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Metagenomics of Imported Multidrug-Resistant *Mycobacterium leprae*, Saudi Arabia, 2017

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Using shotgun metagenomics, we identified an imported case of multidrug-resistant *Mycobacterium leprae* in a Filipino resident of Saudi Arabia in 2017. We determined the phylogenomic lineage (3K1) and identified mutations in *rpoB* and *rrs* corresponding to the multidrug-resistance phenotype clinically observed. Metagenomics sequencing can be used to identify multidrug-resistant *M. leprae*.

Leprosy is a chronic dermatologic and neurologic disease caused by the infectious agent *Mycobacterium leprae* and can lead to severe disabilities; >200,000 new cases are reported annually worldwide, according to the World Health Organization. A total of 242 leprosy cases were reported in Saudi Arabia during 2003–2012; however, little is known about the subtypes and prevalence of drug resistance among these *M. leprae* cases (*1*).

In May 2017, a 30-year-old woman from the Philippines sought treatment at the dermatology clinic of King Fahad Medical City (KFMC) Hospital in Riyadh, Saudi Arabia, for painful systemic skin nodules and joint pain without joint swelling. She had no medical history of leprosy. The initial clinical diagnosis of this patient was inconclusive, but her initial signs and symptoms were suggestive of a connective tissue disease such as systemic lupus erythematosus, and initial clinical improvement was recorded after a short course of empiric steroids and hydroxychloroquine treatment. Other suspected diagnoses included lepromatous leprosy with type 2 erythema nodosum leprosum reaction or other nontuberculosis mycobacterial infection.

We performed a punch skin biopsy of the extensor surface of the forearm and performed Ziehl-Neelsen staining; we observed a florid histiocytic

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proliferation containing numerous *Mycobacterium* bacilli without an obvious granuloma (Appendix Figure 1, https://wwwnc.cdc.gov/EID/article/26/3/19-0661-App1.pdf). We referred the patient to the infectious disease clinic, which performed QuantiFERON-TB Gold (QIAGEN, https://www.quantiferon.com) and took a biopsy for bacterial and fungal culture, and all test results were negative. Mycobacterial culture showed >9 acid-fast bacilli/high-power field on smears, and no growth was observed on Lowenstein-Jensen slants after 8 weeks of incubation.

Her treatment started with a daily regimen of clofazimine (50 mg), dapsone (100 mg), and rifampin (600 mg). Treatment with moxifloxacin (400 mg/d) and macrolides was briefly added (clarithromycin and azithromycin were both stopped because of gastrointestinal side effects) in case of possible nontuberculosis mycobacterial infection. The patient had multiple relapses during 12 months of follow-up and became steroid dependent (i.e., her skin lesions reappeared shortly after steroid treatment ended).

Because initial test reports were inconclusive and the etiologic agent was unconfirmed, we attempted to confirm the etiology by subjecting the patient's skin biopsy sample to metagenomic sequencing; a DNA sequencing protocol without target DNA–enrichment steps (*2*) was needed to unambiguously identify the etiologic agent. From the metagenomics datasets, we reconstructed the near-complete genome of the *M. leprae* species (which we named KFMC-1) at 99.2% completeness when compared with *M. leprae* TN, a strain commonly used for reference (*3*). We assembled the 3.24-Mb genome of *M. leprae* KFMC-1 in 19 DNA segments, and average coverage was 20.02× (Appendix Table 1, Figure 2, panel A). A single-nucleotide polymorphism comparison of *M. leprae* KFMC-1 with a globally representative set of *M. leprae* revealed KFMC-1 was most closely related to 3K1 Ryukyu-2 (Appendix Figure 2, panel B), which was originally isolated in Japan (*4*).

We identified 158 polymorphic sites in the genome (Appendix Table 2), which corresponded to 136 single-nucleotide polymorphisms and 22 insertion/deletions. In total, 53 of the 158 changes were new, and 63 appeared within gene-coding regions, a couple of which helped us predict the multidrug-resistance profile. We identified a G→T nucleotide change, which leads to a nonsynonymous change (Q438H) in the *rpoB* gene (Appendix Figure 2, panel C). This substitution results in rifampin resistance (*5*), matching our clinical records. The C1414A mutation in the *rrs* locus is predicted to confer capreomycin resistance, as observed previously in *M. tuberculosis* (*6*).

