enabled the

discovery of the biased segregation of human mtDNA variants (Hayashi et al., 1991). Zastawny et al. (1998) compared oxidative base damage levels in mitochondrial and nuclear DNA of endogenous pig liver cells using gas chromatography. Higher levels (4.4 to 42.4 times) of five measured bases were found in mtDNA in relation to nuclear DNA. The higher rate of oxidatively modified bases may be due to the large amount of ROS produced in mitochondria, the absence of bound histones in mtDNA, and deficiency of DNA repair enzymes in some restoring routes.

Defects in oxidative phosphorylation (OXPHOS) are genetically unique because the key components involved in this process, respiratory chain enzyme complexes I, III, IV, V, are encoded by both nuclear and mitochondrial genes. Therefore, Rubio-Gozalbo et al. (2000) examined whether there are clinical differences in patients suffering from OXPHOS defects caused by nuclear or mtDNA mutations. 16 families with >=2 two siblings bearing a genetically established OXPHOS deficiency were studied, in four families due to a nuclear gene mutation and twelve due to a mtDNA mutation. Differences in age at onset, severity of clinical course, outcome, and intrafamilial variability in patients affected by an OXPHOS defect due to nuclear or mtDNA mutations were observed. Patients with nuclear mutations became symptomatic at a young age, and had a severe clinical course. Patients with mtDNA mutations showed a wider clinical spectrum of age at onset and severity. Reported differences are of importance regarding the choice of type of genome in further studies of affected patients.

2.2 Point mutations in pathogens

The challenge to identify point mutations accounting for resistance against antiparasitic drugs has been often addressed in veterinary pharmacology. For drug resistance in *Plasmodium*, causative organisms of malaria, a multitude of tests have been available and used for detecting parasites resistant to multiple drugs over the past 15 years (Hunt, 2011). Although the mechanisms by which malaria parasites develop resistance to drugs are unclear, current knowledge suggests that a main mechanism of resistance is the alteration of target enzymes by point mutation. Mutations in dihydrofolate reductase (dhfr) and dihydropteorate synthatase (dhps) cause anti-folate resistance in human malaria parasites against drugs sulphadoxine and pyrimethamin with synergystic anti-malarial effect (Prajapati et al., 2011). A constant monitoring is necessary to keep information about newly emerging drug resistance in *Plasmodium*, e.g. due to *ATP6* gene variants implicated in artemisin resistance (Menegon et al., 2008), and to detect new gene variants associated with resistance to older drugs, e.g. *cyt-B* gene variants in atovoquone resistance (Sutherland et al., 2008).

The principal mechanism of resistance to benzimidazoles is likely to involve changes in the primary structure of beta-tubulins, the building blocks of microtubules (Lacey, 1988). Specifically, point mutations in the beta-tubulin isotype 1 gene leading to amino acid substitutions in codons 167, 198, and 200 are widely thought to be associated with resistance in nematodes and DNA-based assays have been developed to monitor single nucleotide polymorphisms (SNP) (Silvester & Humbert, 2000; Von Samson-Himmelstjerna et al., 2009). These SNPs offer a means to detect the presence of resistance within populations and to monitor the development of resistance. As research progresses, however; it has become clear that other genes may be implicated in benzimidazole resistance and further aspects of anthelmintic resistance/susceptibility (Blackhall et al., 2008). Pan et al. (2011) identified

heat-shock protein 60 (HSP 60) as one of the most frequently expressed biomolecules after albendazole treatment of patients that could be connected with beta-tubulin gene isoform 2 which exhibits a conserved point mutation indicative of benzimidazole resistance in tapeworm *Echinococcus granulosus*.

Detection of point mutations has been beneficial in allowing consistent differentiation of closely related parasitic organisms. By examining the ITS1 region Zhu et al. (1999) established six fixed nucleotide differences between sibling species of *Ascaris suum* (pig nematode) and *A. lumbricoides* (human nematode) that are impossible to distinguish by mitochondrial genes due to existence of different lineages before host affiliations (Levkut et al., 1999; Dubinský et al., 2000; Criscione et al., 2007). The *rrnS* mitochondrial gene was found to be a useful genetic marker for related genotypes G1 (sheep strain) and G3 (buffalo strain) of *Echinococcus granulosus* complex, revealing a total nucleotide uniformity within genotypes and two point mutations (166T→G, 205A→G) between these variants (Busi et al., 2007; Šnábel et al., 2009).

3. Conclusion

DNA base substitutions (mutations) are the most frequent class of genetic variants. Determining the factors that affect the base mutation rate remains a major concern of geneticists and molecular evolutionists. In mammalian nuclear DNA, transition mutations appear to be approximately twice as frequent as transversions. In human mitochondrial (mt) DNA transitions appear to be as much as about 15 times more frequent than transversions. In evaluating 70 species of mammals, birds, reptiles, amphibians, and fish, the ts / tv ratio varied from average of 2.4 in amphibians to 7.8 in birds in mtDNA. This contrasts with plant mtDNA with recorded transversion bias, suggesting that the mitochondrial genomes of plants and animals follow very different patterns of evolution. In mammalian protein-coding genes, it was estimated that transversions become more common than transition after 250 Myr, i.e. the time about which transitions become saturated (at ~25% of sites). Transversions become saturated much more slowly, beginning to reach 50% after about 750 Myr. The observed number of transitional substitutions accumulates approximately linearly for about 100 Myr, whereas the transversional substitutions accumulate linearly for about 250 Myr. Most CpG sites, particularly those in transposable elements, are preferred sites of C methylation. Therefore, the correlation between CpG content and non-CpG mutations could be due to an effect of methyl-CpG per se, to its spontaneous deamination to produce a T:G mismatch and subsequent recruitment of error-prone DNA repair mechanisms, or both. According to the present knowledge, more than 100 mutations of mtDNA have been proved to be linked to human disease. The majority of these mutations are point mutations and large-scale rearrangements (partial deletions or duplications involving 1–10 Kb of DNA). Mitochondria are implicated in the carcinogenic process because of their role in apoptosis and other aspects of tumour biology, and because of generating ROS (reactive oxygen species), presented as major determinant of life span. Intracellular ROS are primarily generated by the mitochondrial respiratory chain and thus constitute a prime target for oxidative damage. Many types of human malignancy such as colorectal, liver, breast, pancreatic, lung, prostate, bladder and skin cancer harbor somatic mtDNA mutations. Mitochondrial DNA is wholly dependent on the nucleus for its maintenance and replication, and so mutations in nuclear DNA can also produce defects in mtDNA, or mtDNA loss.

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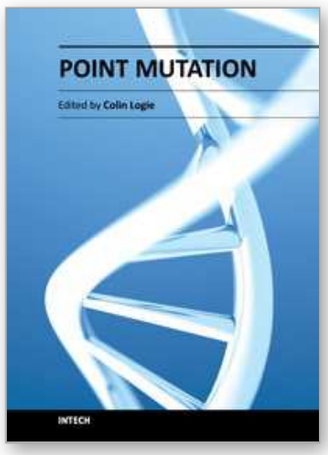

Point Mutation

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This book concerns the signatures left behind in chromosomes by the forces that drive DNA code evolution in the form of DNA nucleotide substitutions. Since the genetic code predetermines the molecular basis of life, it could have been about any aspect of biology. As it happens, it is largely about recent adaptation of pathogens and their human host. Nine chapters are medically oriented, two are bioinformatics-oriented and one is technological, describing the state of the art in synthetic point mutagenesis. What stands out in this book is the increasing rate at which DNA data has been amassed in the course of the past decade and how knowledge in this vibrant research field is currently being translated in the medical world.

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