UNIVERSITI PUTRA MALAYSIA

DISTRIBUTION OF CCL3L1 COPY NUMBER VARIABLE GENE AMONG THREE MAJOR ETHNIC GROUPS IN MALAYSIA

JALILAH JAMALUDDIN

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By

JALILAH JAMALUDDIN

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DISTRIBUTION OF *CCL3L1* COPY NUMBER VARIABLE GENE AMONG THREE MAJOR ETHNIC GROUPS IN MALAYSIA

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August 2017

Chairman : Suhaili Abu Bakar @ Jamaluddin, PhD
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C-C motif Chemokine Ligand 3 Like 1 (*CCL3L1*) is one of the copy number variable genes which clustered within the hotspot for segmental duplication at chromosome 17q12. Many studies from different populations reported that common range copy number of this gene are from 0 – 14 copies. Variable copies of this *CCL3L1* has been proven to correlate with a number of diseases such as Human Immunodeficiency Virus (HIV)-1 infection, tuberculosis (TB), Kawasaki disease, rheumatoid arthritis, Crohn's disease, Systemic Lupus Erythematosus (SLE), Hepatitis C and Psoriasis as this gene plays a crucial role in hosts defending and immunoregulatory process. However, investigation on the variable copies of *CCL3L1* in Asia region is less studied and there is no exclusive report from Malaysia which is known as multi-ethnicities country. Furthermore, Malaysia is also not exceptional to some of those diseases for examples Human Immunodeficiency Virus (HIV)-1 infection and tuberculosis. Hence, the finding of copy number associate to the related diseases should be carried out in Malaysia. Thus, the major aim of this study was to comprehensively examine the distribution of *CCL3L1* variable copies in reference Malaysian including three major ethnics; Malays, Indians and Chinese. The distribution of *CCL3L1* copy number between Malaysian and European populations were also compared. Paralogue Ratio Test (PRT) was performed in order to quantify the *CCL3L1* copies among 178 Malays, 125 Chinese and 90 Indian, and microsatellite analysis was used as a validation tool. PRT is capable of amplifying test and reference regions simultaneously in one PCR reaction by a set of primers. PCR products from PRT and microsatellites assays were then electrophoresed via capillary electrophoresis, and different length of fragments produced was analysed by Peak Scanner Software. One-way ANOVA and independent student T-test were used to analyse the data obtained. This study demonstrated that the *CCL3L1* copies were significantly different ($p<0.0001$) between three major ethnics; Malay, Chinese and Indian with the range of zero to eight copies, zero to ten copies, and zero to eight copies respectively. The mean (median) calculated for Malay, Chinese and Indian were 2.759 (2.869), 3.453 (3.290), and 2.437 (1.970) respectively. Additionally, Malaysian

population possess copy number of *CCL3L1* ranged from zero to ten copies and it was significantly varied when compared to the European population with the p-value of <0.0001. As the conclusion, *CCL3L1* copy number has shown a variation among three major ethnics in Malaysia and subsequently showed a significant difference when compared to the European population. This study offers a fundamental approach in investigating a correlation to susceptibility of related diseases in the future.