After we confirmed the clinical diagnosis as an *M. leprae* infection, we halted moxifloxacin treatment and kept the patient on 3 standard antimicrobial drugs (clofazimine, dapsone, and rifampin). Afterward, the patient left Saudi Arabia and continued her antimicrobial drug course in her country of origin.

The predominant genotypes of *M. leprae* strains in the Middle East are subtypes 2 and 3 (*7*). Most 3K cases are found in countries of East Asia, such as China (*8*), Japan (*9*), Korea (*2*), and the Philippines (*8*). In addition, >37% of the leprosy cases in Saudi Arabia occur in persons from other countries (*1*). Our results suggest that this case of leprosy was imported from the patient's country of origin. Saudi Arabia hosts a massive number of expatriates from all over the world, including persons from *M. leprae*–endemic countries, and also hosts one of the largest recurring religious gatherings in the world. Therefore, genomics-guided infection control efforts are needed to monitor the potential importation and prevent the spread of *M. leprae* infections in the region.

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Three New Cases of Melioidosis, Guadeloupe, French West Indies

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Melioidosis has been detected in the Caribbean, and an increasing number of cases has been reported in the past few decades, but only 2 cases were reported in Guadeloupe during the past 20 years. We describe 3 more cases that occurred during 2016–2017 and examine arguments for increasing endemicity.

Melioidosis, caused by the telluric gram-negative rod *Burkholderia pseudomallei*, is endemic in Southeast Asia and northern Australia (*1*) but may be underdiagnosed in other tropical regions (*2*). Increasing occurrences have been reported in the Caribbean during the past few decades among persons with no exposure to known endemic areas (*3*–*5*). Tropical environmental conditions and the presence of this bacterium in soil samples in the Caribbean support the plausibility of endemicity (*3*). We describe 3 new cases detected in Guadeloupe during 2016–2017.

Patient 1 was a 54-year-old man, receiving renal replacement therapy, with a history of hypertensive vascular nephropathy. He developed a pulmonary form of melioidosis in November 2016. Thoracoabdominal computed tomography (CT) scan showed bilateral nodular lesions. *B. pseudomallei* grew from bronchoalveolar lavage fluid obtained by fiberoptic bronchoscopy. Treatment with ceftazidime (6 g/d intravenously) was given for 2 weeks and switched to trimethoprim/sulfamethoxazole (TMP/SMX) (320/1,600 mg 2×/d orally) for 1 month, then changed to doxycycline because rash developed. The patient complied poorly with treatment; he died in March 2017 under unknown circumstances.

Patient 2 was a 66-year-old woman with a history of arterial hypertension and diabetes mellitus, a subcutaneous abscess in the prepubic area surgically treated without microbiological identification (June 2016), a lumbar hematoma (March 2017), and bacteremic obstructive pyelonephritis caused by *Escherichia coli* (April 2017). In April 2017, she developed a severe and disseminated form of melioidosis with pneumonia, bacteremia, and deep abscess. CT scan showed multiple pulmonary nodes consistent with hematogenous pneumonia, a deep abscess between kidney and psoas, and splenic emboli. *B. pseudomallei* was isolated from blood cultures performed at admission and from the abscess. The patient developed multiple complications: acute respiratory distress syndrome, systemic candidiasis, renal failure, hemodynamic failure, nonspecific encephalopathy, refractory septic shock related to catheter infection, and bacteremia caused by extended spectrum β-lactamase *Klebsiella pneumoniae*. In the intensive care unit, she was treated with ceftazidime (6 g/d for 24 d), then with meropenem (1 g 3×/d) plus TMP/SMX (320/1,600 mg 2×/d). Blood cultures grew *B. pseudomallei* until day 40. The patient died on day 60 from multiple organ failure.

Patient 3 was a 52-year-old man with a history of chronic alcoholism. He developed pneumonia in April 2017. Thoracic tomography showed an excavated condensation of the right middle lobe, right

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Appendix

Materials and Methods

The research protocol was approved by the Institutional Review Board of King Fahad Medical City (Riyadh, Saudi Arabia; #16–345) and Institutional Biosafety and Bioethics Committee of King Abdullah University of Science and Technology (Jeddah, Saudi Arabia; #18IBEC23).

