

Analysis of Transmission Route of MERS Coronavirus Using Decision Tree and Apriori Algorithm

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Abstract— Middle East Respiratory Syndrome, which is a respiratory disease caused by MERS coronavirus, is known to be an endemic disease spread in Kingdom of Saudi Arabia, or KSA. On May 20, 2015, it has massively occurred in Republic of Korea, with 186 confirmed cases, 36 deaths. In this paper, we analyzed some features of MERS-CoV's transmission route by a new molecular approach. We have collected DNA sequences of MERS-CoV from 15 different regions in the world, including some regions of KSA. We have converted the DNA sequences into amino acid sequences and used Apriori and Decision Tree Algorithm to found the similarities and differences between different MERS-CoVs' amino acid sequences. Then, we drew some conclusions about MERS's transmission routes by using these results.

Keywords—Middle East Respiratory Syndrome, MERS, Apriori, Decision Tree Algorithm, transmission route, epidemiological investigation

I. Introduction

Middle East Respiratory Syndrome (MERS) was first reported in Saudi Arabia in 2012. The pathogen was MERS coronavirus, an RNA virus in the family of Coronaviridae [1]. On May 20, 2015, a MERS patient was confirmed in Republic of Korea, which, by July 26, within about two months, caused 186 confirmed cases, with 36 deaths [2][3].

In past cases of MERS-CoV in Saudi Arabia, the transmissions were isolated and managed [3], which, however, changed in the outbreak in Korea. In Korea, the contagion of MERS-CoV was fast through hospital-hospital transmission [2], making it important to get information about how the MERS-CoV is transmitted and the route of transmission.

In previous researches, to identify the genome of MERS-CoV, RNAs extracted from collected samples of MERS-CoV were subjected to RT-PCR amplification and fragments from this process were sequenced [4]. The sequenced RNAs and RNAs that are previously published were gone through phylogenetic analysis and distance calculations by using Molecular Evolutionary Genetics Analysis (MEGA) software, version 5 [4][5]. Also, genetic divergence between the samples was analyzed by Bayesian inference with the use of MrBayes version 3.2.1 [5].

It has been identified that MERS-CoV infections are resulted from zoonotic transmission from the animal reservoir to humans and that the intermediate animal host is the Arabian Camel, *Camelus Dromedarius* [4][6].

Genetic diversity of various samples of the virus from many different regions of KSA is analyzed in previous researches [5]. However, the route of transmission and genetic divergence between the virus of KSA and various parts of the world have not been studied. Moreover, data from recent outbreak of MERS in Republic of Korea is not included in many researches.

In this research, we identified genetic differences of 15 different RNA sequences of MERS-CoV by using 2 algorithms, which are Decision Tree and Apriori. Then we analyzed and drew the route of transmission of MERS CoV from The Kingdom of Saudi Arabia, or KSA, to the world.

II. Materials and Methods

A. Pathogenesis of MERS-CoV

On September 2012, MERS-CoV, the Middle East respiratory syndrome coronavirus was isolated from a patient using a pancoronavirus reverse-transcriptase polymerase chain reaction (RT-PCR) assay [7]. The disease causes hyperthermy, cough, acute respiratory tract infection and multiorganic disfunction that may lead the infected individuals to death [8]. Several studies show that the infection causes acute pneumonia and renal failure and that most patients developed respiratory problems [9]. Other effects include abdominal disorders, inflammation of the pericardium, consumptive coagulopathy, increase in leukocytes and neutrophils, and low blood levels of albumin [9].

B. Transmission of MERS-CoV

Based on phylogenetic studies, MERS-CoV infection was initially thought to spread by zoonotic events via bats [10]. However, serological study indicated that MERS-CoV takes the Arabian Camel, *Camelus Dromedarius* as its intermediate host [11][12].

MERS-CoV enters the host through its spike protein, a type I transmembrane glycoprotein made up of 1353 amino

acids that is located on the virion surface [13]. It is subsequently recognized by cluster of differentiation 26 (CD26), which facilitates the infection of the host cells [14].

C. Apriori Algorithm

Apriori is an algorithm that is used for association rule mining and frequent item set mining [15]. Analyzing transactional databases, the algorithm finds association rules in the data [16]. The first procedure is to count the frequency set of data, which is followed by finding the minimum support value and generating the candidate set. It repeats the procedure of counting and setting candidate set. Using the Hash tree structure and breadth-first search allow the algorithm to count candidate item sets efficiently [17]. From item sets of length $k-1$, it makes candidate item sets of length k and eliminates candidates with an infrequent sub pattern [17]. According to downward closure lemma, those candidate sets includes all frequent item sets of k -length [17]. Then the algorithm scans the transaction database and determines frequent item sets. The algorithm continues analyzing until there are no further successful extensions [17]. In this algorithm, "Accuracy" is computed from two essential concepts "Support" and "Confidence" [16]. DNA sequences are highly appropriate data sets for apriori, compared to various kinds of data [16].

