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On the origin of leprosy

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Leprosy, a chronic, neurological human disease, results from infection with the obligate intracellular pathogen, *Mycobacterium leprae*, a close relative of the tubercle bacillus. *M. leprae* has the longest doubling time of all known bacteria and has never been cultured in the laboratory. Comparison of the 3.27 Mb genome sequence of an armadillo-derived Indian isolate of the leprosy bacillus with that of *Mycobacterium tuberculosis* (4.4 Mb) provides clear explanations for these properties, revealing an extreme case of reductive evolution. Less than half of the genome contains functional genes while pseudogenes, with intact counterparts in *M. tuberculosis*, are abundant. Gene deletion and decay have eliminated many important metabolic activities including siderophore production, part of the oxidative, and all of the microaerophilic and anaerobic respiratory chains, together with numerous, alternative catabolic systems and their regulatory circuits. Genome decay has thus led to metabolic crippling.

To develop tools for molecular epidemiology, we sequenced the genome of a Brazilian isolate of *M. leprae*, chosen because of the high prevalence of leprosy in that country and its great distance from India. In light of the extensive gene decay observed in the Indian strain multiple examples of pseudogene formation and numerous single nucleotide polymorphisms (SNP) were expected. Astonishingly, the two genome sequences were nearly identical differing by a single pseudogene and a mere 118 SNP, distributed almost equally between genes and pseudogenes. On surveying over 300 leprosy biopsies, 78 SNP were found to be informative. Phylogenetic studies revealed that all extant cases of leprosy are attributable to a single clone of *M. leprae* whose dissemination worldwide could be retraced from SNP analysis. The disease seems to have originated in Eastern Africa or the Near East and spread with successive human migrations. Europeans or North Africans appear to have introduced leprosy into West Africa and the Americas within the past 500 years.