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Original Article

Genetic Characterization of the H Gene of MeV Strains (H1, B3, and D4) Recently Circulated in Iran for Improving the Molecular Measles Surveillance in the National Measles Lab

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Abstract

Background: Despite decreasing the global burden of measles disease after the introduction of vaccination, measles remains one of the most devastating childhood diseases. Since genotype B3 is reported as a predominant Measles Virus (MeV) genotype recently, the current study aimed to better understand MeV genetic variation by analyzing the complete sequence of Hemagglutinin (H) gene associated with outbreaks of circulated genotypes in Iran.

Methods: Nine positive measles specimens were selected from three circulated different genotypes H1, B3, and D4. Two different regions of MeV RNA were detected by RT-PCR assay. Sequence data and phylogenetic trees were analyzed and constructed by MEGA X software program. Moreover, missense and silent mutations in critical positions of the MeV-H protein were investigated.

Results: The result of phylogenetic analysis from the C-terminus of the Nucleoprotein gene (NP-450) and the complete H gene revealed that the mean sequence diversity was 0.06%-0.08% and 0.04%, respectively. Genotype H1 had the highest mutation in this study; however, the substitutions in genotype B3 fundamentally occurred in critical epitopes. Moreover, genotype D4 was more stable than genotypes B3 and H1.

Conclusion: Mutations were investigated in the whole sequence of H protein. Moreover, the mutations that occur in the critical sites of the protein have an important effect on the pathogenicity of the virus. In this way, we were able to illustrate why genotype B3 is more transmissible than other measles genotypes and is the most important circulating genotype around the world.

Keywords: Molecular analysis; Hemagglutinin protein; Amino acid substitution; Vaccine efficacy; B3 genotype

Introduction

MeV belongs to the genus Morbillivirus in the Paramyxoviridae family and carries a non-segmented negative-strand RNA genome. H is one of the most substantial glycoproteins among

surface proteins in MeV (1). The main epitopes of the H protein are categorized into five types: Receptor-Binding Epitope (RBE), Neutralizing Epitope (NE), Hemagglutinating and Noose Epitope (HNE), Sugar-Shielded Epitope (SSE), and Loop Epitope (LE) (2, 3). Furthermore, 13 conserved cysteine residues were located in the structure of the H protein that affected on antibodies responses (4, 5).

During the life cycle of MeV, one epitope or more can be faced with antigenic variations that may affect the virus circulating pattern and vaccine efficacy (6).

Considerably, during 2016-2017, only 5 measles genotypes including B3, D4, D8, D9, and H1 were reported (7, 8). Moreover, genotype B3 has been identified as a predominant genotype from 2012 in Iran (9) and worldwide from 2017 (10). In 2012, World Health Assembly (11) endorsed the Global Vaccine Action Plan (GVAP) to eliminate measles in five WHO regions by 2020, but milestones have not yet been met (12, 13).

The evaluation of potential mutations in MeV-H epitopes may explain the defect of neutralization of MeV in post-immunization sera. This type of evaluation could help to improve the WHO strategies for MeV elimination and eradication in Iran as a country categorized in Eastern Mediterranean Region (EMR). The study aimed at the complete sequence of the MeV-H gene associated with outbreaks of circulated genotypes in Iran for a better understanding of the genetic variation of MeV.

Materials and Methods

The study protocol was confirmed by the Ethics Committee of Tehran University of Medical Science (11160-92-01-27-22047).

Sample

All measles-suspected specimens were obtained from throat swabs and/or urine of patients around Iran by the Ministry of Health and Medical Education of Iran on the base of the WHO procedures. All samples were transmitted to the National Measles Laboratory (NML) of Iran according to the WHO protocol. Among all specimens, nine samples were selected from three different genotypes (H1, B3, and D4) that circulated in Iran during 2009–2013 (at least one case from every outbreak). These samples are collected from individuals aged range from >4 months to 60 yr. The history of vaccination showed that, one (11.1%) had been vaccinated, six (66.7%) had not been vaccinated, and two (22.2%) had unknown vaccination status. In addition, the AIK-C strain was used as genotype A.