The DNA from the patient sample was extracted using the ZymoBIOMICS DNA/RNA Miniprep Kit (Zymo Research, Freiburg, Germany). NuGEN Ovation Ultralow Library System V2 (NuGen, Manchester, UK) was used for library preparation. A total of 3.51 billion 150 bp pair-end Illumina reads were obtained from Illumina Hiseq4000 instrument. We performed the reference-guided assembly using *M. leprae* TN strain as the reference. Single-nucleotide polymorphisms (SNPs) were called for two iterations and filtered with Genome Analysis Toolkit (*1*) (GATK) which had a read depth of 3 or higher; an alignment quality score (MQ) ≥40; SNPs

subtyping of *M. leprae* KFMC-1 was done based on SNP subtypes (A–P) defined by surveying the informative SNPs described by Marc Monot et al. in 2009 (*2*). Phylogenies were generated by aligning all SNPs from representative genomes from various linages of leprosy genomes (*3*) using maximum likelihood.

The SNP in the *rpoB* gene was examined by nested PCR of 10 ng of genomic DNA with the method described (*4*) and the C1414A variant in *rrs* was verified with semi-nested PCR with 98°C for 2 min followed by 35 cycles of denaturation (98°C for 10 sec), primer annealing (62°C, 30 sec for first-round PCR, forward 5′-CGCGTTGTTCGTGAAATCT-3, reverse 5′-ATGCTCGCAACCACTATCCA-3; or 60°C 30 sec for second-round PCR, 1492R GGCTACCTTGTTACGACTT) and extension (72°C, 30 sec), and final extension at 72°C for 2 min. A PCR premix (Q5 Hot Start High-Fidelity 2X Master Mix, New England Biolabs).

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Appendix Table 1. Comparison of *M. leprae* KFMC-1 and *M. leprae* TN assemblies*

Category	*M. leprae* KFMC	*M. leprae* TN
Sequence size	3243015	3268203
Number of contigs	19	1
GC content (%)	57.8	57.8
contigs (> = 50000 bp)	14	1
Median sequence size	94825	3268203
Mean sequence size	141002.1	3268203
Longest contig size	497079	3268203
N50 value	318796	NA
L50 value	5	1

*KFMC, King Fahad Medical City; NA, not applicable.

Appendix Table 2. SNPs/INDEL present in *M. leprae* KFMC-1*

POS	Type	REF (TN)	ALT (KFMC)	Novelty	Annotation	ML code
73	SNP	T	G	No	missense_variant	ML0001
12484	Indel	A	AACCACAGCTAGAC	No	intergenic_region	MLP000002-ML0008c
14226	Indel	C	CATAT	Yes	intergenic_region	ML0009-ML0010c
15439	SNP	G	A	No	pseudogene	ML0010c
17425	SNP	G	A	Yes	intergenic_region	ML0013c-ML0014
26545	SNP	G	A	No	synonymous_variant	ML0020c
40852	SNP	G	T	Yes	pseudogene	ML0034
52851	SNP	T	C	No	missense_variant	ML0042
57633	SNP	T	G	No	pseudogene	ML0046c
61425	SNP	A	G	No	missense_variant	ML0049c
62545	SNP	G	T	No	missense_variant	ML0051c
73073	Indel	CGATCAA, GCCAGGA, ATCAAGT, TGATCAA, GCCAGGA, ATCAAGTT	C	Yes	pseudogene	ML0058c
77864	SNP	T	C	No	synonymous_variant	ML0061
86658	SNP	G	A	Yes	intergenic_region	ML0064c-ML0065
100574	SNP	A	G	No	pseudogene	ML0080c
132150	SNP	G	A	Yes	synonymous_variant	ML0102
157960	SNP	C	T	No	intergenic_region	ML0116c-ML0117
160627	SNP	G	T	Yes	synonymous_variant	ML0119c
175636	SNP	C	T	Yes	missense_variant	ML0131
286105	SNP	C	T	Yes	synonymous_variant	ML0214
313361	SNP	A	G	No	missense_variant	ML0238c
328634	SNP	G	C	No	missense_variant	ML0252
330125	SNP	G	A	No	missense_variant	ML0252