D. Decision Tree Algorithm

Decision tree is an algorithm that represents proceedings for assessing or grouping an interesting item with graphical means. It expresses function by mapping an applicable realm's constituent to a relevant range of constituent with characters or figures that represents a class [18]. At the tree's inner node, it finds a text which outputs in possible small degree. Divided by the result of each test, it reaches a leaf that includes a class character or figure which corresponds to a desirable item. Each leaf shows the number of examples of each class that falls on the leaf. These leaves are often not just one class, thereby choosing the class characters that occur most frequently [19]. The nodes spread to both sides, starting from root decision node, a branch that represents several emulous options usable for the decision makers. By the tip of these first branches, there is an end node or an uncertainty node. The end node shows a fixed value. It expresses the possible consequences as well as each of their probabilities. Above these first uncertainty nodes' branches, there might be more root decision nodes and more uncertainty nodes, which commonly take turns until respective way ends in an end node [20].

III. Results

A. Apriori Algorithm

The result analyzed by apriori algorithm expresses this kinds of patterns. (**Position=amino**)

MERS coronavirus in South Korea

1. amino5 is L 200
2. amino2 is L 195
3. amino8 is L 194
4. amino1 is L 190
5. amino3 is L 189
6. amino6 is L 187
7. amino7 is L 186
8. amino9 is L 186
9. amino4 is L 183

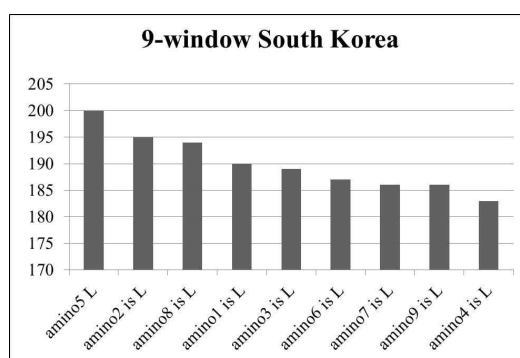


Figure 1. 9-window South Korea MERS-CoV amino sequence.

Figure 1 shows the analyzed result of MERS CoV of South Korea that has been yielded with 9 windows. In 9, 13, and 17 windows, 114, 168, and 253 rules were found respectively, adding up to 535 rules in total. We took the data of the most representative rule in each virus and each window to find similarities between the sequence patterns of the viruses.

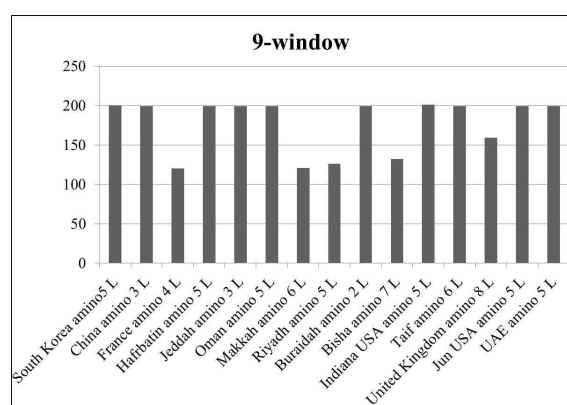


Figure 2. 9-window MERS-CoV amino sequence.

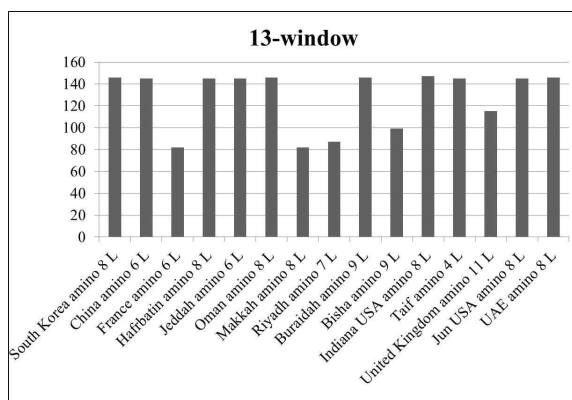


Figure 3. 13-window MERS-CoV amino sequence.

