

## Genetics and epidemiology of Middle East Respiratory Syndrome-Coronavirus (MERS-CoV)

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### ABSTRACT

**Background and aims:** Middle East respiratory syndrome (MERS) is a viral respiratory illness caused by a coronavirus. After the primary onset of MERS in Saudi Arabia, in September 2015 cases began to increase. The number of laboratory-affirmed cases by MERS-CoV in the Middle East has been being increased recently.

**Methods:** In this current review article, by using the terms “MERS” and “coronavirus” we first searched for English language articles in the PubMed database, published in last five years. Then by a detailed review of related articles, we provided a comprehensive information about epidemiology, genetic, host and coronavirus treatment.

**Results:** More importantly, evidences of human-to-human transmission in Europe and America indicate that the viral adaptations in humans may precede a large-scale epidemic. The genome of Coronaviruses is a linear positive-sense single stranded large RNA and they are enveloped viruses that have a helical symmetric nucleocapsid. Some new insights have been provided in previous few months in to the animal Coronavirus hosts, transmissibility, contagion of MERS Co-V and ideal laboratory diagnostic methods.

**Conclusion:** It seems crucial to control this new human infection “MERS-CoV” by collaborating global and local health authorities and their continual support for further research on it.

**Keywords:** Middle East respiratory syndrome, Coronavirus, Transmission.

### INTRODUCTION

Middle East Respiratory Syndrome (MERS) is a respiratory infection caused by MERS-Coronavirus (MERS-CoV) and is known to be new to humans.<sup>1</sup> The infection was at first assigned HCoV-EMC2 however after worldwide agreement it was renamed to MERS-CoV.<sup>2</sup> MERS-CoV is genetically linked to obtained sequence from bats originated from Europe, Africa, Asia and Middle East.<sup>3</sup> The most common symptoms of

MERS are shortness of breath (48%), cough (87%), fever (87%) and gastrointestinal symptoms (35%) and patients develop acute respiratory illness.<sup>4</sup> Studies performed on cases identified in family clusters in Saudi Arabia hospitals.<sup>4-6</sup> and some European countries.<sup>7,8</sup> also demonstrate that every person with MERS-CoV can show different respiratory and non-respiratory symptoms. This disease was first reported by health

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officials in the eastern province of Saudi Arabia in September 2012.<sup>9</sup> After a short time a patient with acute respiratory illness caused by the same virus was identified in London.<sup>7</sup> There was an outbreak of MERS infection in April 2014 in Saudi Arabia where 688 individuals has been infected and 282 MERS related deaths have been reported.<sup>10</sup> Shortly thereafter, some new cases were identified in United States, South Korea, Philippines and United Kingdom. The WHO reported 1227 laboratory confirmed MERS cases and 449(39%) MERS related deaths from September 2012 to 10 March 2015.<sup>11</sup> It is worthy to note that the worldwide health and economy have been affected by outbreak of MERS. In addition, the global health and economical outcomes of MERS prevalence may be decreased by employing anticipating approaches.<sup>12</sup>

After the primary onset of MERS in Saudi Arabia, in September 2015 cases began to increase due to hajj pilgrimage.<sup>13</sup> While a total number of 1029 infected cases and 452 MERS related deaths have been reported in Saudi Arabia,<sup>14</sup> there were only two diagnosed cases in United States with no death. The first case diagnosed for MERS in the U.S was confirmed on May 2, 2014 by Center of Disease Control and Prevention (CDC) in a man who had been in Saudi Arabia one week earlier. The second patient was identified on May 12, 2014 in Florida.<sup>15,16</sup>

