UNIVERSITI PUTRA MALAYSIA

GENOMIC SEQUENCING AND CHARACTERIZATION OF FOUR HUMAN RHINOVIRUS-C STRAINS FROM MALAYSIAN PATIENTS

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GENOMIC SEQUENCING AND CHARACTERIZATION OF FOUR HUMAN RHINOVIRUS-C STRAINS FROM MALAYSIAN PATIENTS

By

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

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GENOMIC SEQUENCING AND CHARACTERIZATION OF FOUR HUMAN RHINOVIRUS-C STRAINS FROM MALAYSIAN PATIENTS

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Human rhinovirus (HRV) is one of the respiratory viruses responsible for acute respiratory tract infections (ARTI). HRVs infect both upper and lower respiratory tracts, especially in children. HRVs were initially classified into two clusters, HRV-A and HRV-B. A novel HRV strain, HRV-C was discovered in year 2006. There is a limited number of HRV-C complete genome in the GenBank. Hence, the objective of the present study is to sequence and characterize the Malaysian HRV-C complete genome. Four RNA samples were collected from children with respiratory signs and symptoms hospitalized in Universiti Malaya Medical Center (UMMC). These samples were previously confirmed as HRV-C by sequencing of VP4/VP2 region. Two steps reverse transcription polymerase chain reaction (RT-PCR) was performed. The complete genome was amplified using several sets of modified and redesigned primers. To understand the phylogenetic relationship of Malaysian HRV-Cs, MEGA6 software was used to construct phylogenetic trees. Characteristics of Malaysian HRV-C were determined and recombination was investigated using Recombination Detection Program (RDP) software. Approximately 7.1 kbp of four Malaysian HRV-Cs complete genome sequences were obtained. All the genes in Malaysian HRV-C coding region exhibited similar genomic features as other HRV-Cs. Malaysian HRV-C showed similar receptor utilization, immunogenic sites and antiviral sites with other HRV-Cs. Based on VP4/VP2 sequences, Malaysian HRV-Cs were classified as HRV-C6, C22, C23 and C42. Pairwise distance threshold further confirmed the classification based on VP4/VP2 sequences. Three Malaysian HRV-Cs (C22, C23 and C42) represent the first complete genome were successfully sequenced. No recombination was identified. Negative selective pressure was the dominant selective pressure exerted on Malaysian HRV-C and other HRV-Cs coding sequences. In conclusion, the present study provided four HRV-C complete genome sequences which will lead to a better understanding of functional sequences, predicted receptor usage, secondary structure and selective pressure in HRV-C.

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

PENJUJUKAN GENOMIK DAN PENCIRIAN EMPAT STRAIN RHINOVIRUS-C MANUSIA DARIPADA PESAKIT MALAYSIA

Oleh

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Rhinovirus Manusia (HRV) merupakan salah satu virus pernafasan yang bertanggungjawab dalam jangkitan saluran pernafasan akut (ARTI). HRVs menjangkiti kedua-dua saluran pernafasan atas dan bawah, terutamanya di kalangan kanak-kanak. Pada permulaan, HRVs dikategorikan dalam dua kumpulan, iaitu HRV-A dan HRV-B. Satu strain HRV baru, iaitu HRV-C telah ditemui pada tahun 2006. Bilangan genom lengkap HRV-Cs dalam GenBank adalah amat terhad. Oleh itu, kajian ini dijalankan untuk menjujuk dan menciri genom lengkap HRV-C Malaysia. Empat sampel RNA HRV-C telah dikumpulkan daripada kanak-kanak yang menunjukkan tanda-tanda dan gejala-gejala pernafasan dalam Pusat Perubatan Universiti Malaya (PPUM). Penjujukan susunan kawasan VP4 / VP2 dalam kajian sebelum ini telah mengesahkan bahawa sample tersebut mengandungi HRV-C. Dua langkah tindak balas berantai polymerase telah dijalankan. Genom lengkap HRV-C Malaysia telah diamplifikasikan dengan menggunakan beberapa set primer yang telah diubahsuai dan direka semula. Perisian MEGA6 telah digunakan untuk membina pokok filogeni untuk memahami hubungan filogenetik HRV-Cs Malaysia. Ciri-ciri dan rekombinan HRV-C Malaysia ditentukan dengan menggunakan perisian RDP. Kira-kira 7.1 kbp empat genom lengkap HRV-C Malaysia telah dijujukkan. Semua gen dalam kawsan pengecod HRV-C Malaysia menunjukkan cirri-ciri genomik yang sama berbanding dengan HRV-C yang lain. HRV-C Malaysia menunjukkan penggunaan reseptor, tapak immnogenik dan tapak antivirus yang sama dengan HRV-C yang lain. HRV-C Malaysia diklasifikasikan sebagai HRV-C6, C22, C23 dan C42 berdasarkan penjujukan susunan VP4/VP2. Paras pemasangan-segi berjarak telah mengesahkan klasifikasi berdasarkan penjujukan susunan VP4/VP2. Tiga HRV-C Malaysia (C22, C23 dan C42) yang mewakili genom lengkap yang pertama telah berjaya dijujukan. Tiada rekombinan dapat dikenalpasti. Tekanan negative terpilih merupakan tekanan yang paling dominan dalam kawasan pengecod HRV-C Malaysia dan HRV-Cs yang lain. Kesimpulannya, kajian ini telah memberikan empat HRV-C genom lengkap yang akan memberikan pemahaman yang lebih baik dalam penjujukan berfungsi, peramalan penggunaan reseptor, struktur sekunder dan tekanan terpilih dalam HRV-C.