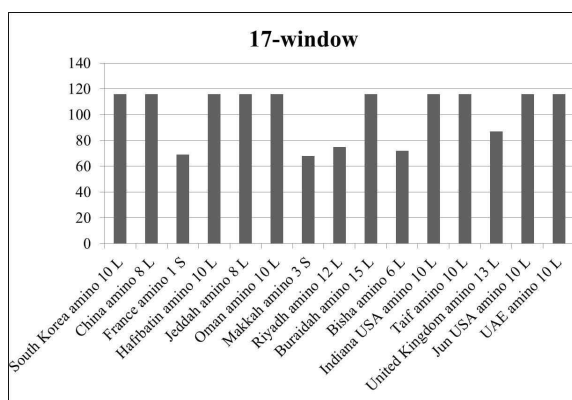


Figure 4. 17-window MERS-CoV amino sequence.

Figure 2, 3, and 4 is the analyzed data of 15 viruses under 9, 13, 17 window. 9 window: South Korea amino 5 Leucine, China amino 3 Leucine, France amino 4 Leucine, Hafribatin amino 5 Leucine, Jeddah amino 3 Leucine, Oman amino 5 Leucine, Makkah amino 6 Leucine, Riyadh amino 5 Leucine, Buraidah amino 2 Leucine, Bisha amino 7 Leucine, Indiana USA amino 5 Leucine, Taif amino 6 Leucine, United Kingdom amino 8 Leucine, Jun USA amino 5 Leucine, UAE amino 5 Leucine. 13 window: South Korea amino 8 Leucine, China amino 6 Leucine, France amino 6 Leucine, Hafribatin amino 8 Leucine, Jeddah amino 6 Leucine, Oman amino 8 Leucine, Makkah amino 8 Leucine, Riyadh amino 7 Leucine, Buraidah amino 9 Leucine, Bisha amino 9 Leucine, Indiana USA amino 8 Leucine, Taif amino 4 Leucine, United Kingdom amino 11 Leucine, Jun USA amino 8 Leucine, UAE amino 8 Leucine. 17 window: South Korea amino 10 Leucine, China amino 8 Leucine, France amino 1 Serine, Hafribatin amino 10 Leucine, Jeddah amino 8 Leucine, Oman amino 10 Leucine, Makkah amino 3 Serine, Riyadh amino 12 Leucine, Buraidah amino 15 Leucine, Bisha amino 6 Leucine, Indiana USA amino 10 Leucine, Taif amino 10 Leucine, United Kingdom amino 13 Leucine, Jun USA amino 10 Leucine, UAE amino 10 Leucine.

According to the results, the 15 viruses share similar sequences based on the fact that every rule is related to Leucine, except that 17-window France and Makkah viruses include rules that express Serine. This result indicates that these viruses, despite the differences, have significant similarities, which make same symptoms in humans and make them as one species. However the viruses also display considerable differences, which will be analyzed using Decision Tree.

B. Decision Tree Algorithm

We converted gene sequences of 15 different MERS-Cov viruses that broke out in 15 distinct places around the world into amino acid sequences corresponding to each codon of the genome. We then analyzed the samples with Decision Tree Algorithm by using see 5.0 program from www.rulequest.com and drew a diagram of biological correlation between the viruses based on the data (Figure 5).

Table IV of the Appendix shows the index of similarity between 15 MERS-CoVs' amino acid sequence by compiling statistics on various rules extracted using decision tree algorithm, under 9 Window. From this data, we were able to discover mutational relationship among the viruses and infer their biological correlation, which is presented in Figure 5.

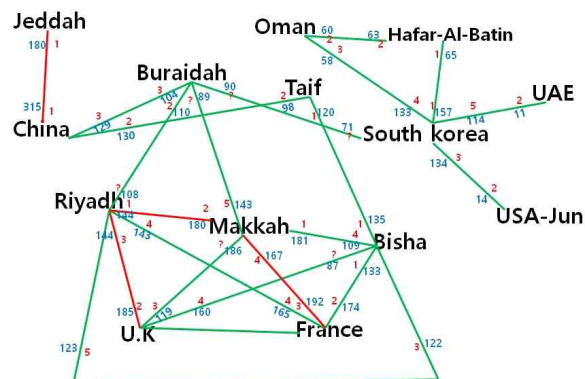


Figure 5. Mutational relationship between MERS-CoVs around the world

According to Table IV of the Appendix, MERS-CoV viruses of Makkah (column g), Riyadh (column h), and Bisha(column j) generally show high similarity with other classes of MERS-CoV viruses, which indicates that MERS-Cov first broke out in Middle East, and that these three regions can be an original source of MERS-CoV viruses that broke out in foreign countries. The figures of France (column c) and U.K. (column m) are also particularly high, showing that these MERS outbreaks were directly resulted from the three regions, the original source of MERS-CoV virus. Specifically, the amino acid sequence between France and Makkah, U.K. and Riyadh shows relatively high interrelationship. This fact can be a proof that the MERS-CoV of U.K. and France mutated directly from Makkah and Riyadh MERS-CoV.

