UNIVERSITI PUTRA MALAYSIA

SCREENING OF IMPORTANT VIRUSES IN FELINES AND MOLECULAR CHARACTERIZATION OF PARVOVIRUS ISOLATE FROM A TIGER IN MALAYSIA

NUR FARAHIYAH BINTI AHMAD NADZRI

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By

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Chairman : **Abdul Rahman Omar, PhD**
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Animals under the family *Felidae* both domesticated and in the wild are potentially harbouring viruses of importance to other animals and humans. Canine Parvovirus (CPV) is a single stranded DNA virus which known to cause severe disease in younger unvaccinated animals. Despite the widespread vaccination of domestic carnivores, CPV is still an important pathogen of domestic and wild carnivores. In addition, CPV able to infect a wide range of feline hosts, hence, allowing it to infect both cats and dogs. Although, CPV is well studied in canine, limited information is available on it occurrence in various species of felids found in Malaysia. This study investigated detection of viruses of potential importance in different species of felines namely leopards, feral cats and tigers in Malaysia based on virus isolation in *Crandell Rees* feline kidney (CRFK) cells, polymerase chain reaction (PCR) using gene-specific primers and sequence analysis. From a total of 36 samples collected, 11 samples showed cytopathic effect in cell culture and were subjected to PCR using specific primers for feline herpesvirus (FHV), feline calicivirus (FCV), canine distemper virus (CDV) and CPV. However, only one sample from a tiger was detected positive for canine parvovirus (CPV). The entire viral genome of the sample CPV/MY/MT4 was amplified by PCR for sequencing using Sanger sequencing approach. Genome sequencing of the isolate revealed substitution of amino acid which characterized the isolate as variant CPV namely new CPV-2a with a characteristic's amino acid substitution at position 297 of VP2 gene from serine to alanine (297-Ser-Ala). Additionally, at amino acid residue 426, isolate CPV/MY/MT4 have amino acid substitution aspartic acid to asparagine (Asp-426-Asn), which also revealed that the isolate has specific amino acid for CPV-2a.

In addition, CPV/MY/MT4 was found to be phylogenetically close to new CPV-2a strain from other countries namely USA and Japan. The rest of the other new CPV-2a strains had distinct lineage but shared molecular relationship with the isolate CPV/MY/MT4. In conclusion, genome sequencing of the isolated CPV provided valuable information of

the molecular characteristic of the isolate for further study on the importance of this virus in tigers and species of felids

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PENYARINGAN VIRUS PENTING DALAM KUCING DAN PENCIRIAN MOLEKUL PARVOVIRUS DIASINGKAN DARIPADA HARIMAU DI MALAYSIA

Oleh

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Haiwan di bawah famili *Felidae* yang didomestikasi dan liar berpotensi mengandungi virus yang penting bagi haiwan dan manusia lain. Parvovirus kanin (CPV) adalah virus DNA bebenang tunggal yang diketahui menyebabkan penyakit yang teruk pada haiwan yang tidak divaksinasi. Walaupun karnivor domestik divaksinasi secara meluas, CPV masih merupakan patogen penting bagi karnivor domestik dan liar. Di samping itu, CPV dapat menjangkiti pelbagai perumah dalam spesis kucing, oleh itu ia dapat menjangkiti kedua-dua kucing dan anjing. Walaubagaimanapun, CPV hanya dikaji dengan teliti dalam anjing, dan maklumat untuk pelbagai spesis felid yang terdapat di Malaysia adalah terhad. Kajian ini dijalankan bagi menyiasat pengesanan virus yang penting dalam spesis kucing yang berbeza seperti harimau bintang, kucing liar dan harimau di Malaysia berdasarkan pengasingan virus dalam sel buah pinggang *Crandell Rees* felin (CRFK), reaksi rantai polimerase (PCR) dan analisis urutan. Daripada sejumlah 36 sampel yang dikumpulkan, 11 sampel menunjukkan kesan sitopatik dalam kultur sel dan PCR telah dijalankan menggunakan primer yang spesifik bagi feline herpesvirus (FHV), feline calicivirus (FCV), canine distemper virus (CDV) dan CPV. Walau bagaimanapun, hanya satu sampel dari harimau yang dikesan positif bagi parvovirus kanin (CPV). Hampir keseluruhan genom virus (CPV / MY / MT4) telah diamplifikasi melalui PCR menggunakan pendekatan penjujukan Sanger. Jujukan genom menunjukkan penggantian asid amino yang mencirikan virus sebagai CPV-2a baru (CPV2a dengan 297-Ser-Ala). Tambahan pula, pada asid amino di kedudukan 426, virus CPV/MY/MT4 mempunyai penggantian asid amino, asid aspartik kepada asparagine (Asp-426-Asn) yang juga menunjukkan virus CPV / MY / MT4 mempunyai amino asid yang spesifik dengan CPV-2a.

Pengasingan virus CPV / MY / MT4 secara filogenetiknya, dikait rapat dengan strain baru CPV-2a China dan berkongsi asal-usul dengan strain baru CPV-2a dari USA dan Jepun. Jujukan CPV-2a baru yang selebihnya mempunyai garis keturunan yang tersendiri tetapi mempunyai hubungan molekular bersama dengan virus CPV/MY/MT4.

Penjujukan genom CPV terpencil memberikan maklumat yang penting mengenai ciri molekul virus tersebut.

