



UNIVERSITI PUTRA MALAYSIA

***MOLECULAR EPIDEMIOLOGY AND GENETIC DIVERSITY OF
PLASMODIUM KNOWLESI INFECTING LONG-TAILED MACAQUES
(MACACA FASCICULARIS RAFFLES) ON THE WEST COAST OF
PENINSULAR MALAYSIA***

LEE COL LIN

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PENINSULAR MALAYSIA**

By

LEE COL LIN

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in
Fulfillment of the Requirements for the Degree of Master of Science**

December 2015

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirements for the degree of Master of Science

**MOLECULAR EPIDEMIOLOGY AND GENETIC DIVERSITY OF
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LEE COL LIN

December 2015

Chairman: Reuben Sunil Kumar Sharma, PhD
Faculty: Veterinary Medicine

This study was undertaken to ascertain the molecular epidemiology of *Plasmodium knowlesi* infecting wild Long-tailed macaques (*Macaca fascicularis*) on the west coast of Peninsular Malaysia, and to determine its spatial distribution and risk factors for infection. Genetic analysis based on the Circumsporozoite Protein (CSP) gene of *P. knowlesi* was done to infer the genetic assemblage of the parasite. A total of 781 blood samples were collected from wild *M. fascicularis* captured from 77 locations representing four different habitats; urban, sub-urban, plantation/orchards and secondary forest. Five states on the west coast of the country were sampled, namely, Penang, Perak, Selangor, Negeri Sembilan and Melaka, and the area was arbitrary divided into three zones. Ten human infected blood samples from Kuala Kubu Baru, Selangor were included in the study. Screening for *P. knowlesi* infection was conducted using nested PCR targeting the 18S SSU rRNA and phylogenetic characterization was done using the CSP gene. Prevalence of infection was 13.4% (15.1% male and 11.1% female) with Zone 1 exhibiting the highest prevalence (29.8%), followed by Zone 3 (15.6%) and Zone 2 (5.3%). Macaques inhabiting the plantation/orchards were the most infected (18.2%), followed by sub-urban (16.5%), secondary forest (15.7%), and urban (9.8%) areas. The adult macaques showed the highest prevalence of *P. knowlesi* infection (16.6%), followed by the juveniles (13.1%) and sub-adults (9.7%). Spatial distribution analysis revealed two hotspots of infection in the country; on the northwest (Penang and north Perak) and southwest (Negeri Sembilan). Risk factor analysis showed that all putative factors except gender, posed a risk for infection with this parasite among the macaques. Stepwise binary logistic regression analysis revealed that macaques from Zone 1, sub-urban and plantation/orchards, and adults, have higher risk of infections compared to conspecifics in the other categories. Genotypic analyses of 192 *P. knowlesi* CSP gene sequences (178 from macaques and 14 from humans) produced 25 different haplotypes with 14 polymorphic sites. The overall nucleotide diversity (π = 0.0196) and haplotype diversity (H_d = 0.836) was high, but genetic differentiation between the zones and habitats was low (F_{ST} < 0.05). The three most commonly encountered haplotypes PkMH18 (f = 62), PkMH13 (f = 26) and PkMH04 (f = 18), were widely distributed across the sampling locations, with the former predominating in the northwest region of the country. All eight haplotypes from

humans were found to be identical with that obtained from the macaques. Phylogenetic analysis clustered macaque and human isolates from within the Southeast Asia region. This study represents the first attempt to elucidate the molecular epidemiology, spatial distribution and genetic diversity of *P. knowlesi* infection among *M. fascicularis* in Peninsular Malaysia. Increasing destruction of forest habitats for human activities in Southeast Asia has narrowed the malaria transmission interface between macaques and humans. Comprehensive epidemiological investigations should be carried out in order to shed more light on the transmission dynamics of this deadly zoonotic disease in the region.



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sebagai memenuhi keperluan untuk ijazah Master Sains

**EPIDEMIOLOGI MOLEKUL DAN KEPELBAGAIAN GENETIK
PLASMODIUM KNOWLESI YANG MENJANGKITI KERA (*MACACA
FASCICULARIS*) DI PANTAI BARAT SEMENANJUNG MALAYSIA**