In general, the amino acid sequences of Makkah, Riyadh, France, U.K, Bisha are highly analogous with a few

differences, which leads to a conclusion that the four viruses would probably share a great extent of biological inheritance.

TABLE 1. RULE EXTRACTION UNDER 9 WINDOW

Region of the virus	Rule
Jeddah	Position 1=R Position 2=V Position 5=I
China	Position 1=R Position 2=V Position 5=F

This is an especially noticeable result. Table I shows the rules for Jeddah (column e) and China (column b) MERS-CoV's amino acid sequence. According to the table, two viruses share the two same rules, the rule pos1=R and pos2=V shown in both column e and b amino acid sequence. And according to Table IV, Jeddah and China viruses have the highest correlation with the largest similar figures. Consequently, we inferred that the two MERS-CoV viruses derived from two highly analogous viruses or just one virus.

We also used results under Window 13 and 17 to prove the conclusions we drew using results of Window 9. Table V and VI of Appendix show the index of similarity among 15 MERS-CoVs' amino acid sequence under Window 13 and 17.

In the Table V, the fact that columns of MERS CoVs from Makkah (column g), Riyadh (column h), and Buraidah (column i) has figures that are much higher than any other columns proves the fact that these three regions are the biological center of various MERS-CoV. This result gets even more conclusive with the results under Window 17. According to the Table VI, the center columns from Table IV and V (g, h, and i) also have bigger figures in results of Window 17.

In the column c (France) and column m (U.K.) of Table V, it is well shown that correlation between these regions and center regions (g, h) is strong. It is also noticeable that mutual correlation between U.K. and France are established. These tendencies are also well shown in the result in Table VI. These individual facts prove the conclusion that the outbreaks of MERS in England and France were caused from the center regions, which are Makkah, Riyadh, and Buraidah.

TABLE 2. RULE EXTRACTION UNDER 13 WINDOW

Region of the virus	Rule
Jeddah	Position 1 = C Position 8 = B
China	Position 4 = S Position 8 = N Position 10 = M

TABLE 3. RULE EXTRACTION UNDER 17 WINDOW

Region of the virus	Rule
Jeddah	Position 3 = I Position 17 = L
China	Position 11 = A Position 13 = A Position 15 = L

As we did with the results under Window 9, we tried to find corresponding rules between Jeddah and China that were extracted under Window 13 and Window 17. Table II and Table III show the results of rules extracted under Window 13 and Window 17 with the highest frequency. They do have differences, but with low frequency, (which was lower than 0.7), so, it is hard to say that these rules are extracted properly and represent the whole sequence. Rather, figures in Table V and VI show that MERS from Jeddah and China are considerably correlated to each other since the figure of row e is exclusively high in column b and vice versa, which provides the conclusion that MERS-CoV from Jeddah and China has a similar biological background and could be from same MERS-CoV type.

IV. Discussion

Since MERS coronavirus is an endemic disease and was first detected just a few years ago, it has not been internationally studied in depth. Consequently, it resulted in commotion when it battered South Korea in 2015. Specifically, the transmission route of MERS coronavirus has not been discovered yet [21]. In many cases of serious outbreaks like this, for instance Ebola outbreak, researchers use transmission dynamics or epidemiology to determine the transmission route and to prevent further damages. They use mathematical modeling or population data to identify the features of transmission [22] [23]. Apart from these methods, we discovered features of the transmission route with a new molecular approach by analyzing DNA sequences of various types of the virus. In detail, we collected the DNA sequence from the sites of MERS outbreak and the regions where the virus was spread, and then we converted the sequences to the form of protein and investigated similarities and differences using Apriori algorithm and Decision Tree. As a result, we made some achievements including finding the three biological center regions of MERS transmission in Kingdom of Saudi Arabia, and we believe this new method of epidemiologic investigation can be applied in studying other infectious diseases.

However, since we had to analyze the data from two algorithms ourselves, without any help of a program, there might be some data that has not gone through meticulous analysis and the results that we found are speculations at best. Therefore, more algorithms that analyze data from Apriori and Decision Tree Algorithms would be required. In addition, the validity and certainty of this new epidemiologic method should be verified by further research. We hope that this new method

will be widely used for epidemiologic research of various diseases and contribute to hygienic improvement of mankind.

