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Amino acid variation in glycoproteins B (gB), H (gH) and L (gL) of Herpes Simplex Virus 1(HSV-1) isolated from child with gingivostomatitis in Basrah city/Iraq

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Abstract

Viral glycoproteins play a key role in virion adhesion to various cellular receptors, virus entry occurs through the union of the viral envelope with the cell membrane or through endocytosis. The study aimed to obtain the sequence of three viral glycoproteins(UL1-Glycoprotein-gL, UL22-Glycoprotein-gH and UL27-Glycoprotein-gB) for the purpose of identifying amino acid differences. One HSV1 DNA sample was sent to Macrogen /South Korea for determining of whole genome sequences. Then three genes were selected. Studied genes UL1, UL22 and UL27 have been registered in the NCBI under the accession numbers; PV780005.1, PV780004.1 and PV780003.1, respectively. gL had a unique amino acid change A91V. gH sequences showed three unique substitutions: C100T without causing any amino acid change, A1667G resulting in an amino acid change V555A and G2163T resulting in an amino acid change P720T. gB sequence showed the most variation in nucleotide sequence. There were eleven unique substitutions: six (G568A, G1687A, C1798T, G1851A, G2002A and G2566T) without causing any amino acid change. Moreover, five substitutions showed four amino acid changes; T827K, N829P, A844P and R896C. The current study conclude that gB aa sequences revealed that most of the aa differences were located within cytoplasmic tail domain of gB (T827K, N829P, A844P and R896C), and this region may play a role in restricting fusion activity. In gH observed change in aa P720T may lead to altered virus entry kinetics. Also, A91V amino acid change in gL within the gL domain was known to interact with gH and may affect gH/gL cell surface expression, cell fusion, and virus entry.

Keywords: WGS, Glycoproteins , gB, gH, gL.

Introduction

The family Herpesviridae is one of the most complex human viruses, due to their large genomes and viral particle composition. Among them, herpes simplex virus 1 (HSV-1) (Henaff et al., 2012).

HSV virion composed of a linear double stranded DNA of ~152 kb encoding at least 74 distinct genes, coated by an icosapentahedral capsid consists of 162 capsomeres made of six different viral proteins, inclosed by 20-23 different viral tegument proteins that have a crucial role in various stages of viral life cycle (Albecka et al., 2017). The lipid bilayer envelope of HSV-1 contains 11 glycoproteins involved in the early stages of viral attachment and penetration (De Mello et al., 2016).

The presence of the four glycoproteins: gB, gD and gH/gL and their receptors in the host cell has been shown to be sufficient to transfer the viral content into the host cell (Karasneh and Shukla, 2011).

Glycoproteins gH and gL form a heterodimeric protein complex, where Glycoprotein gH is an 838aa glycoprotein encoded by the UL22 gene, while Glycoprotein gL, a 224aa glycoprotein encoded by the UL1 gene (Heldwein, 2016). HSV-1 gH is an 838-residue type 1 membrane glycoprotein. The ectodomain contains 7N-glycosylation sites and 8 cysteine residues forming at least 2 disulfide bonds between cysteines 5 and 6 (residue 554 and 589) and cysteines 7 and 8 (residues 652 and 706) (Cairns et al., 2005). gL is always seen in association with H1 domain of gH. Sequences of domain H1 and gL vary significantly among herpesviruses and cannot be interchanged except between HSV-1 and HSV-2 (Muggeridge, 2000; Cairns et al., 2005). Deleting of gH or gL or both of them inhibits the heterodimer formation and results in a lethal phenotype where the viral envelope bind to the plasma membrane without the ability to enter the host cell (Roop et al., 1993). Although wild-type viruses cause a limited amount of virus-induced cell fusion, certain mutations cause extensive virus-induced cell-to-cell fusion (syncytial,

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or syn, mutations).These syncytial mutations are located predominantly within the UL20 gene (Melancon et al., 2007); the UL24 gene (Jacobson et al., 1998); the UL27 gene, encoding glycoprotein gB (Foster et al., 2001); and the UL53 gene, coding for gK (Hutchinson et al., 1992; Jam et al., 2018).

In recent years, there have been studies on the most important viruses that cause diseases in Basrah Governorate, as in studies Jassim et al., 2025, Al-Abadi et al., 2024, Ghali et al., 2022, Shihab et al., 2020, and Atbee et al., 2020; Abbas et al., 2024. The aim of the study was to sequence three viral genes encoding viral glycoproteins (UL1-Glycoprotein-gL, UL22-Glycoprotein-gH and UL27-Glycoprotein-gB) involved in entry and cell-to-cell fusion and identified amino acid differences between studied genes with different sequences.