After a short time in May 14, 2014 the first case was reported in Netherlands. The first case in South Korea was identified in May 2015. A number of 19 individuals in South Korea had MERS and 184 cases reported with infection.<sup>17</sup> Another report indicated the infection of 74 persons with 10 MERS related death in United Arab Emirates.<sup>18</sup> A total of 19 infected cases and 6 related death was also reported in March 12, 2015 in Jordan.<sup>19</sup> After Jordan, officials of Qatar reported 10 CoV infected individuals with 40% fatality in March 2015.<sup>20</sup> Iran

ranked in 7th position in WHO's report because of 5 infected person and 2 death.<sup>21</sup> Other countries like United Kingdom, Germany, Kuwait, etc. reported less than 5 infected cases. Because of MERS transmission by infected person's respiratory secretions, it is not surprising that its prevalence is much higher in neighboring area in Middle East than other regions.<sup>22</sup>

The genome of Coronaviruses is a linear positive-sense single stranded large RNA and they are enveloped viruses that have a helical symmetric nucleocapsid. The Coronaviruses genomic size is about 26 to 32 kilobases which encodes both structural and non-structural proteins including one structural nucleocapsid protein and one non-structural protein (NSP2) responsible for the viral RNA synthesis.<sup>23</sup> There is a methylated nucleotide cap in 5'-end of its genome and the 3'-end has a poly A sequence. Six various strains of Coronaviruses are currently known to infect humans, however, the molecular clock analyses have not been able to identify MERS-CoV ancestors.<sup>24</sup> Coronavirus uses full-length minus-strand process for genome replication. Transcription of this virus is really complicated and begins with interruptive extension of mRNAs that contains 5' and 3' end sequences.<sup>25</sup> Coronavirus Genomic RNA encodes for ORF1a and ORF1b, after translation by ribosomal frame shifting proteins pp1a and pp1ab are processed into the viral polymerase (RdRp) and other non-structural proteins involved in RNA synthesis. Structural proteins are expressed as subgenomic RNAs. Each RNA (genomic and subgenomic) is translated to yield only the protein encoded by the 5'-ORF.<sup>26</sup>

These types of viruses were first extracted from chicken in 1973. In addition to human, this virus can infect birds, cats, dogs, pigs and rodents. Dipeptidyl peptidase 4 (DPP4, CD26) has been identified as a cellular receptor for MERS-CoV.<sup>27</sup> The kidney and lung pathology

of infection is consistent with distribution of this receptor in mammalian tissues.<sup>27</sup> Upper respiratory and gastrointestinal tract of mammals and birds are the first targets of infection.<sup>28</sup> Epithelial cells are most common target for Coronaviruses but they also can target macrophages and other distributed cells. Coronavirus uses endocytosis mediated methods in host cells after attachment to the S protein of host receptors. After fusion of virus membrane with endosomal membrane mediated by S2 protein, the RNA genome of virus is released into cytoplasm. After replication and transcription of structural and non-structural proteins new virions release by exocytosis.<sup>29</sup>

Nowadays, no specific therapy or vaccine has been identified for Corona-Virus related infections.<sup>30</sup> However the factors that were used during SARS epidemic of 2003, might be useful against the related MERS coronavirus. The clinical experience from SARS proposes that various mediations including broad spectrum antiviral ribavirin with and without corticosteroids, interferon alfa with corticosteroids, ribavirin with lopinavir and ritonavir, and convalescent plasma may improve the outcome in patients. In most viral infections, the timing of the start of antiviral factors is serious.<sup>31</sup> One of the recent studies compared oseltamivir effect against ribavirin and reported no significant response to ribavirin, however, the treatment were started after 10-14 days of side effects which may have prompted to the poorer outcomes.<sup>32</sup> According to a number of studies, it seems that the use of ribivirin in appropriate time, may improve the outcome and decrease MERS related mortality.<sup>33</sup>

## CONCLUSION

The appearance of MERS-CoV highlighted the importance of Coronaviridae family as human pathogens. Two highly pathogenic Coronaviruses have been identified in china; SARS-CoV (2003) and

MERS-Cov (2012), both widely spread and caused considerable negative outcomes to global health and economy.