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Appendix

TABLE 4. Index of Similarity Among 15 MERS-CoV Viruses' Amino Acid Sequence under 9 Window

	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o
a	67	116	149	65	30	58	109	103	90	66	12	79	147	14	11
b	74	72	113	39	180	24	100	101	104	83	2	98	117	7	2
c	15	99	177	15	20	12	167	143	94	133	2	73	159	3	1
d	157	93	151	33	22	60	111	98	77	55	17	76	151	5	9
e	55	375	95	22	21	17	99	89	79	69	2	67	109	4	3
f	133	107	147	63	28	11	105	96	99	79	14	80	131	16	7
g	29	85	172	16	16	14	168	164	89	107	2	65	176	1	0
h	36	85	165	7	26	16	180	150	78	122	1	59	185	2	2
i	71	129	135	29	41	26	143	108	110	83	6	88	139	4	3
j	35	92	174	18	18	13	181	123	81	83	1	120	160	5	9
k	142	98	155	56	27	44	103	106	88	54	2	75	147	10	9
l	69	130	121	34	21	23	128	100	114	135	5	92	133	5	4
m	56	108	132	19	32	19	113	144	86	87	4	82	218	9	4
n	134	95	137	61	32	52	124	99	94	58	11	83	120	4	12
o	114	120	139	54	27	64	112	94	85	57	13	77	143	12	5

TABLE 5. Index of Similarity Among 15 MERS-CoV Viruses' Amino Acid Sequence under 13 Window

	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o
a	88	64	82	59	16	29	72	95	90	37	6	41	91	0	2
b	63	70	71	26	139	11	66	74	69	48	0	59	76	1	0
c	30	65	112	9	11	4	99	119	63	82	3	43	130	0	1
d	153	65	77	22	14	18	68	86	67	60	9	43	89	1	0
e	53	286	47	18	13	8	55	65	56	52	0	34	77	1	1
f	149	85	68	46	10	7	64	98	86	40	8	36	72	1	3
g	29	52	113	8	12	4	113	115	63	91	3	40	121	1	0
h	33	61	112	7	8	10	103	128	58	82	7	56	105	0	1
i	67	91	80	20	15	13	93	94	86	55	6	70	79	3	0
j	30	68	91	15	12	8	96	117	64	83	1	82	103	1	0
k	152	72	61	42	3	27	72	95	74	42	2	49	77	2	3
l	66	81	91	11	20	6	89	82	89	103	0	59	72	2	0
m	43	83	96	14	11	9	77	103	79	64	1	56	133	1	0
n	134	65	59	51	12	28	64	92	76	45	8	54	84	0	1
o	139	70	66	47	14	17	64	89	92	48	8	47	69	3	0

TABLE 6. Index of Similarity Among 15 MERS-CoV Viruses' Amino Acid Sequence under 17 Window

	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o
a	52	70	64	25	17	26	52	61	81	60	3	2	75	3	0
b	40	60	60	6	146	7	44	74	68	23	2	1	58	2	0
c	21	48	111	11	12	5	81	86	61	73	0	1	79	0	0
d	121	71	61	17	13	10	49	56	45	53	3	2	81	6	3
e	38	227	63	6	12	7	34	60	56	29	0	2	50	2	0
f	105	76	53	32	11	7	55	50	68	54	2	1	74	1	2
g	29	54	103	7	8	5	90	77	59	72	1	3	77	0	0
h	22	59	97	6	10	2	90	81	60	64	2	1	94	2	0
i	56	70	79	10	24	6	63	56	84	48	1	4	86	2	1
j	50	61	103	14	8	4	73	77	51	48	5	2	92	1	1
k	111	69	60	25	23	17	45	51	57	51	0	1	73	7	1
l	118	63	55	25	15	11	68	38	60	58	2	3	64	7	3
m	33	74	76	14	15	6	70	77	56	40	0	5	121	1	1
n	109	79	68	21	13	18	49	54	60	49	3	3	63	0	2
o	95	68	68	29	8	18	55	52	55	57	2	4	74	4	2

Indexes

a: South Korea
b: China
c: France
d: Hafar Al-Batin, Kingdom of Saudi Arabia
e: Jeddah, Kingdom of Saudi Arabia
f: Oman
g: Makkah, Kingdom of Saudi Arabia
h: Riyadh, Kingdom of Saudi Arabia
i: Bisha, Kingdom of Saudi Arabia
j: Buraidah, Kingdom of Saudi Arabia
k: Indiana, United States of America
l: Taif, Kingdom of Saudi Arabia
m: United Kindom
n: Florida, United States of America
o: United Arab Emirates