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I certify that a Thesis Examination Committee has met on 2 January 2015 to conduct the final examination of Khaw Yam Sim on his thesis entitled "Genomic Sequencing and Characterization of Four Human Rhinovirus-C Strains from Malaysian Patients" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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This is to confirm that:

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LIST OF ABBREVIATIONS

AEBA	Acute exacerbation bronchial asthma
AIC	Akaike information criterion
Bp	Base pair
C&S	Culture and sensitivity
Cre	*Cis*-acting replication element
CVB3	Coxsackievirus
dN	Rate of non-synonymous
dS	Rate of synonymous
E.coli	*Escherichia coli*
F	Forward primer
FEL	Fixed effects likelihood
G	Gamma
GG1	Genetic group 1
GG2	Genetic group 2
GSP	Gene specific primer
GTR	General Time Reversible
HEV	Enterovirus
HRV	Human rhinovirus
I	Invariant
ICAM-I	Intracellular adhesion molecule I
IFEL	Internal fixed effects likelihood
IRES	Internal ribosome entry site
LDLR	Low-density lipoprotein receptor
LFA-1	Lymphocyte function-associated antigen 1 adhesion
NASBA	Nucleic acid sequence based amplification
NCR	Non-coding region
NGS	Next generation sequencing
NPA	Nasopharyngeal aspirate
NPS	Nasopharyngeal swab
NTP	Nucleoside triphosphate
ORF	Open reading frame
PCBP2	Poly(rc)-binding protein 2
PCR	Polymerase chain reaction
Pol	Polymerase
PPT	Polypyrimidine tract
Pro	Protease
R	Reverse primer
RACE	Rapid amplification of cDNA ends
RMA	Respiratory multicode assay
rNTP	Ribonucleotide-5’ triphosphate
RDP	Recombination Detection Program
RT	Reverse-transcriptase
RT-PCR	Reverse-transcriptase polymerase chain reaction
SLAC	Single likelihood ancestor counting
TdT	Terminal deoxynucleotidyl Transferase
UMMC	University Malaya Medical Center
VPg	Viral protein genome-linked

CHAPTER 1

INTRODUCTION

Human rhinovirus (HRV) is first identified by Price (1956) using tissue culture methods. HRV is one of RNA respiratory viruses that recognized as a common cold pathogen that irritating human for over 50 years (Gern, 2010). HRV consists of more than 100 different serotypes and classified into several groups based on structural and biological properties. These classifications include phylogenetic relationships, receptor usage, threshold divergence of VP1 and VP4/VP2 genes sequence, immune cross reactivity and susceptibility towards capsid binding antiviral. Basically, HRVs are clustered into three groups, HRV-A, HRV-B and HRV-C. HRV-C was discovered in year 2006 due to the dramatic development of molecular diagnostics techniques (Kistler et al., 2007a; Lau et al., 2007; McErlean et al., 2007; Arden et al., 2006; Lamson et al., 2006). Unlike other HRVs, no suitable classical tissue culture system is available for cultivation of HRV-C (Bochkov et al., 2011; Lau et al., 2007). Hence, not many studies have been performed on the basic biological properties of this HRV. Recently, a study performed by Bochkov and his colleagues (2011) revealed the successful cultivation of two HRV-Cs using nasal tissue from sinus surgery. This vital breakthrough has catalyzed the explosive interest in HRV-C and revolutionized the understanding of this virus.