POS	Type	REF (TN)	ALT (KFMC)	Novelty	Annotation	ML code
365435	SNP	G	A	No	missense_variant	ML0283
383599	SNP	C	G	No	pseudogene	ML0301c
441420	Indel	CAT	C	Yes	intergenic_region	ML0349c-ML0350c
459887	SNP	C	T	No	pseudogene	ML0368
481476	SNP	A	G	No	synonymous_variant	ML0387
494674	SNP	T	G	No	missense_variant	ML0397c
504437	SNP	G	C	Yes	intergenic_region	ML0405-ML0406
508481	SNP	T	C	No	missense_variant	ML0410
509325	SNP	C	G	No	missense_variant	ML0411
517971	SNP	C	T	Yes	intergenic_region	ML0841-ML0842
528451	SNP	C	T	No	pseudogene	ML0428
533403	SNP	A	G	No	pseudogene	ML0433
561823	Indel	G	GGT	Yes	pseudogene	ML0463c
686240	SNP	A	C	No	pseudogene	ML0567
694090	SNP	T	C	No	missense_variant	ML0569c
711197	SNP	T	C	No	pseudogene	ML0585c
714396	SNP	C	T	No	synonymous_variant	ML0589c
736703	SNP	G	T	Yes	missense_variant	ML0605
790218	SNP	C	T	Yes	pseudogene	ML0652
831215	SNP	G	T	No	pseudogene	ML0693
832152	SNP	T	C	No	pseudogene	ML0694c
890453	SNP	A	G	No	missense_variant	ML0747c
904824	SNP	G	C	No	synonymous_variant	ML0763
938372	SNP	C	T	No	pseudogene	ML0794c
944191	Indel	C	CA	Yes	pseudogene	ML0797c
958228	Indel	A	AC	Yes	pseudogene	ML0809
972005	SNP	T	G	No	pseudogene	ML0821
1000186	SNP	C	T	Yes	intergenic_region	ML0841-ML0842
1041037	SNP	C	T	Yes	synonymous_variant	ML0876

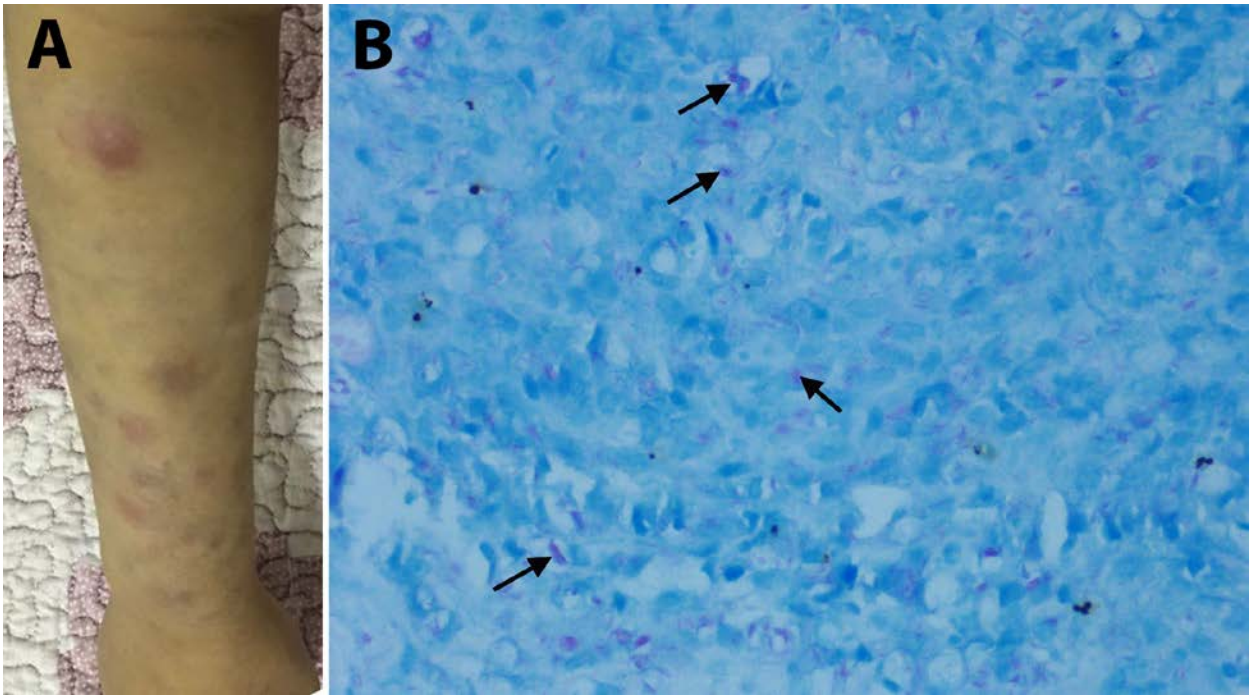
POS	Type	REF (TN)	ALT (KFMC)	Novelty	Annotation	ML code
1066586	SNP	T	C	Yes	pseudogene	ML0900c
1076949	SNP	G	C	No	missense_variant	ML0909
1087397	SNP	T	C	No	synonymous_variant	ML0917
1104232	SNP	C	G	No	pseudogene	ML0934
1133492	SNP	T	G	No	intergenic_region	ML0964-ML0965c
1133721	Indel	C	CG	Yes	intergenic_region	ML0964-ML0965C
1143423	SNP	T	C	No	pseudogene	ML0975c
1144840	SNP	T	G	Yes	synonymous_variant	ML0977
1155582	SNP	T	G	No	synonymous_variant	ML0988
1227051	SNP	G	T	No	intergenic_region	ML1061-ML1062
1257185	SNP	T	C	No	intergenic_region	ML1092c-ML1093
1265267	SNP	T	G	No	pseudogene	ML1097
1295192	SNP	A	G	No	missense_variant	ML1119
1324009	SNP	C	G	No	missense_variant	ML1132
1339813	SNP	T	C	No	synonymous_variant	ML1150
1342557	SNP	C	A	Yes	non_coding_transcript_exon_variant	MLP000016
1348426	SNP	T	C	No	intergenic_region	ML1152c-ML1153
1351149	SNP	C	G	No	intergenic_region	ML1154c-ML1155
1529088	SNP	A	G	No	pseudogene	ML1284c
1532258	SNP	G	A	No	missense_variant	ML1286
1533315	Indel	C	CG	Yes	pseudogene	ML1287
1587912	SNP	G	T	Yes	missense_variant	ML1334
1605956	SNP	G	A	No	intergenic_region	ML1345-ML1346
1607562	SNP	A	G	Yes	missense_variant	ML1346
1614069	SNP	T	C	No	pseudogene	ML1353c
1625045	SNP	T	G	No	synonymous_variant	ML1363
1640789	SNP	A	G	Yes	pseudogene	ML1376
1642875	SNP	G	T	No	pseudogene	ML1378
1643162	SNP	T	C	No	pseudogene	ML1378

