



## Single Nucleotide Polymorphisms in Structural Genes of *Mycobacterium tuberculosis*

Vladimir Nier\*

Department of Radionuclide Diagnostics, Medical Radiological Research Centre, Obninsk, Russia

### DESCRIPTION

Single nucleotide polymorphisms (SNPs) in the genomes of two strains of *Mycobacterium TB*, H37Rv and CDC1551 (unpublished). Our published *M. tuberculosis* SNP frequency data is incorrectly represented in the paper. According to the scientists, "A comprehensive analysis of H37Rv and CDC1551 strains reveals a greater frequency of polymorphism, about 1 in 3,000 bp, with nearly half of the polymorphism occurring in intergenic areas. In other words, 50% of polymorphisms are found in only 10% of the genome. While this rate is larger than previously thought, it nevertheless indicates lesser nucleotide diversity than other diseases in restricted comparisons."

We first published an estimated average number of synonymous substitutions per synonymous site ( $K_s$  value) based on comparative sequence analysis of eight *M. tuberculosis* structural gene loci (open reading frames) that indicated that this pathogen had approximately 1 synonymous difference per 10,000 synonymous sites. Given the relatively huge population size of *M. tuberculosis* and paleopathologic data suggesting its existence in humans as early as 3700 B.C., this conclusion was surprising. In comparison to other human bacterial diseases, further sequence analysis of two megabases in 26 structural genes or loci in strains recovered internationally verified the dramatic reduction of silent (synonymous) nucleotide alterations. A large study (approximately 2 Mb of comparative sequence data) of 12 genes potentially involved in ethambutol resistance and 24 genes encoding protein targets of the host immune system found that the original estimate of 1 synonymous nucleotide change per 10,000 synonymous sites in structural genes in this pathogen was correct. SNPs in putative regulatory regions of structural genes (intergenic regions) and nonsynonymous nucleotide alterations in structural genes were not included in our estimation. Because it was difficult to rule out the potential that these polymorphisms developed as a result of selective pressure caused by antimicrobial agent treatment or even lengthy *in vitro*

passage, we did not include them in our calculations. Many values of importance to evolutionary biologists and population geneticists are estimated using synonymous nucleotide alterations (neutral mutations).

Fraser et al estimate  $K_s$  is based on a genome-wide frequency of SNPs (1/3,000 nucleotide sites), with 50 percent of them likely in intergenic regions and 50 percent in structural genes. There would be roughly 1,500 total SNPs in a 4.4 Mb genome, with about 750 in orfs (90 percent of genome=3,960,000 bp) and 750 in intergenic regions (10 percent of genome=440,000 bp). According to these calculations, the frequency of all SNPs found in structural genes is around 1/5,280 bp. (The researchers gave an estimate of 1,300 overall SNPs [translating to 1/6,000 bp] at a meeting conducted at the Banbury Center last December.) These values deviate from our estimate (1/10,000) as expected, owing to the fact that they include both synonymous and nonsynonymous nucleotide polymorphisms.

We looked at orfs scattered along the chromosome of *M. tuberculosis* strains CDC1551 and H37Rv (accessible in public databases). Surprisingly, the number of nonsynonymous SNPs outnumbered those that were synonymous. Only about 323 synonymous SNPs were discovered in orfs, resulting in a synonymous SNP frequency of about 1/12,260 bp.

*M. tuberculosis*, a pathogen that infects one-third of the world's population, has a remarkable, if not unique, molecular evolution history. It's crucial to get precise statistics on the frequency of its genuine SNPs across the genome. Our original estimate of 1 synonymous nucleotide change per 10,000 synonymous sites in structural genes in wild populations of this disease is still valid.

A single-nucleotide polymorphism occurs when a single nucleotide in the genome gets substituted in the germline. Although some definitions need that the substitution is found in a significant proportion of the population.

**Correspondence to:** Vladimir Nier, Department of Radionuclide Diagnostics, Medical Radiological Research Centre, Obninsk, Russia, Email: Vladimir@nier.ru

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