Cell Culture

Nine selected samples from the archive of the measles national lab were processed and prepared to culture in Vero/hSLAM cells (the seed of Vero/hSLAM was provided by the NML cell bank) to obtain purified virus stock. Briefly, Vero/hSLAM cells were cultured in Dulbecco's Modified Minimal Essential Medium (DMEM; GIBCO-BRL), supplemented with 10% fetal calf serum (FCS, GIBCO-BRL, Gaithersburg, MD), 100U ml^{-1} penicillin, 100 µg ml^{-1} streptomycin and incubated under the condition of 37°C and 5% CO_2. The virus was harvested when Cytopathic Effects (CPE) in Vero/hSLAM monolayer appeared.

RT-PCR Amplification

Viral RNA was extracted from specimens by using a QIAamp viral RNA mini kit (Qiagen, Hilden, Germany). Isolated viruses are confirmed by reverse transcription-polymerase chain reaction (RT-PCR). The 600 bp fragment containing the NP-450 region was amplified using a primer pair previously designed by the WHO (14). The complete H gene (1854 bp) was amplified using three new overlapping fragments using primer pairs including (HEM-F1: 3'-CTT AGG GTG CAA GAT CAT CCA CA-5'/ HEM-R1: 3'-ACA GCG ACA TGT TTG AGA ATT GA-5'), (HEM-F2: 3'-AAT CAG TTC CTA GCT GTC TCA-5' / HEM-R2: 3'-GGG ATA GTC AGC CAA TAC ACA-5') and (HEM-F3: 3'-GTT GCG RAT GGA GAC ATG CTT C-5' / HEM-R3: 3'-GGG TGA CAT CAT GTG ATT GGT

TAC-5'). The cycling conditions were: 30 min at 50 °C, 15 min at 95 °C, 30 cycles of 45 sec at 94 °C, 50 sec at 53 °C and 120 sec at 72 °C, and a final elongation of 10 min at 72 °C. The reaction products were purified and sequenced using the above primers with a bidirectional approach.

Sequence and Phylogenetic Analysis

The nucleotide sequences were aligned with the reference strains listed by the WHO that were received from GenBank of National Center for Biotechnology Information (NCBI) Databases (http://ncbi.nlm.nih.gov/). Obtained sequences of the H gene were deposited in GenBank under accession numbers: *MH920633*, *MH91885*, and *MH922967-MH9229973*. Additionally, achieved NP-450 sequences were entrusted in GenBank under accession numbers: *JX857304*, *JX183265*, *HM236424*, *JX183274*, *KC708873*, *KC708877*, *HM998700*, *HM440227* and *GQ504213*.

Consequently, the nucleic acid sequences were analyzed using the Clustal W program implemented in MEGA X for multiple alignments. Moreover, based on 450 nucleotides from the C-terminus of the MeV-N gene and the complete nucleotide sequences of the MeV-H gene (1854 bp), phylogenetic trees were constructed using the Neighbor-Joining method (1000 bootstraps). The evolutionary distance was calculated by Kimura's two-parameter model.

Epitope Analysis

In general, 144 positions in the MeV-H protein were summarized from the recently published literature. The MeV-H protein sequence and its three-dimensional structure (PDB ID: 2RKC) were retrieved from the UniProt (https://www.uniprot.org/uniprot) and Protein Data bank (PDB) (https://www.rcsb.org/structure) databases, respectively. The substitutions were analyzed by MEGA X and Spdbv software.

Results

RT-PCR Results

All RT-PCR products derived from nine MeV isolates were confirmed by gel electrophoresis (Fig. 1) and sequenced.