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

KELAZIMAN GEN *CCL3L1* YANG MEMPUNYAI PELBAGAI BILANGAN DI KALANGAN TIGA KUMPULAN ETNIK UTAMA DI MALAYSIA

Oleh

JALILAH BINTI JAMALUDDIN

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C-C motif Chemokine Ligand 3 Like 1 (*CCL3L1*) ialah satu daripada gen yang mempunyai pelbagai bilangan terkumpul dalam kawasan yang sentiasa mengalami segmen penduaan di kromosom 17q12. Banyak kajian dari pelbagai negara dengan julat antara 0 – 14 salinan. Kepelbagaian salinan gen *CCL3L1* ini telah dibuktikan berkait dengan beberapa penyakit tertentu seperti jangkitan Human Immunodeficiency Virus (HIV), batuk kering (tibi), penyakit Kawasaki, radang sendi, penyakit Chron, Lupus Eritematosus Sistemik (SLE), Hepatitis C and Psoriasis memandangkan gen ini memainkan peranan penting dalam pertahanan hos dan proses pengawalan imunisasi. Bagaimanapun, kajian terhadap kepelbagaian salinan gen *CCL3L1* di rantau Asia kurang dikaji dan tiada laporan eksklusif daripada Malaysia yang dikenali sebagai negara berbilang etnik. Tambahan pula, Malaysia tidak terkecuali mengalami penyakit seperti HIV dan tibi. Oleh itu, kajian terhadap kaitan bilangan dengan penyakit berkait perlu dijalankan di Malaysia. Maka, objektif utama kajian ini adalah untuk menyelidik secara menyeluruh pengagihan kepelbagaian bilangan salinan gen *CCL3L1* di kalangan penduduk Malaysia yang sihat termasuk tiga etnik utama; Melayu, India dan Cina. Taburan salinan gen *CCL3L1* antara penduduk Malaysia dan Eropah juga telah dibandingkan. Ujian berkadar paralog (PRT) telah dijalankan untuk mengira bilangan salinan gen *CCL3L1* di dalam 178 Melayu, 125 Cina dan 90 India, dan analisis mikrosatelit telah digunakan bagi mengesahkan bilangan salinan. PRT berkebolehan untuk menggandakan kawasan ujian dan rujukan secara serentak dalam satu reaksi PCR menggunakan satu set primer sahaja. Amplikon daripada PRT dan mikrosatelit kemudiannya dielektroforesis melalui kapilari elektroforesis dan perbezaan saiz fragmen yang terhasil dianalisa menggunakan 'Peak Scanner Software v1.0.' Ujian ANOVA dan ujian 'independent student T' telah digunakan untuk menganalisis data yang telah diperolehi. Kajian ini telah menemukan bilangan salinan *CCL3L1* telah menunjukkan perbezaan yang ketara ($p<0.0001$) antara tiga kumpulan etnik utama; Melayu, Cina dan India dengan masing-masing antara sifar ke lapan, sifar ke sepuluh dan sifar ke lapan bilangan salinan. Purata (median) telah dikira untuk Melayu, Cina dan India dengan

masing-masing menunjukkan 2.759 (2.869), 3.453 (3.290), dan 2.437 (1.970). Tambahan pula, penduduk Malaysia boleh memiliki dari sifar kepada sepuluh salinan terhadap bilangan *CCL3L1* dan hasil kajian juga menunjukkan perbezaan yang signifikan berbeza apabila dibandingkan kepada penduduk Eropah dengan nilai $p<0.0001$. Sebagai kesimpulan, gen *CCL3L1* menunjukkan kepelbagaian bilangan di antara tiga kumpulan etnik utama di Malaysia dan kemudiannya menunjukkan perbezaan yang signifikan apabila dibandingkan dengan penduduk Eropah.

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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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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

a-CGH	Array Comparative Genomic Hybridization
AASV	ANCA-associated small vasculitis
ADHD	Attention deficit hyperactivity disorder
AHR	Allelic Homologous Recombination
ANOVA	Analysis of Variance
AMY1	Salivary amylase
C4	Complement component 4
CCL3L1	C-C motif Chemokine Ligand 3 Like 1
CCR5	C-C Chemokine Receptor 5
CGH	Comparative Genomic Hybridization
CNV	Copy Number Variation
CYP2D	Cytochrome P450 family 2 subfamily D
DBMT1	Deleted malignant brain tumors 1
DEFB	Beta defensin
DNA	Deoxyribonucleic Acid
ECACC	European Collection of Authenticated Cell Cultures
FCGR	Fc fragment of IgG receptor
FISH	Fluorescence *in situ* Hybridization
FoSTeS	Fork Stalling and Template Switching
HIV	Human Immunodeficiency Virus
HRC	Human Random Control
Indels	Insertions and Deletions
LTR	Long Terminal Repeat
NAFLD	Non-alcoholic fatty liver disease
NAHR	Non-allelic Homologous Recombination
NGS	Next Generation Sequencing
NHEJ	Non-homologous End Joining
MIP	Macrophage inflammatory protein
PCR	Polymerase Chain Reaction
PRSS1	Protease serine 1
PRT	Paralogue Ratio Test
qPCR	Real time Quantitative PCR
SLE	Systemic Lupus Erythematosus
SNCA	Alpha-synuclein
SNP	Single Nucleotide Polymorphism
STR	Short Tandem Repeat
TB	Tuberculosis
UGT2B	UDP glucuronosyltransferase family 2 member B