Oleh

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Kajian ini telah dijalankan untuk menentukan epidemiologi molekula jangkitan *Plasmodium knowlesi* dalam kera liar (*Macaca fascicularis*) di kawasan pantai barat Semenanjung Malaysia dan untuk menentukan taburan spatial dan faktor risiko yang berkaitan dengan jangkitan. Analisis genetik berdasarkan gen Circumsporozoite Protein (CSP) *P. knowlesi* dilakukan untuk membuat kesimpulan himpunan genetik parasit. Sebanyak 781 sampel darah telah dikumpulkan dari kera liar, *M. fascicularis* yang ditangkap dari 77 lokasi yang mewakili empat habitat yang berbeza; bandar, pinggir bandar, ladang/kebun dan hutan sekunder. Lima negeri di pantai barat negara ini telah disampel, iaitu, Pulau Pinang, Perak, Selangor, Negeri Sembilan dan Melaka, dan kawasan itu dibahagi kepada tiga zon. Sepuluh sampel darah manusia dari Kuala Kubu Baru, Selangor yang sah dijangkiti *P. knowlesi* telah disertakan dalam kajian ini. Saringan untuk jangkitan *P. knowlesi* telah dijalankan dengan menggunakan kaedah PCR tersarang yang mensasarkan 18S SSU rRNA dan pencirian filogenetik telah dilakukan dengan menggunakan gen CSP. Prevalen jangkitan *P. knowlesi* adalah 13.4% (15.1% jantan dan 11.1% betina) dengan Zon 1 menunjukkan prevalen tertinggi (29.8%), diikuti oleh Zon 3 (15.6%) dan Zon 2 (5.3%). Jangkitan dalam kera yang datang dari ladang/kebun adalah paling tinggi (18.2%), diikuti oleh kawasan sub-bandar (16.5%), hutan sekunder (15.7%), dan bandar (9.8%). Kera dewasa menunjukkan kelaziman jangkitan *P. knowlesi* tertinggi (16.6%), diikuti oleh remaja (13.1%) dan sub-dewasa (9.7%). Analisis taburan spatial mendedahkan dua titik panas jangkitan di negara ini; di barat laut (Pulau Pinang dan utara Perak) dan barat daya (Negeri Sembilan). Analisis faktor risiko menunjukkan bahawa semua faktor, kecuali jantina, adalah risiko jangkitan parasit di antara kera. Analisis binari regresi logistik langkah demi langkah mendedahkan bahawa kera dari Zon 1, sub-bandar dan ladang/kebun, dan dewasa, mempunyai risiko yang lebih tinggi berbanding dengan kera dalam kategori lain. Analisis genotip berdasarkan 192 jujukan gen CSP *P. knowlesi* (178 dari kera dan 14 dari manusia) menghasilkan 25 haplotip berbeza dengan 14 tapak polimorfik. Kepelbagaian keseluruhan nukleotida ($\pi = 0.0196$) dan kepelbagaian haplotip ($H_d = 0.836$) adalah tinggi, tetapi perbezaan genetik antara zon dan habitat adalah rendah ($F_{ST} < 0.05$). Tiga haplotip yang paling biasa adalah PkMH18 ($f = 62$), PkMH13 ($f = 26$) dan PkMH04 ($f = 18$), dan mereka ditemui secara meluas di seluruh

lokasi persampelan, dengan PkMH13 mendominasi rantau barat laut negara ini. Kesemua lapan haplotip dari sampel manusia didapati serupa dengan yang diperolehi dari kera. Analisis filogenetik mendapati bahawa isolat kera dan manusia adalah berkelompok dalam rantau Asia Tenggara. Kajian ini merupakan percubaan pertama untuk menjelaskan epidemiologi molekul, taburan spatial dan kepelbagaian genetik *P. knowlesi* antara *M. fascicularis* di Semenanjung Malaysia. Peningkatan kemusnahan habitat hutan untuk aktiviti manusia di Asia Tenggara telah mengurangkan jurang aliran malaria antara kera dan manusia. Penyiasatan epidemiologi secara komprehensif perlu dijalankan untuk menjelaskan lebih lanjut tentang dinamik aliran penyakit zoonotik yang membawa maut di rantau ini.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

°C	degree celcius
μl	microlitre
μM	micromolar
1x	one time
An	<i>Anopheles</i>
bp	base pair
C	Cystine
CaCl ₂	calcium chloride
cm	centimetre
COI	cytochrome oxidase subunit I
COII	cytochrome oxidase subunit II
CSP	Circumsporozoite Protein
cyt	cytochrome
Cytb	cytochrome b
D	Aspartic acid
DNA	deoxyribonucleic acid
dNTP	deoxynucleotide triphosphate
E	Glutamic acid
EDTA	ethylenediamine tetraacetic acid
ExPasy	Expert Protein Analysis System
F	Phenylalanine
F _D	Fu and Li's D
F _{ST}	genetic differentiation
ft	feet
G	Glycine
GAG	glycosaminoglycan
GPI	glycosylphosphatidylinositol
GPS	Global Positioning System
h	hour
Hd	haplotype diversity
HRP-II	histidine-rich protein II
HSPG	heparin sulphate proteoglycan
I	Isoleucine
K	Lysine
kb	kilobase
kDa	kilo Dalton
kg	kilogram
km	kilometer
L	Leucine
LAMP	loop-mediated isothermal amplification
LB	Lysogeny Broth
lb	pound
LDH	lactate dehydrogenase
M	Methionine
m	metre
mg	milligram
MgCl ₂	magnesium chloride
min	minute