Evaluation of Nucleotide Sequences

Consequently, two phylogenetic trees were constructed by using the Neighbor-Joining method (1000 bootstraps) based on Kimura's two-parameter model. According to the analysis of two phylogenic trees, these nine MeV isolates were clustered within genotypes D4, B3, and H1 (Fig. 2). By comparison of entire sequences of the NP-450 and the complete H gene, the mean diversity was computed 0.06%-0.08% and 0.04%, respectively.

Mutation Variability

To more an understanding of the antigenic variability of measles genotypes, amino acid substitution in the whole sequence of H protein was analyzed (Table 1). In addition, the current study focused on four critical epitopes and 13 important cysteine residues of MeV-H protein on Iran (Fig. 3) and GeneBank strains. These reported results included the mutations in which at least 50% of GeneBank strains have the same and have been demonstrated in the following:

1- RBE

T191P, H448R, K460R, and A471E substitutions were found within genotypes B3 strains. The G546S was detected in the ALK-C strain and genotypes D4. In addition, the ALK-C strain had N481Y certain substitution.

2- NE

In this study, the S244L were found within genotype H1 and S240N in genotype B3 as well as H1. Moreover, genotype D4 and H1 strains had G211S substitution. Although this residue does not classify into the NE, it is the same epitope for interaction with antibodies.