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Genetic variations is termed as diversity of DNA between individuals, which occur within human genome in multiple forms including single nucleotide polymorphism (SNP), inversion, translocation, microsatellite and copy number variation (CNV), which make us unique from each other (Feuk et al., 2006; Griffiths et al., 2000). SNP is a variation of single base in DNA sequence and associated with most common diseases as results from missense, nonsense and frameshift. However, the discovery of variation involved in CNV has changed the perspective towards genetic variation. (Ku et al., 2010; Zhang et al., 2009; Feuk et al., 2006; Schork et al., 2000).

Researchers discovered at least 12% of the human genome comprises with the CNVs, which has been defined as variation in copy number of genetic materials (1 Kbp or larger) when compared to a reference genome (McCarroll & Altshuler, 2007; Feuk et al., 2006; Sharp et al., 2005; Bailey, 2002). In view of health aspect, CNVs have a higher tendency towards missense mutations or frameshifts as a result of deletion or duplication of exon materials in the DNA sequence without apparent phenotypic effect (de Smith et al., 2008). However, these alteration is a significant key to the structural genomic diversity, and most of the genes with CNV show relationship towards certain disease (Zhang et al., 2009; Wain et al., 2009; Sharp et al., 2005).

Many genes with CNV have been identified and quantified such as beta-defensin (*DEFB*), alpha-synuclein (*SNCA*), Fc fragment of IgG receptor III (*FCGR3*) and salivary amylase gene (*AMY1*). C-C motif Chemokine Ligand 3 Like 1 (*CCL3L1*) is one of the interesting genes with CNV to be explored. *CCL3L1* is located on the chromosome 17q12, encode for macrophage inflammatory protein (MIP) 1α, which is a chemokine that involves in a variety of immune cells and plays a part in anti-tumour immunity (Kouno et al., 2004; Modi, 2004). Different common range of *CCL3L1* copy number observed among populations such as zero to four copies in United Kingdom (Carpenter et al., 2011; Walker et al., 2009), zero to six copies in America (Carpenter et al., 2014), zero to fourteen copies in Africa (Carpenter et al., 2014; Gonzalez et al., 2005), zero to ten copies in China (Li et al., 2012), one to nine copies in Korea (Kim et al., 2012), and zero to ten copies in Japan (Nakajima et al., 2007). Thus, it is worth to identify the frequency copy number of this gene in Malaysia population as well. Besides that, in order to achieve the association of *CCL3L1* towards related diseases, a baseline information of this gene in Malaysian population must first be established.

Furthermore, changes in *CCL3L1* copy number was found to be associated with Human Immunodeficiency Virus (HIV) 1 infection (Huik et al., 2010; Kulkarni et al., 2008; Shalekoff et al., 2008; Nakajima et al., 2007; Gonzalez et al., 2005), Systemic Lupus Erythametosus (SLE) (Mamtani et al., 2008), tuberculosis (TB) (Mamtani et al., 2011),

and rheumatoid arthritis (Ben Kilani et al., 2016; McKinney et al., 2008), thus it is interesting to find out if there is a similar association in reference Malaysian population according to ethnicities and generate a possible relationship to these diseases.