After WHO's declaration about emerging MERS-CoV and the first two cases of MERS-CoV infection on September 23, 2012, all of the clinicians and researchers have cooperated for prevention a SARS-like epidemic. Unravelling of genomic characteristics of MERS-CoV including its genome structure, phylogenetic associations with other coronaviruses, tissue and species tendency, and target receptor, has upgraded our comprehension of the clinical exposure, pathogenesis, epidemiology, transmission and planning a diagnostic and therapeutic methods of this novel human coronavirus. Nevertheless, concerning questions about animal hosting potency of the virus, evolutionary process, transmission, and the prognostic variables and therapeutic methods of the infection, remain unclear. So it seems crucial to control this new human infection "MERS-CoV" by collaborating global and local health authorities and their continual support for further research on it.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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## REFERENCES

1. De Groot RJ, Baker SC, Baric RS, Brown CS, Drosten C, Enjuanes L, et al. Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group. *J Virol.* 2013; 87(14): 7790-2.
2. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with

- pneumonia in Saudi Arabia. *N Engl J Med*. 2012; 367(19): 1814-20.
3. Memish ZA, Mishra N, Olival KJ, Fagbo SF, Kapoor V, Epstein JH, et al. Middle East respiratory syndrome coronavirus in bats, Saudi Arabia. *Emerg Infect Dis*. 2013; 19(11): 1819-23.
  4. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. *N Engl J Med*. 2013; 369(5): 407-16.
  5. Albarrak AM, Stephens GM, Hewson R, Memish ZA. Recovery from severe novel coronavirus infection. *Saudi Med J*. 2012; 33(12): 1265-9.
  6. Memish ZA, Zumla AI, Al-Hakeem RF, Al-Rabeeah AA, Stephens GM. Family cluster of Middle East respiratory syndrome coronavirus infections. *N Engl J Med*. 2013; 368(26): 2487-94.
  7. Mailles A, Blanckaert K, Chaud P, van der Werf S, Lina B, Caro V, et al. First cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infections in France, investigations and implications for the prevention of human-to-human transmission, France, May 2013. *Euro Surveill*. 2013; 18(24).
  8. Buchholz U, Muller MA, Nitsche A, Sanewski A, Wevering N, Bauer-Balci T, et al. Contact investigation of a case of human novel coronavirus infection treated in a German hospital, October-November 2012. *Euro Surveill*. 2013; 18(8).
  9. Bialek SR, Allen D, Alvarado-Ramy F, Arthur R, Balajee A, Bell D, et al. First confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in the United States, updated information on the epidemiology of MERS-CoV infection, and guidance for the public, clinicians, and public health authorities - May 2014. *MMWR Morb Mortal Wkly Rep*. 2014; 63(19): 431-6.
  10. Dyer O. Saudi Arabia reveals 113 previously undisclosed cases of Middle Eastern respiratory syndrome. *BMJ*. 2014; 348: g3822.
  11. WHO. Middle East respiratory syndrome coronavirus (MERS-CoV): summary of current situation, literature update and risk assessment. WHO; 2015.
  12. Khan K, Sears J, Hu VW, Brownstein JS, Hay S, Kossowsky D, et al. Potential for the international spread of middle East respiratory syndrome in association with mass gatherings in Saudi Arabia. *PLoS Curr*. 2013; 5(8): 407-16.
  13. Kumar A, Beckett G, Wiselka M. Middle East respiratory syndrome coronavirus (MERS-CoV) in pilgrims returning from the Hajj. *BMJ*. 2015; 351: h5185.
  14. Drosten C, Muth D, Corman VM, Hussain R, Al Masri M, HajOmar W, et al. An observational, laboratory-based study of outbreaks of middle East respiratory syndrome coronavirus in Jeddah and Riyadh, kingdom of Saudi Arabia, 2014. *Clin Infect Dis*. 2015; 60(3): 369-77.
  15. Schneider E, Chommanard C, Rudd J, Whitaker B, Lowe L, Gerber SI. Evaluation of Patients under Investigation for MERS-CoV Infection, United States, January 2013-October 2014. *Emerg Infect Dis*. 2015; 21(7): 1220-3.
  16. Shahkarami M, Yen C, Glaser C, Xia D, Watt J, Wadford DA. Laboratory Testing for Middle East Respiratory Syndrome Coronavirus, California, USA, 2013-2014. *Emerg Infect Dis*. 2015; 21(9): 1664-6.
  17. Cowling BJ, Park M, Fang VJ, Wu P, Leung GM, Wu JT. Preliminary epidemiologic assessment of MERS-CoV outbreak in South Korea, May-June 2015. *Euro Surveill*. 2015; 20(25).
  18. Tynell J, Westenius V, Rönkkö E, Munster V, Melén K, Österlund P, et al. Middle East respiratory syndrome coronavirus (MERS-CoV) shows poor replication and weak induction of antiviral responses in human monocyte-derived macrophages and dendritic cells.. *J Clin Virol*. 2015; 70: S56-S7.