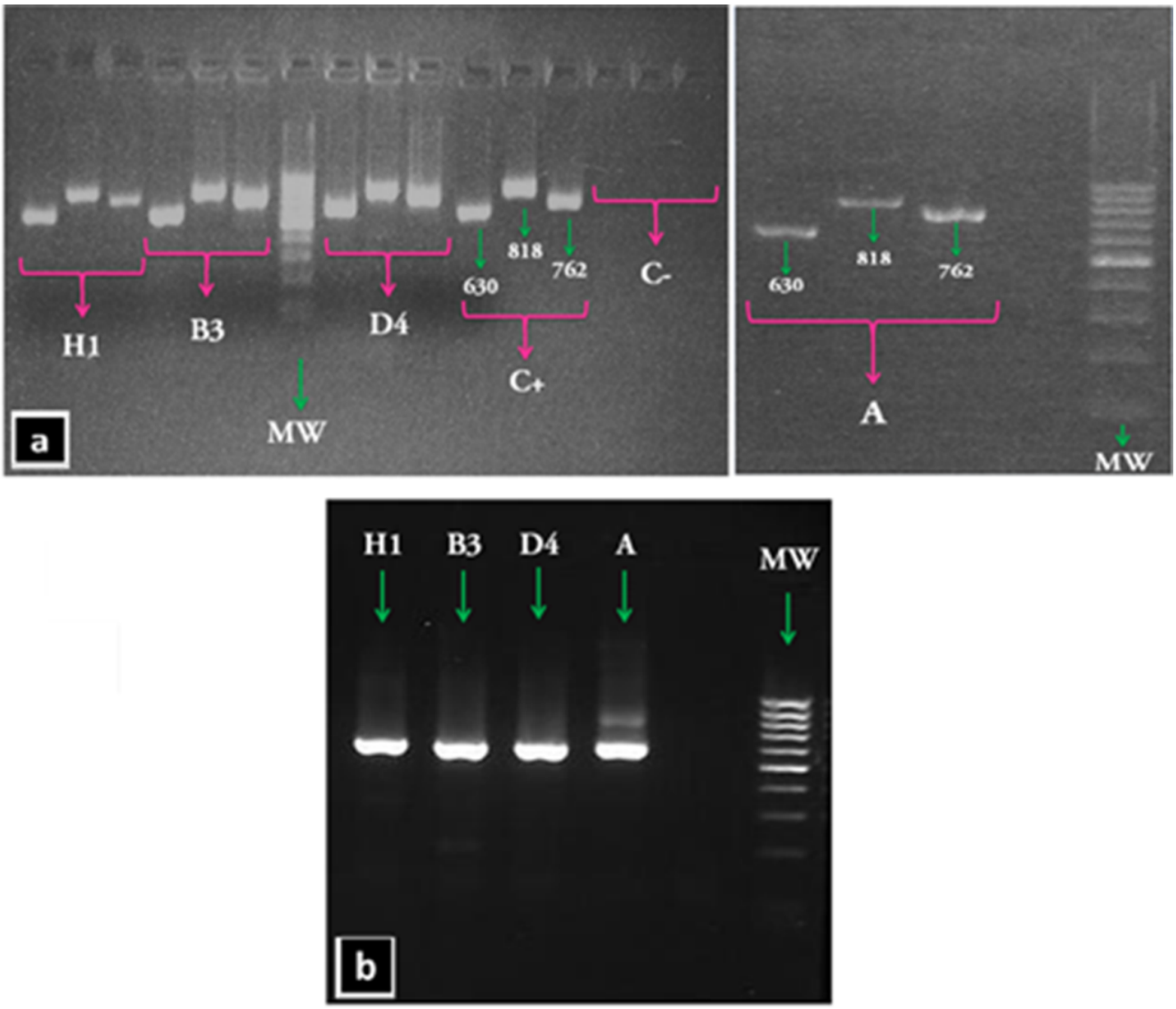

Fig. 1: Agarose gel electrophoresis of complete MeV-H gene (1854 bp) and 450 nucleotides from C-terminus of the MeV-N gene (NP-450): RT-PCR amplification of measles species that circulated in Iran (genotypes H1, B3 and D4) and the ALK-C, vaccine strain (A genotype). Three overlapping amplicons for each sample (630,818 and 762bp fragments respectively) to the complete sequence of MeV-H protein **(a)** a couple of amplicons for the 450 nucleotides C-terminus of N gene **(b)**
C -: negative control C +: positive control MW: Molecular Weight (1kb)