ML	Maximum Likelihood
ml	millilitre
mM	milimolar
mm	millimetre
MOH	Ministry of Health
MSP	merozoite surface protein
MSP-1	merozoite surface protein-1
mtDNA	mitochondria deoxyribonucleic acid
N	Asparagine
NCBI	National Center for Biotechnology Information
ng	nanogram
NJ	Neighbour-joining
nm	nanometer
OR	odds ratio
ORF	open reading frame
P	Proline
<i>P.</i>	<i>Plasmodium</i>
PCR	polymerase chain reaction
PERHILITAN	Department of Wildlife and National Parks Malaysia
pi	nucleotide diversity
qPCR	quantitative polymerase chain reaction
RDT	rapid diagnostic test
RNase	ribonuclease
rpm	revolution per minute
S	Serine
sec	second
SSU rRNA	small subunit ribosomal RNA
TAE	Tris-acetic acid-EDTA
T _D	Tajima's D
U	unit
UV	ultraviolet
V	Alanine
V	volt
w/v	weight over volume
WHO	World Health Organization

CHAPTER 1

GENERAL INTRODUCTION

Malaria is a disease of public health importance and is caused by the blood protozoan parasites of the genus *Plasmodium* which is transmitted by *Anopheles* mosquitoes. The parasite is known to infect humans and a wide range of animal taxa (Coatney *et al.*, 1971; Rich and Ayala, 2006; Ramasamy, 2014). Human malaria is widely distributed across tropical and sub-tropical regions, covering 97 countries, including Asia, Africa and South America (World Health Organization, 2014). Latest statistical reports by the World Health Organization (2014) indicate that 1.2 billion people are living in areas with high risk of malaria transmission, accounting for over 584,000 deaths of which 78% involve children aged under 5 years (WHO, 2014).

For over 100 years since the discovery of the *Plasmodium* parasites, numerous studies have been carried out and five species are known to infect humans; *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi* (Eyles *et al.*, 1960; Chin *et al.*, 1965; Singh *et al.*, 2004; Ramasamy, 2014; Ta *et al.*, 2014; White *et al.*, 2014). Among these, *P. vivax* is reported to be the most widely distributed species of human malaria especially in Asia and South America, whereas *P. falciparum* predominates only in sub-Saharan Africa region but is the most lethal cause of infections (Eyles *et al.*, 1960; Chin *et al.*, 1965; Guerra *et al.*, 2008; 2010; Hay *et al.*, 2010; Tilley *et al.*, 2011).

Over 30 *Plasmodium* species have been described in non-human primate thus far, infecting a wide range of monkeys, apes and lemurs (Kantele and Jokiranta, 2011; Ramasamy, 2014). Macaques are found to harbour the most variety of non-human *Plasmodium* species, namely, *P. knowlesi*, *P. inui*, *P. cynomolgi*, *P. coatneyi* and *P. fieldi* (Coatney *et al.*, 1971; Fooden, 1982; 1994; Lee *et al.*, 2011). In Malaysia, two most common macaque species, the Long-tailed macaque (*Macaca fascicularis*) and the Pig-tailed macaque (*Macaca nemestrina*) have been commonly studied for malaria infections and are known to harbour zoonotic *Plasmodium* species (Eyles *et al.*, 1962; Coatney *et al.*, 1971; Southwick and Cadigan, 1972; Fooden, 1982; 1994; Vythilingam *et al.*, 2008; Lee *et al.*, 2011). *Macaca fascicularis* is the most abundantly distributed macaque in forested area of Southeast Asia, especially in Peninsular Malaysia (Southwick and Cadigan, 1972; Fooden, 1982; 1995). Of all known non-human primate species, *P. knowlesi* (Chin *et al.*, 1968; Antinori *et al.*, 2013), *P. inui* (Coatney, 1966) and *P. cynomolgi* (Coatney *et al.*, 1961; Eyles 1960; Schmidt *et al.*, 1961; Ta *et al.*, 2014) are proven to be zoonotic and transmissible to human via the bite of the *Anopheles* s group of mosquito.