POS	Type	REF (TN)	ALT (KFMC)	Novelty	Annotation	ML code
1677493	SNP	G	C	No	synonymous_variant	ML1397
1700105	SNP	T	C	Yes	missense_variant	ML1417
1701590	SNP	G	C	No	intergenic_region	ML1418c-ML1419c
1725797	SNP	C	G	No	pseudogene	ML1436c
1741830	Indel	G	GCAACAACGTC	Yes	pseudogene	ML1449c
1813428	Indel	A	AGT	No	pseudogene	ML1502c
1839270	SNP	A	G	No	pseudogene	ML1524c
1841279	Indel	C	CG	Yes	pseudogene	ML1527c
1843283	SNP	C	A	No	pseudogene	ML1528
1868993	SNP	G	T	No	pseudogene	ML1545
1876289	SNP	G	A	Yes	pseudogene	ML1552
1926696	SNP	T	C	No	intergenic_region	ML1600c-ML1601c
1955004	SNP	C	A	Yes	synonymous_variant	ML1629
1971193	SNP	G	A	No	pseudogene	ML1636
2011747	SNP	T	G	No	pseudogene	ML1668c
2011783	SNP	G	A	Yes	pseudogene	ML1668c
2030803	SNP	G	A	No	missense_variant	ML1685c
2040883	SNP	G	A	No	pseudogene	ML1693
2043287	SNP	A	G	No	synonymous_variant	ML1694c
2066936	SNP	G	T	Yes	missense_variant	ML1713
2100523	SNP	C	G	No	missense_variant	ML1740c
2104127	SNP	T	C	No	intergenic_region	ML1743c-ML1744c
2142011	Indel	CT	C	No	pseudogene	ML1767c
2148809	SNP	G	A	No	pseudogene	ML1773c
2155013	SNP	T	G	No	pseudogene	ML1778c
2174865	SNP	G	C	No	intergenic_region	ML1795-ML1796
2205779	Indel	TA	T	No	pseudogene	ML1822
2211034	Indel	TAC	T	Yes	intergenic_region	ML1825c-ML1826c
2235048	SNP	C	T	No	pseudogene	ML1851c