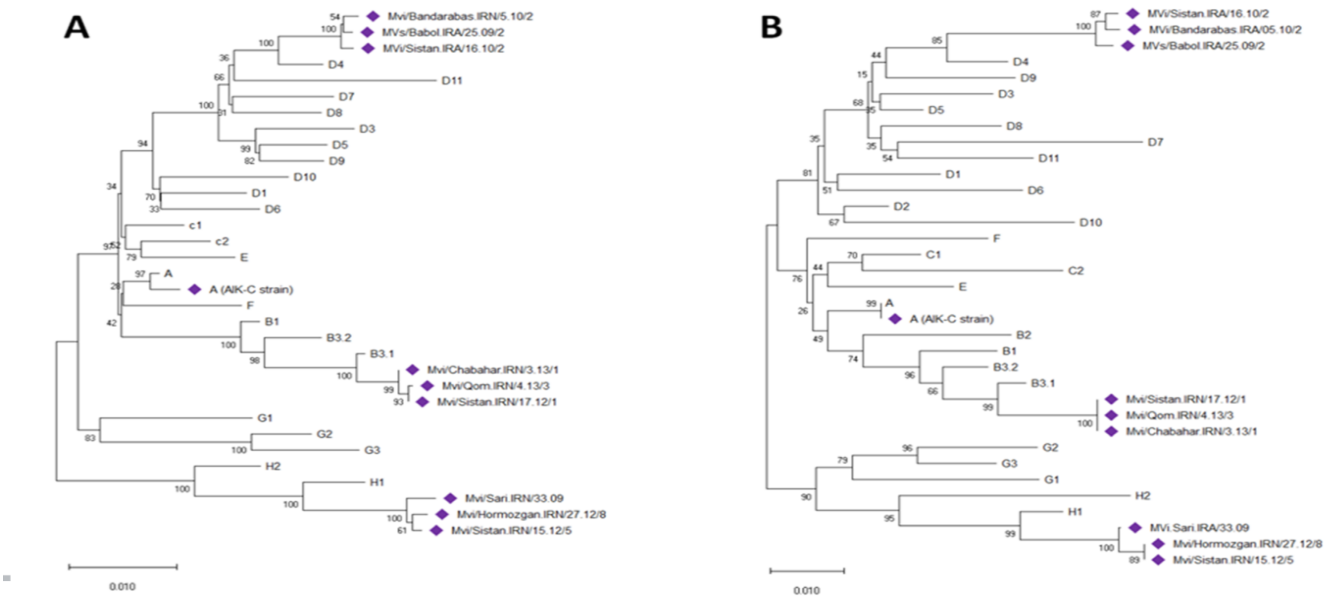

Fig. 2: Phylogenetic trees: The complete MeV-H gene (A) the 450 nucleotides of C-terminus region of MeV-NP gene (B). Nine representative wild-type measles isolates from different outbreaks in Iran (genotypes D4, B3, and H1) and ALK-C vaccine strain in compared with all WHO reference measles strains

3- HNE

HNE is well conserved among analyzed MeV strains, but the H1 strains had a proline-to-leucine substitution at position 397 (P397L). Further, the A400V mutation was found in genotype B3 strains.

4- SSE

D416N, T174A, and T176A were detected in genotype D4 strains. Further, N178T and A182T were recognized in genotype B3 and H1 strains, respectively.

5- Conserved Cysteine Residues

In this study, cysteine residues were strictly conserved.

Total, integrated results of critical epitope analysis revealed that the most variation in these areas belongs to the genotype B.

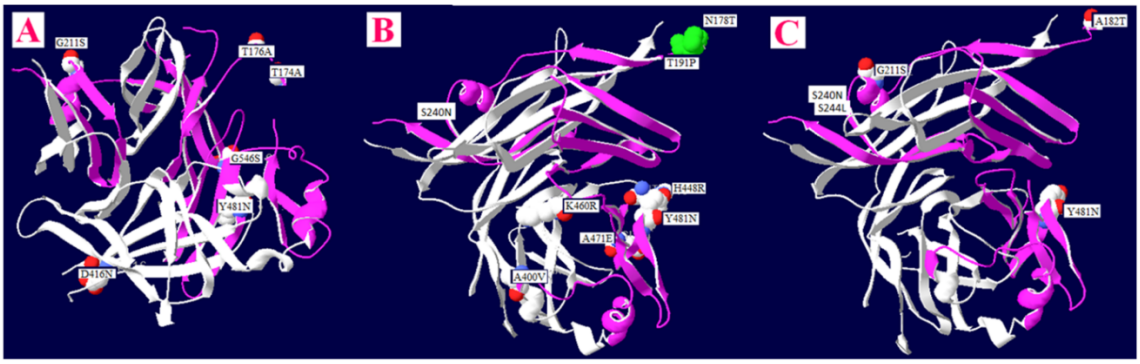

Fig. 3: Ribbon diagram of MeV-H protein structure and substitutions in its critical sites: PDB ID: 2RKC. Genotype D4 **(A)**, Genotype B3 **(B)** and Genotype H1 **(C)**. Total overlapping area that involved in critical epitopes of RBE, NE, HNE, and SSE are shown purple. The illustrated substitutions obtained from nine representative measles isolates from different outbreaks in Iran

Table 1: The obtained substitutions in the whole protein sequence of MeV-H in three genotypes B3, D4, and H1

	Genotype	*Substitutions*
* In Iranian Sequences	**B3**	H17Y, S46F, N178T, T191P, S211G, S240N, R243G, L276F, D283G, S285G, R302G, E303D, T307I, T338P, I346V, K348R, A400V, H448R, K460R, A471E, Y481N, N484T, G546S, V608A
	D4	S46F, T174A, T176A, G211S, R243G, Y252H, L276F, L284F, L296F, G302R, S305A, T338P, D416N, I473V, Y481N, N484T, G546S
	H1	P18S, V40A, S46F, D149N, T164N, A182T, G211S, S240N, R243G, S244L, L276F, V280I, N282K, R302G, E303G, T338P, A359T, K364N, N405S, T420A, V421A, L423P, F476L, Y481N, N484T, D493H, G546S, V562T, K576R, T609N, T614A
* In The GenBank Sequences	**B3**	H17Y, S46F, T191P, S211G, S240N, R243G, L276F, D283G, S285G, R302G, E303D, T338P, I346V, K348R, H448R, K460R, A471E, Y481N, N484T, G546S, V608A
	D4	S46F, T174A, T176A, G211S, R243G, Y252H, L276F, L284F, L296F, G302R, T338P, D416N, I473V, Y481N, N484T, G546S
	H1	P18S, V40A, S46F, D149N, T164N, G211S, S240N, R243G, L276F, V280I, N282K, R302G, E303G, T338P, A359T, K364N, P397L, N405S, T420A, V421A, L423P, F476L, Y481N, N484T, G546S, V562T, K576R, T609N, T614A