The discovery of a large focus of *P. knowlesi* human malaria cases in the Kapit Division of Sarawak (Singh *et al.*, 2004), has evoked interest among many researchers studying the infection in humans. The polymerase chain reaction (PCR) assay using molecular markers like the small subunit ribosomal RNA (SSU rRNA) and circumsporozoite protein (CSP) gene (Singh *et al.*, 2004) is now the choice technique for the detection of malaria in primates and humans due to its sensitivity and specificity

compared to traditional microscopy. Molecular tools are able to differentiate morphologically similar species like *P. malariae* and *P. knowlesi*, leading to the discovery that *P. knowlesi* is a prominent form of human malaria in many parts of Southeast Asia (Jongwutiwes *et al.*, 2004; Singh *et al.*, 2004; Cox-Singh *et al.*, 2008; Ng *et al.*, 2008; Luchavez *et al.*, 2008; Ramasamy, 2013; William *et al.*, 2013, 2014; Yusof *et al.*, 2014). A recent survey (Yusof *et al.*, 2014) highlighted the widespread nature of human *knowlesi* infections in most states of Peninsular Malaysia, corroborating the recent statistical report by the Ministry of Health, Malaysia (2013) which demonstrated that *P. knowlesi* accounted for 38.4% of the total human malaria cases reported in 2012 in Malaysia. In Sabah, East Malaysia, a similar increase of *P. knowlesi* cases have been observed since 2014, inversely correlated with the decrease in *P. vivax* and *P. falciparum* infection in humans (William *et al.*, 2013; 2014).

The devastating effects of the disease are of major concern in Asia. As such, Malaysia together with its Asian partners has committed to strive towards a National Malaria Elimination goal by the end of 2020 (Roll Back Malaria Partnership, 2012; Sanders *et al.*, 2014). Latest statistics revealed that in Malaysia, there were 5306 malaria cases in 2011, 4725 cases in 2012, and 3810 cases in 2013; the highest among the vector borne parasitosis in the country (Ministry of Health Malaysia, 2012; WHO World Malaria Report, 2013; 2014). Apart from the traditional species that cause malaria in humans, *P. knowlesi* is now recognised as a parasite that can cause severe disease with high fatalities (Cox-Singh *et al.*, 2008; Mohamed and Roshan, 2009; William *et al.*, 2011; Barber *et al.*, 2013). It is also considered the most rampant (Daneshvar *et al.*, 2009; Singh and Daneshvar, 2010; Ministry of Health Malaysia, 2012; William *et al.*, 2013; Yusof *et al.*, 2014) and most severe (Barber *et al.*, 2013) form of human malaria in Malaysia, being responsible for over half of the malaria related deaths in the country (Rajahram *et al.*, 2012).

Over the years, several entomological studies have been conducted in Malaysia to elucidate the mosquito vectors involved in the transmission of *P. knowlesi* in human and macaques. These studies have incriminated the *Leucosphyrus* Group of mosquitoes as major vectors, including *An. latens* in Kapit, Sarawak (Vythilingam *et al.*, 2006), *An. cracens* in Pahang (Vythilingam *et al.*, 2008), *An. introlatus* in Hulu Selangor (Vythilingam *et al.*, 2014) and previously, *An. hackeri* in mangrove areas of Selangor (Wharton and Eyles, 1961). With the changing landscape in the country and the conversion of forested habitats for human-related activities and industry, it is likely that the spatial distribution patterns of both macaques and the mosquito vectors will be affected, leading to alterations in the transmission dynamics of the disease.

Previous studies on non-human primate malarias in the country have focused mainly on *Plasmodium* detection, prevalence and vector diversity, leaving paucity in areas of molecular epidemiology, population genetics and phylogenetic affinities of the parasite. The present investigation was therefore designed to contribute to the understanding of non-human primate malaria in the country, caused by the zoonotic *P. knowlesi* with the following specific objectives:

1. To ascertain the molecular epidemiology of *Plasmodium knowlesi* infecting wild Long-tailed Macaques (*Macaca fascicularis*) on the West Coast of Peninsular Malaysia.
2. To determine the spatial distribution patterns and habitats that support *Plasmodium knowlesi* infection among these primates.
3. To evaluate the genetic composition and phylogenetic affinities of *Plasmodium knowlesi* isolated from macaques and humans by characterizing the Circumsporozoites Protein (CSP) gene.



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