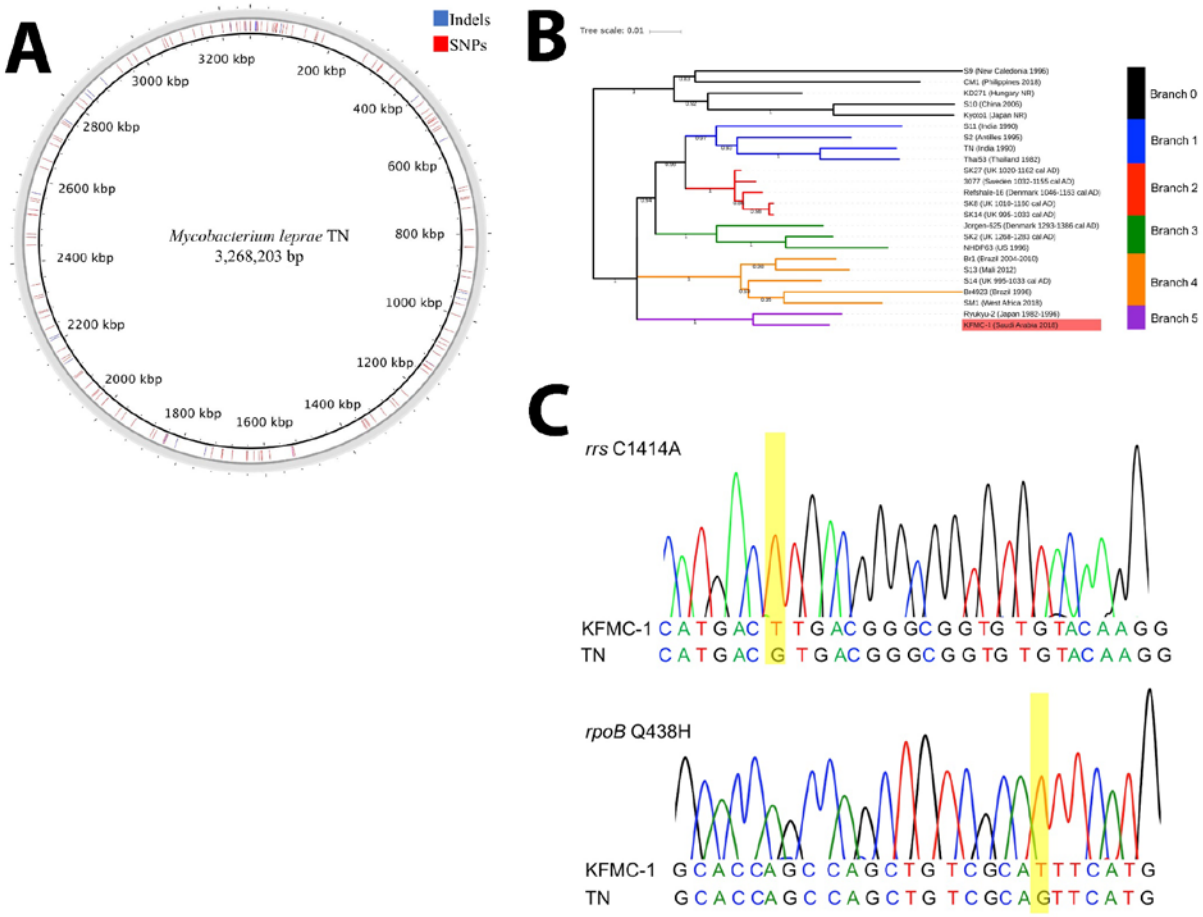
POS	Type	REF (TN)	ALT (KFMC)	Novelty	Annotation	ML code
2263547	SNP	G	A	No	intergenic_region	ML1883-ML1884
2275492	SNP	C	A	Yes	missense_variant	ML1891c
2278551	SNP	C	A	No	pseudogene	ML1893c
2312059	SNP	C	G	No	start_lost	ML1926c
2317249	SNP	C	T	Yes	pseudogene	ML1933
2344787	SNP	G	A	No	synonymous_variant	ML1957c
2441339	SNP	C	T	No	missense_variant	ML2053c
2459766	SNP	A	G	No	missense_variant	ML2069
2468130	SNP	C	A	No	missense_variant	ML2075c
2514637	SNP	C	T	Yes	intergenic_region	ML2114c-ML2115c
2515916	SNP	G	T	Yes	pseudogene	ML2115c
2526543	SNP	G	T	Yes	pseudogene	ML2125c
2547925	SNP	C	G	Yes	pseudogene	ML2145
2553176	SNP	T	G	No	pseudogene	ML2149
2567248	Indel	AGTG	A	No	intergenic	ML2159c-ML2160
2631245	SNP	G	A	Yes	synonymous_variant	ML2213c
2651703	SNP	C	A	Yes	intergenic_region	ML2233-ML2234
2691666	SNP	G	A	Yes	pseudogene	ML2267
2706236	SNP	T	G	No	pseudogene	ML2281c
2711942	SNP	T	G	No	pseudogene	ML2287c
2747358	SNP	T	C	Yes	missense_variant	ML2320c
2751783	SNP	A	G	No	synonymous_variant	ML2322c
2757405	Indel	GC	G	No	pseudogene	ML2325c
2804726	SNP	C	A	No	synonymous_variant	ML2354c
2818521	SNP	T	C	No	synonymous_variant	ML2357c
2835913	Indel	CGTGT	C	Yes	pseudogene	ML2367
2844969	Indel	CAT	C	Yes	intergenic_region	ML2375c-ML2376c
2887094	Indel	C	CATA	Yes	intergenic_region	ML2415-ML2416c
2935685	SNP	A	C	No	pseudogene	ML2462c