***** The investigation was done both in nine Iranian sequences and in the sequences that were retrieved from NCBI

Discussion

Measles remains one of the most devastating childhood diseases, despite decreasing the global burden of measles disease after the introduction of vaccination. Genotype D4 was the predominant MeV in Iran and disrupted transmission successfully occurred in 2013 (9, 15). However, new outbreaks of imported B3 genotypes were identified in Iran in 2012. The lack of immunity against MeV due to unvaccinated people as well as primary and secondary vaccine failures in this outbreak may remarkable (16). Therefore, the evaluation of the vaccine efficacy against currently circulating MeV genotypes is necessary.

Moreover, genetic characterization of MeV strains is essential to determine the new outbreaks in countries close to elimination. For MeV genotyping, Global Measles and Rubella Laboratory Network (GMRLN) recommends sequencing of NP-450 or/and the complete coding region of the H gene (17). In this study, based on two recommended regions for MeV genotyping, phylogenetic trees were compared. For the entire sequences, the mean diversity was computed at 0.06% to 0.08% for NP-450 and 0.04% for the complete H gene. Therefore, a higher mean diversity among whole sequences of the NP-450 gene was observed rather than the complete H gene.

Since variation in antigenic sites is one of the most powerful strategies that are used by viruses to escape from immune recognition and subsequently neutralization (18). Therefore, substitutions in hot spot regions affect the function of the H protein and virus pathogenicity (1, 18, 19).

Presented N481T substitutions in the H proteins of the Edmonston strains, lead to achieving the capacity to interact with CD46 as an efficient receptor (20-22). N481Y have identified in the H protein of the Iran vaccine strain (ALK-C). Fortunately, this characteristic helps to increase vaccine efficacy.

Similarly, Gly546 of H protein introduces high flexibility in affinity binding to CD46 and nectin-4 as the cellular receptors (23). The G546S mutation was demonstrated in genotypes D4 and ALK-C strain. Consequently, these strains use Nectin-4 and CD46 less efficiently than others.

T191P mutation was observed in genotype B3. Based on the previous study the amino acid substitution at position 191–195 (near to RBS) reduces the power of H–SLAM interaction (24).

Mutations of H448R and K460R in B3 strains were found in this study which may lead to increasing the interaction with CD46. Luca Perabo demonstrated that arginine cause to restore the binding receptor ability (25, 26).

In the current study genotypes, H1 that was obtained from GenBank have P397L substitution within the HNE region. These observations by previous studies (27) suggest that some structural differences among the HNE may create particular escape mutants even in the presence of vaccine-derived antibodies.

In the present study, S240N mutation was visualized within B3 and H1 strains. Moreover, S244N substitution within NE was identified in H1 strains. These kinds of mutations lead to decreasing MeV neutralization (28, 29).

The D416N substitution was observed in the D4 strains that cause to achieve the capacity of N-Linked glycosylation and as a result, suppressed antigenicity. Moreover, due to N178T substitution in B3 and H1 genotypes, the glycosylation site has been missed that usually leads to an increase in the ability of the humoral system in neutralization.

Already, substitutions in MeV have created a negative selection pressure (Missense/Silent <1) (18, 30). Surprisingly, in this study, the observed values of selection pressure in H1 genotypes tend to get closer to number one, which theoretically, could be triggered by the positive selection pressure in MeV.