19. Johnson RF, Via LE, Kumar MR, Cornish JP, Yellayi S, Huzella L, et al. Intratracheal exposure of common marmosets to MERS-CoV Jordan-n3/2012 or MERS-CoV EMC/2012 isolates does not result in lethal disease. *Virology*. 2015; 485: 422-30.
20. Farag EA, Reusken CB, Haagmans BL, Mohran KA, Stalin Raj V, Pas SD, et al. High proportion of MERS-CoV shedding dromedaries at slaughterhouse with a potential epidemiological link to human cases, Qatar 2014. *Infect Ecol Epidemiol*. 2015; 5: 28305.
21. Yavarian J, Rezaei F, Shadab A, Soroush M, Gooya MM, Azad TM. Cluster of Middle East respiratory syndrome coronavirus infections in Iran, 2014. *Emerg Infect Dis*. 2015; 21(2): 362-4.
22. WHO. Infection prevention and control during health care for probable or confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection Interim guidance Updated 4 June 2015. WHO; 2015.
23. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. *Methods Mol Biol*. 2015; 1282: 1-23.
24. Corman VM, Baldwin HJ, Tateno AF, Zerbinati RM, Annan A, Owusu M, et al. Evidence for an Ancestral Association of Human Coronavirus 229E with Bats. *J Virol*. 2015; 89(23): 11858-70.
25. Cui L, Wang H, Ji Y, Yang J, Xu S, Huang X, et al. The Nucleocapsid Protein of Coronaviruses Acts as a Viral Suppressor of RNA Silencing in Mammalian Cells. *J Virol*. 2015; 89(17): 9029-43.
26. Madhugiri R, Fricke M, Marz M, Ziebuhr J. RNA structure analysis of alphacoronavirus terminal genome regions. *Virus Res*. 2014; 194: 76-89.
27. Raj VS, Mou H, Smits SL, Dekkers DH, Muller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature*. 2013; 495(7440): 251-4.
28. De Groot R, Baker S, Baric R, Enjuanes L, Gorbalenya A, Holmes K, et al. *Family Coronaviridae*. Amsterdam, The Netherlands: Elsevier Academic Press; 2012: 806-28.
29. Sawicki SG, Sawicki DL, Siddell SG. A contemporary view of coronavirus transcription. *J Virol*. 2007; 81(1): 20-9.
30. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *Lancet*. 2003; 361(9374): 2045-6.
31. Momattin H, Mohammed K, Zumla A, Memish ZA, Al-Tawfiq JA. Therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV)-possible lessons from a systematic review of SARS-CoV therapy. *Int J Infect Dis*. 2013; 17(10): e792-8.
32. Hsu LY, Lee CC, Green JA, Ang B, Paton NI, Lee L, et al. Severe acute respiratory syndrome (SARS) in Singapore: clinical features of index patient and initial contacts. *Emerg Infect Dis*. 2003; 9(6): 713-7.
33. Sung JJ, Wu A, Joynt GM, Yuen KY, Lee N, Chan PK, et al. Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. *Thorax*. 2004; 59(5): 414-20.

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