POS	Type	REF (TN)	ALT (KFMC)	Novelty	Annotation	ML code
2964999	SNP	T	C	No	synonymous_variant	ML2490c
2981212	SNP	G	A	No	synonymous_variant	ML2501
3016175	SNP	T	C	No	synonymous_variant	ML2534c
3057114	SNP	G	C	No	intergenic_region	ML2563-ML2564c
3063817	SNP	C	A	Yes	missense_variant	ML2568c
3076050	SNP	G	C	No	intergenic_region	ML2574c-ML2575c
3102778	SNP	A	C	No	missense_variant	ML2597
3132639	SNP	G	A	No	synonymous_variant	ML2622c
3152586	SNP	C	T	No	synonymous_variant	ML2634c
3175296	SNP	A	C	No	intergenic_region	ML2652-ML2653
3202695	SNP	A	G	No	intergenic_region	ML2670c-ML2671
3221210	SNP	G	A	Yes	pseudogene	ML2676c
3221615	Indel	AATAT	A	Yes	intergenic_region	ML2676c-ML2677
3236317	SNP	G	A	No	missense_variant	ML2687c
3243731	SNP	A	G	No	pseudogene	ML2694
3254050	SNP	C	T	Yes	synonymous_variant	ML2700
3256572	SNP	C	T	No	synonymous_variant	ML2700
3257047	Indel	GCCCA	G	Yes	pseudogene	ML2701
3268175	SNP	G	T	No	intergenic_region	ML2713c-ML0001

*ALT, alternative; KFMC, King Fahad Medical City; POS, position; REF, reference; SNP, single-nucleotide polymorphism.



Appendix Figure 1. A) Photographs of forearm skin lesions. B) Histopathology of the skin biopsy using Ziehl-Neelsen staining (100X). Arrows showing *M. leprae* bacilli.



Appendix Figure 2. A) *M. leprae* KFMC-1 genome comparison against the *M. leprae* TN as the reference genome. BLASTn matches above 90% nucleotide identity are colored in gray. The vertical bars represent the polymorphic sites in *M. leprae* KFMC-1 when compared to the *M. leprae* TN strain. The SNP positions in the genome are shown in red while the nucleotide insertions and deletions (Indels) shown in blue; The gray outer circle shows *M. leprae* KFMC-1 shared identity (according to BLASTn) with *M. leprae* TN genome as the reference. B) Phylogenetic lineages of *M. leprae* KFMC-1 with the representatives from *M. leprae* isolates based on SNP sites using a maximum likelihood approach using the Tamura-Nei model. Bootstrap percentages from 1,000 replicates are shown next to the branches. The scale indicates the

number of substitutions per site. C) Chromatograms of *M. leprae* KFMC-1 showing the Q438H mutation in *rpoB* and C1414A mutation in *rrs*. KFMC, King Fahad Medical City; SNP, single-nucleotide polymorphism.