In order to determine the *CCL3L1* copy number, there are numerous methods available including SNP array technologies, Next Generation Sequencing (NGS), Fluorescence *in situ* hybridization (FISH), Real-time quantitative polymerase chain reaction (qPCR), and Paralogue Ratio Test (PRT) (Ceyhan-Birsoy et al., 2016; Walker et al., 2009; Perry et al., 2007; Gonzalez et al., 2005). In this study, PRT and microsatellite analysis were used to measure *CCL3L1* copy number among three major ethnics in Malaysia; Malay, Chinese and Indian. The PRT assay was designed specifically to amplify test and reference loci simultaneously by only a single pair of primer (Armour et al., 2007). PRT showed accuracy in measuring the copy number with the minimum amount of DNA required is 10 ng per reactions (Walker et al., 2009).

Furthermore, PRT is a system that offers a very simple, rapid, yet inexpensive method for quantifying copy number, compatible for application to genotype more than thousands of samples (Armour et al., 2007). As for the additional support to confirm the accuracy and validate the copy number measured by PRT, microsatellite analysis was introduced. The agreement between these two approaches; PRT and microsatellite analysis should be able to confirm the final copy number calling from the investigation (Walker et al., 2009). The results of frequency among the ethnics were further analysed using One-Way ANOVA to obtain the significant value and independent student T-test to compare between Malaysian and European population.

1.2 Problem Statement

Malaysia is one of the multi-ethnic countries, so does *CCL3L1* copy number will be differ significantly among three major ethnics in the Malaysian population? Based on data recorded in Malaysia, it showed that most of HIV, SLE and rheumatoid arthritis cases reported were from Malay, Chinese and Indian respectively (HIV/STI Sector, Division of Disease Control, 2017; Shaharir et al., 2016; Shahrir et al., 2008). Thus, this may indicate that each of major ethnic groups in Malaysia has a different susceptibility towards diseases related to *CCL3L1* which is valuable to be explored in future studies.

In fact, there are lack of reports that demonstrated copy number of *CCL3L1* from Malaysian population. If the *CCL3L1* is found to be variable in Malaysia, then does it follow the other populations with a similar range of copy number? As previous findings showed that there is different copy number among populations observed for example zero to four copies in United Kingdom (Carpenter et al., 2011; Walker et al., 2009), zero to ten copies in China (Li et al., 2012) and one to nine copies in Korea (Kim et al., 2012). Thus, it is important to identify the copy number of *CCL3L1* in Malaysia as well. Hence, it is worth and important to have the information of this gene in Malaysia population as a baseline platform for further investigation towards related diseases in the future.

1.3 Significance of Study

This is the first report in quantification of *CCL3L1* copy number among three major ethnics (Malay, Chinese and India) and provide a more understanding of population genetic diversity among ethnicities. Besides that, the variability of *CCL3L1* copy number has been proven to vary in different populations but such information is yet to be reported in Malaysia. Hence, findings from the current study will redound to the benefit of information in genetic variation based on population especially copy number variable database.

Indeed, this study will help other researchers to further investigate related diseases through case-control study as this study offers a fundamental starting point. In future, a correlation achieved by existence of the gene variable copies towards disease susceptibility between ethnics may be proven and potentially be considered as a risk assessment approach. Ultimately, the information on the number of gene copies per individual can be used as a personalised treatment in the future, in which it is considered to be more economical. In addition, the current study may also strengthen the reliability of the PRT assay in quantifying copy number of *CCL3L1* in the Malaysian population.

1.4 Objectives

1.4.1 General Objectives

The aim of this study was to investigate the distribution of *CCL3L1* copy number among three major ethnics; Malay, Chinese, and Indian and also as Malaysian population.

1.4.2 Specific Objectives

1.4.2.1 To establish *CCL3L1* copy number typing in the three major groups of Malaysia.
1.4.2.2 To identify and compare the frequencies of *CCL3L1* copy number in the three major ethnic groups of Malaysia.
1.4.2.3 To compare the frequencies of *CCL3L1* copy number between Malaysian and European population.

1.5 Hypothesis

This study hypothesized that the copy number of *CCL3L1* varies significantly among Malay, Chinese and Indian ethnicities from Malaysia. Furthermore, distribution of *CCL3L1* copy numbers in Malaysian is different significantly when compared to the other populations.

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