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Mini Review

Genomics of Newly Discovered Leprosy Pathogen: *Mycobacterium lepromatosis* and Its Geographic Isolation in Mexico

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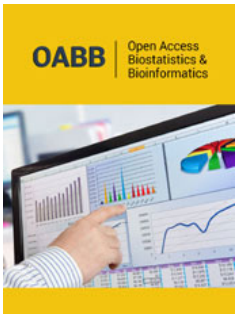

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Overview

Leprosy is a chronic dermatologic infection that has plagued human populations for thousands of years. *Mycobacterium leprae*, the etiological agent for leprosy, has puzzled scientists since its identification by Hansen in 1873 [1]. Leprosy is one of the leading causes of treatable neuropathy [2]. It has been affecting mankind since the earliest historically recorded identification and far beyond (2000 B.C, in ancient Indus civilization) [3]. Leprosy is also one of the earliest recognized diseases which have a proven association with the bacterial pathogen, *M. leprae* [3]. In 2008, a new bacterium, *M. lepromatosis* was discovered in Mexico which was also reported to cause leprosy [4]. *M. lepromatosis* was found to be associated with a typical severe form of lepromatous leprosy (LL), called Diffuse Lepromatous Leprosy (DLL) which is usually seen in the Americas [5-7]. DLL is characterized by an unusual form of immune reaction against the pathogen, called Lucio's phenomenon, characterized by diffuse, non-nodular cutaneous infiltration with sharply demarcated skin lesions, which often gets infected to result in life threatening situations [8,9].

Epidemiology

Genome sequence analysis of *M. leprae* and *M. lepromatosis* shows that both the organisms have diverged from a common ancestor about 13.9 million years ago, long before ancient humans stepped out of Africa. Still, most of the human infection of *M. lepromatosis* has been detected only in Western Mexico and the Caribbean islands, at the Multibacillary-LL (Lepromatous Leprosy) / Multibacillary-DLL (MB-LL/MB-DLL) end of the disease spectrum, co-existing with *M. leprae infections* [1]. In a few cases, *M. lepromatosis* is also found in other countries like Brazil, the USA, Indonesia, British Isis, Singapore & Myanmar, both in human and non-human hosts. [7,10-14]. Although India harbors the largest number of confirmed and newly diagnosed leprosy cases till date, there are no confirmed reports for *M. lepromatosis* infection in India so far [15]. This might be due to the fact that the majority of leprosy cases in India are tuberculoid (TT) in nature, whereas in Mexico the majority are (Lepromatous) LL [7]. Few hypotheses have been proposed to explain the paradox of asymmetric distribution but none of them have specifically addressed the incidence of negligible Lucio's leprosy cases and no recorded *M. lepromatosis* infection till date from India, where more than 60% of the total leprosy cases of the world has been reported.

Genomics

M. leprae and *M. lepromatosis*, together named as the *M. leprae* complex, can cause leprosy individually or by co-infection [1,16]. *M. leprae* was the only known organism to cause leprosy until 2008, when two cases of leprosy in Mexico were identified to be caused

by *M. lepromatosis* [7,16]. The nine-banded armadillo (*Dasypus novemcinctus*) is the only other natural host of *M. leprae* [17]. Mice footpads and Zebrafish are also used as animal models for the study of leprosy [17,18]. The main drawback in research of leprosy is its long doubling time in animal host and non-availability of artificial media for culture [19]. Recent advancements in molecular techniques and comparative genomics have taken an important role in research of leprosy. Analysis of 22,814 nucleotides has revealed a 9.1% variation between *M. leprae* and *M. lepromatosis*, providing evidence for a species-level divergence that occurred approximately 13.9 million years ago [19]. Nucleotide variations are mostly confined to a large number of pseudogenes present in either of the bacteria and fewer variants could be seen in functional genes, in any of the genomes [20]. Armadillo-derived *M. leprae* DNA has been used to carry out whole genome sequencing of the TN strain of *M. leprae*, originally isolated from a patient in Tamil Nadu, India [21]. This analysis revealed that the genome sequence of the TN strain of *M. leprae* contains 3,268,210 bp and has an average G+C content of 57.8% [21]. The leprosy bacillus, which has gone through a massive reductional evolution and downsizing of its genome, has the smallest and most A+T-rich genome of any known mycobacterium. The recent (2001) bioinformatic analysis brought to light 1614 genes coding for proteins and a further 50 that encode stable RNAs. These comprise a mere 49.5% of the genome with the rest being occupied by pseudogenes, inactive reading frames with functional counterparts in other mycobacteria, or regulatory sequences. 1116 pseudo-genes were found initially but this figure increased to 1293 when other genome sequences became available for comparison [21,22]. Since *M. lepromatosis* also cannot be cultured in vitro and an animal model is not yet available, the only source of its DNA is infected human tissue or from cultured strains in Armadillos. A total of 3,206,741 bases of the *M. lepromatosis* Mx1-22A genome were represented in the 126 contigs. These genes aligned to the 3.27-Mb circular genome sequence of the Tamil Nadu (TN) reference strain of *M. leprae* with one exception [23]. The exception was a 2.3-kb contig bearing five mycobacterial pseudogenes. In a nutshell, the genome of *M. lepromatosis* appears to harbor at least 1,477 genes encoding proteins [i.e. Coding DNA Sequence (CDS)] and 1,334 pseudogenes.