Based on the mentioned above, current measles vaccines may not be effective enough against antigenic changes in various wild-type MeV strains during the years. So, these variations may one of the important causes of MeV outbreaks within the highly vaccinated population.

On the other hand, according to the WHO reports, is claimed that genotype B3 is the most commonly circulating measles genotype worldwide, recently (10) and it is involved in the re-emergence of measles even among vaccinated individuals.

However, in the present study genotype H1 had the highest frequency in sequence variation; the mutations in genotype B3 fundamentally occurred in critical epitopes. For example, the existence of mutations in four critical positions of RBE in genotype B3 may change the capacity of MeV in interaction with its receptors. Particularly, the presence of arginine in substitutions of H448R and K460R in genotype B3 leads to enhancement of the binding MeV to CD46. Unlike the genotype B3 mutation of G546S in genotypes, D4 and A cause to these strains use Nectin-4 and CD46 less efficiently than other which may decrease the pathogenesis of MeV. Moreover, no mutation was observed within RBE in genotype H1.

S240N and A400V mutations in genotype B3 were observed within NE and HNE, respectively. These kinds of mutations cause reduced MeV neutralization and create particular escape mutants. Similarly, S240N and S244L mutations in genotype H1 and G211S in both genotypes H1 and D4 were visualized which had the same characteristics.

In like manner, mutations within critical sites of SSE were demonstrated in genotypes B3, H1, and D4 but not in genotype A, which may influence virus neutralization.

Totally, in the current study genotype, B3 had the highest frequency in critical epitopes of MeV-H protein. This characteristic of genotype B3 may cause it more pathogenic than other

commonly circulated genotypes which are responsible for the risk of vaccine failure.
In addition, in this study was demonstrated genotype D4 is more stable than genotypes B3 and H1.
Similar to this study, the previous study has disclosed a strong relationship between the titer of measles-neutralizing antibodies and protective immunity. It is done in the National Measles Lab of Iran, and the neutralization of measles antibody rates against three genotypes (D4, B3, and H1) in the serum of vaccinated children was investigated using the FRNT test (15). Furthermore, the results in the mentioned study indicated that the anti-MeV antibody titers in the vaccinated sera were adequate to neutralize all circulating genotypes in Iran; while the B3 genotype had the lowest geometric mean titers of antibody (32.0) compared to D4 (95.9), H1 (90.5) and A (76.1) (15). The result of the current study and the previous one indicated why genotype B3 is the most common circulating strain worldwide.
Despite a vaccination campaign in 1996 which terminated measles vaccine coverage in over 95% of Iran, 12.4% of sera were detected as sensitive to measles by NT (29). The sequence variation in MeV can be the reason for this phenomenon that demonstrated its potential risk in this study.
The pathogenicity of genotypes B3 and C2 were measured in a macaque animal model, and exhibited that genotype B3 is more pathogenic than other MeV genotypes (30). Additionally, genotype B3 was reported in patients who developed SSPE symptoms (31). Genotype B3 have some characteristic including a high mutation rate in critical epitopes which can be the reason for more pathogenicity of B3 in comparison with other genotypes.
Generally, in this study, mutations were investigated in the whole sequence of H protein, especially in its critical sites. Moreover, mutation in critical sites is effective in escaping from the immune system or spreading the virus more widely. In this way, we were able to illustrate why genotype B3 is more transmissible than other measles genotypes and is the most important circulating genotype around the world.

Conclusion

The results of the current study based on bioinformatics and our previous study using serological data demonstrated that genotype B3 is the most important circulating genotype around the world. MeV can re-enter communities with high-level immunity. Therefore, warning about the new outbreaks and the effectiveness of the measles vaccine must be considered essential data to achieve WHO goals toward eradication and elimination of measles.
This study suggests the investigation of sequence diversity on fusion proteins needed to illustrate the mechanism underlying the observed differences in the efficacy of MeV.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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