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

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LIST OF ABBREVIATIONS

α	Alpha
ATV	Antibiotic-trypsin-versene
bp	Base pair
BSA	Bovine serum albumin
β	Beta
CO_2	Carbon dioxide
CDS	Coding DNA sequence
CDV	Canine distemper virus
CRFK	Crandell Rees feline kidney
CPE	Cytopathic effect
CPV	Canine parvovirus
CPV-2	Canine parvovirus-2
CPV-2a	Canine parvovirus-2a
CPV-2b	Canine parvovirus-2b
C	Cytosine
˚C	Degree Celsius
DMEM	Dulbecco's modified Eagle's medium
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acids
dNTP	Dinucleotide triphosphate
EDTA	Ethylenediaminetetraacetic acid
FBS	Fetal bovine serum
FCV	Feline calicivirus
FHV	Feline Herpesvirus
FW	Formula weight
γ	Gamma
g	Gram
G	Guanine
h	Hour
IU/mL	International unit per milliliter
kbases	Kilo bases
kbp	Kilo base pair
L	Liter
$MgCl_2$	Magnesium chloride
µg	Microgram
µg/µL	Microgram per microliter
µg/mL	Microgram per mililiter
µL	Microliter
µm	Micrometer
mM	Millimolar
min	Minute
mL	Milliliter
nm	Nanometer
NGS	Next generation sequencing
OD	Optical density
ORF	Open reading frames
PBS	Phosphate buffered saline
PEG	Polyethylene glycol

PCR	Polymerase chain reaction
p.i.	Post infection
rpm	Revolutions per minute
SPCR	Simulated PCR
NaCl	Sodium chloride
SDS	Sodium dodecyl sulfate
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
NaOH	Sodium hydroxide
cm^2	Square centimeter
$TCID_{50}$	Median tissue culture infective dose
T	Thymine
Tris-Base	2-Amino-2-(hydroxymethyl)-1,3-propanediol
Tris-Cl	Trisaminomethane chloride
Tris-HCl	2-Amino-2-(hydroxymethyl)-1,3-propanediol hydrochloride
V	volt
v/v	volume per volume
w/v	weight per volume
xg	x gravity, measure of centrifugal force

CHAPTER 1

INTRODUCTION

Animals under family *Felidae* both domesticated and in the wild are potentially harbouring viruses of importance to other animals and humans. Some of the viruses that are potentially important in felines are Feline Herpesvirus (FHV), Feline Calicivirus (FCV), Canine Distemper Virus (CDV) and Canine Parvovirus (CPV).

Feline Herpesvirus (FHV) and Feline Calicivirus (FCV) are categorized in the Feline upper respiratory tract infection. These two viruses are most important as they account the larger number of all diagnosed feline upper respiratory infections, with FHV as the primary pathogens in cats (Maes, 2012).

Outbreak of Canine Distemper virus (CDV) in various felines in Wildlife Park, California during the fall 1992 (Appel *et al.,* 1992) had shown that feline species are also susceptible to canine virus infection. Even domestic cats have been reported to be susceptible to CDV infection without the development of clinical diseases (Appel *et al.,* 1974). Infection and mechanism of transmission of CDV in felids species is still unknown, though there are report in explaining how the epizootic CDV in felids (Appel *et al.,* 1995).

Canine Parvovirus (CPV) emerged in the canine population during the late 1970s in the canine population. Less than a decade later, a CPV variant, named CPV-2a and CPV-2b emerged (Truyen and Parrish, 1992) emerged due to antigenic drift that spread worldwide within a year. As a result of adaptation to feline transferrin receptor, this CPV variants are now able to infect felines as well as canines. Although these antigenic variants occurred subtly, it still remains an importance as it can infect cats (Ikeda *et al.,* 2000), while still remaining a threat to dogs.

Advancement in sequencing techniques has provided great insight on the realm of virus genome analysis, enabling an increasing number of research studies of the canine parvovirus (Decaro *et al.,* 2005; Decaro *et al.,* 2005b). In advancement of other sequencing techniques, Sanger sequencing technique is still considered as the gold standard as it still constantly produces a high-quality sequence read up to 1 kb. It was found possible, in this study, to employ a direct purified amplicon approach for Sanger sequencing.

Although all the four important viruses in felines are well established in in domestic cats in other parts of the country, not much are known for their occurrence in Malaysia, especially in non-domestic felids. Thus, based on this statement, the hypothesis of this study is that feline species can potentially harbor viruses of veterinary importance to felines, with the null hypothesis that viruses of veterinary importance to felines are absent in felines species. Feline species especially tiger can potentially harbor viruses of

importance to felines. Thus, this study investigated detection of viruses of potential importance in different species of felines namely leopards, feral cats and tigers in Malaysia. Genome sequencing and gene analysis obtained from these strains could provide an insight to understand the potential of canine parvovirus strains in felids species.

Hence, the objectives of this study are:

a. To screen viruses of veterinary importance of felines by means of polymerase chain reaction (PCR) and by isolation in cell culture.
b. To detect viruses of veterinary importance of felines by using gene specific primers which targets the viruses that are important to felines.
c. To sequence a near complete genome of canine parvovirus isolated from a tiger.
d. To determine the molecular characteristics of the sequenced canine parvovirus.

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