From the aforementioned analysis, it is also found that four repeat families, RLEP (37 copies), REPLEP (15 copies), LEPREP (8 copies), and LEPRPT (5 copies) were present in the most recent common ancestor (MRCA) of *M. leprae* and *M. lepromatosis* [24]. The same research group has found that the levels of conservation between the repeats in the two species are proportional to their copy number and no additional repetitive DNA was detected in *M. lepromatosis* [24]. *M. lepromatosis* has intact orthologs for 95% of the CDS present in *M. leprae*, but a further 132 CDS appear to have been pseudogenized in *M. lepromatosis*. It is noteworthy that four of them (ilvX, proA, cysE, cysK) once encoded enzymes required for amino acid biosynthesis. Twenty-six *M. leprae* pseudogenes appear to have functional counterparts in *M. lepromatosis* [24].

Now the question is whether there are genetic differences between the Indian and Mexican populations, which induce the opposite ends of the disease spectrum in leprosy (TT vs LL) and thereby, disfavor the *M. lepromatosis* infection in one of these two affected populations. Since the *M. leprae* and *M. lepromatosis* have diverged 13.9 M years ago, it might not be possible for *M. lepromatosis* to have evolved anew in Mexico and infected humans there; when they colonized that part of the world some 10,000 (or more) years back [20]. Still, the reason behind *M. lepromatosis* specifically targeting Mexicans while largely sparing Asians on the other side of the Pacific Ocean, remains unclear as no case of *M. lepromatosis* infection is reported in India, Philippines, only few isolated cases are reported in Myanmar, Singapore and recently in Indonesia. Specific targeting of the population in Mexico on the eastern side of pacific is also supported in a recent study of *M. lepromatosis* infection rate in Mexico, Brazil and the USA [14]. It reports that 63% of LL cases of Mexico have *M. lepromatosis*, whereas for Brazil the ratio is only 21% and less than 2% in the USA [14]. This ratio goes very well with the fact that early humans came to the Americas around 15,000 years back through ~1000 km wide Beringia land bridge (present-day Bering strait). They rapidly colonized both North and South America and as they were travelling, they might have encountered *M. lepromatosis* [25,26]. Resulting leprosy might have slowed down a group of humans who have patients in their families, especially while crossing nearly impossible Darien Gap to South America. Therefore a possible hypothesis might be drawn from the argument above to explain the reason behind the one-third prevalence of *M. lepromatosis* infection in Brazil than in Mexico [14]. Present-day Mexican genome, with a share on ancestry with early settlers who might have slowed down in the population flow towards the south, may give us clues on the variation that might have led to susceptibility for leprosy caused by *M. lepromatosis*. Taken together, a comparative genomic/ epigenomic/ transcriptomic analysis between the Indian and Mexican populations specifically targeting leprosy-associated genes and associated host factors could shed light on solving the aforementioned question addressing the anomaly regarding *M. lepromatosis* susceptibility.

Inference

In summary, there is no explanation for the asymmetric distribution of *M. lepromatosis* yet, which is associated with Diffuse Lepromatous Leprosy. The probable reason behind this might be geographic or genomic. Knowing which one is correct, would empower us to prevent and treat leprosy better. If this isolation of *M. lepromatosis* is solely due to geographic reasons, then there is a high chance that *M. lepromatosis* might infect Indians once it crosses the geographic barrier. Thorough knowledge of the same would enable us to take better preventive steps by developing novel vaccines and hence prevent a major DLL outbreak in the Indian subcontinent in future. On the other hand, if genomic variation is the key, then understanding the pathways and mechanisms of host-pathogen interactions at a genomic level for both the bacilli

and human host would tremendously improve drug designing and provide more efficient and specific treatment for leprosy.

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