Since the discovery of HRV-C in year 2006, various studies demonstrated that HRV-C is accountable for severe respiratory diseases particularly in children worldwide including Asia (Fuji et al., 2011; Linsuwanon et al., 2009; Tan et al., 2009; Lau et al., 2007), Australia (Arden et al., 2010, McErlean et al., 2007; Arden et al., 2006), Africa (Smuts et al., 2011), America (Espinola et al., 2013; Dominguez et al., 2008; Kistler et al., 2007a; Lamson et al., 2006) and Europe (Rahamat-Langendoen et al., 2013; Renwick et al., 2007). Generally, HRV was found in nasal specimens such as nasal swab and nasopharyngeal aspirate. Despite nasal specimens, HRV-C has been detected in stool, pericardial fluid, urine and plasma from hospitalized child with pneumonia and acute pericarditis and also neonate with severe pneumonia and bronchoalveolar lavage (Broberg et al., 2011; Fuji et al., 2011; Tapparel et al., 2009a). Recently, remnant of HRV-C RNA was identified in stool specimens (Savolainen et al., 2013). These findings suggested that HRV-C infection is a systematic infection in human with severe respiratory tract disease. In addition, HRV-C has a closer relationship with HRV-A than HRV-B and higher occurrence of HRV-A and HRV-C than HRV-B has been reported in respiratory samples (Lau et al., 2010; Dominguez et al., 2008). Some researchers reported HRV-C may induce severe diseases compared to other HRVs (Kaida et al., 2011; Mak et al., 2011). HRV-C has its role to be dominant among HRV for causing severe human respiratory illnesses (Lee et al., 2012; Fuji et al., 2011; Smuts et al., 2011; Arden et al., 2010; Lau et al., 2009; Linsuwanon et al., 2009; Miller et al., 2009a Miller et al., 2009b; Lau et al., 2007; McErlean et al., 2007; Renwick et al., 2007; Lamson et al., 2006). For example, HRV-C has shown more frequent role in lower respiratory tract disease, febrile wheeze in infants and toddlers, and induced asthma exacerbations in older children (Lee et al., 2012; Bizzintino et al., 2011; Miller et al., 2009b; Wisdom et al., 2009; Lau et al., 2007).

Currently, there is no suitable anti-rhinoviral therapy available and it is still under extensive study. Vaccine development has only assured effectiveness against the homotypic HRV (Hyypia et al., 1998). HRV neutralizing antibodies bound to the capsid of this virion have been identified (Smith, 2001). This study showed that HRV capsid can be one of the targets to develop a vaccine against HRV. Moreover, antigenic peptides from 4 HRV capsid proteins particularly VP1 protein have been reported to have cross-immunogenicity between different serotypes (McCray and Werner, 1987). Several studies have proposed that VP1 protein may be considered as one of the potential HRV capsid region to develop HRV vaccine in the future (Edlmayr et al., 2011; Edlmayr et al., 2009). On the other hand, a wide range of potential viral therapy has been demonstrated to hinder the HRV infection in cell culture (*in vitro*) but not in human (*in vivo*). These viral therapies include natural anti-viral cytokine, anti-viral compounds blocking the infection site by stabilizing the capsid structure, interference with specific virus-host cell receptor and viral proteases. So far, pleconaril is the most successful antiviral example that showed that the effectiveness to reduce the duration and severity of HRV infections (Pevear et al., 2005; Zhang et al., 2004). However, not all the HRVs are susceptible to pleconaril. Ledford et al. (2004) demonstrated the relationship of amino acid within drug-binding pocket of HRV with pleconaril susceptibility. A minority group of HRV-B with a slightly distinct sequence in VP1 is found to be resistant to pleconaril. Moreover, most of the HRV-Cs partially display this type of characteristic and may be resistant to pleconaril. Hence, knowing the genetic information of HRV-C is important for drug and vaccine development.

HRV incidents in Malaysia were reported by Etemadi et al. (2013) and Chan et al. (2012). The clinical manifestations of Malaysian HRV infection and molecular typing have been discussed (Etemadi et al., 2013; Chan et al., 2012). The clinical symptoms were wheezing, asthma exacerbations, bronchiolitis, coryza and fever (Chan et al., 2012). Patients from Malaysia and worldwide showed a range of 26-30% HRV infection rate (Etemadi et al., 2013). A total of 28 HRV-C complete coding sequences were available in GenBank when this thesis was prepared. Due to the limited number of HRV-C complete genome, it hampers further understanding on HRV-C at a wider scale.

Objectives of the study

1. To sequence the complete genome of Malaysian HRV-C.
2. To determine the relationships of Malaysian HRV-Cs with those publicly available HRV-Cs.
3. To characterize the genomic features of Malaysian HRV-C
4. To determine the presence of recombination in Malaysian HRV-C.

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