Materials and Methods

Samples collection

The present study was conducted during the period from December 2023 to June 2025. A total of 107 samples from both sexes were collected. Samples were collected under the supervision of a specialist physician from Basrah teaching hospital and Al-Fayhaa teaching hospital in Basrah governorate. The mucocutaneous lesion samples of herpetic labialis and herpetic gingivostomatitis were collected using cotton-tipped swabs to swab the lesions. After that, swaps were kept in the viral transport media (VTM) and frozen in a deep freezer at -80ºC until used for molecular detection.

Molecular detection of herpes simplex virus 1 and 2

Extraction and amplification of HSV DNA

Herpes simplex virus DNA was extracted according to FavorPrepTM mini kit and following the manufacturer's instructions. The detection of HSV 1 and 2 was performed by multiplex PCR. The designed forward and reverse primers; 5'-GACGTCACCGTTTCGCAGGTGT-3';5'-CGTTGGCCGGTTTCAGCTCCAT-3' and 5'-CGCGCCTCCGAAAGATGGTGTT-3', 5'-TCGTCCAGCCCGGCGAAGATAA-3' for detection of UL5 (HSV1) and UL27 (HSV2) genes, respectively, were used to amplify target sequences 217bp and 412bp, respectively (Yasaghi *et al*., 2022). The total volume of reaction 25 µl was prepared by mixing 5 µl of DNA with 12.5 µl of Master mix, 1 µl of each forward and reverse primers, and 5.5 µl of free nuclease water. The PCR conditions were set as follow: the reaction was submitted to the first step of denaturation at 95˚C for 15 min. followed by 35 cycles of 45 sec. of denaturation at 94 ˚C, annealing step was set at 58.5 ˚C for 45 sec., an extension step at 72 ˚C for 45 sec with a final extension conducted at 72˚C for 7 min. The amplified products were visualized on 1.5 % agarose gel.

Sequencing of viral genes encoding glycoproteins

One HSV1 DNA sample was sent to Macrogen /South Korea for sequencing by using next generation sequencing (NGS) for determining of whole genome sequences using a long PCR amplicon-based strategy. Then three genes were selected, which are:UL1, UL22 and UL27. Molecular identification of studied sequence was performed by multiple sequence alignments (MSA) of each gene sequences with the National Center for Biotechnology Information (NCBI(database using the Basic Local Alignment Search Tool (BLAST) computer program for top 100 Blast. The multiple sequence alignments (MSA) of these genes were done with different sequences of top 100 Blast that downloaded from the GenBank database of NCBI to identify any mutations at these genes that change in the amino acid. The evolutionary history was inferred using the Neighbor-Joining method (1). The evolutionary distances were computed using the p-distance method (2) and are in the units of the number of base differences per site. Evolutionary analyses were conducted in MEGA12 (3).

Results

Molecular detection and whole genome sequencing

Molecular results showed positive samples (Figure, 1) for the presence HSV1, while no DNA amplification was found for HSV2. The genome was deposited in the GenBank Bioproject PRJNA1245448 SRA : SRP576211 Whole Genome Sequencing of Human Herpes Simplex Virus Type 1 from a Clinical Case in Basrah City. The contigs deposition in NCBI database is ongoing.

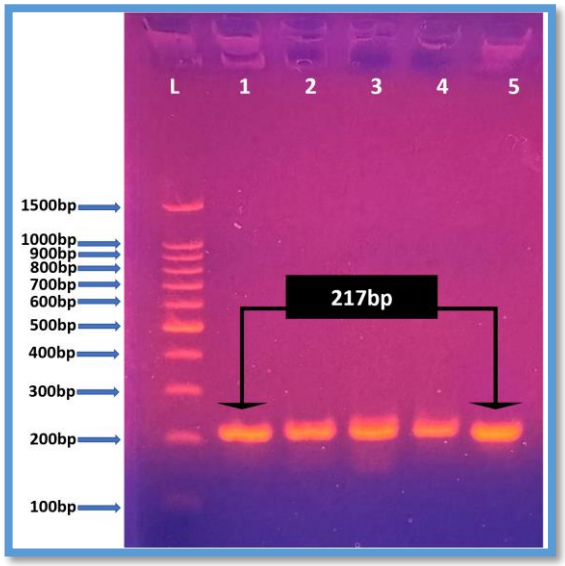


Figure 1. Agarose gel electrophoresis of HSV1 PCR products
Ladder = DNA Lane 1-5 = positive results (217 bp)

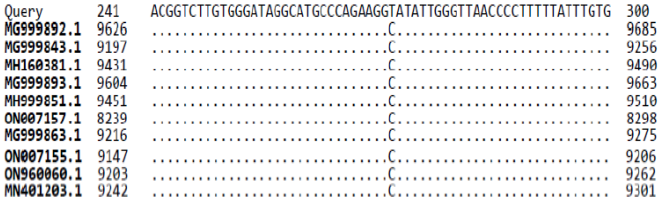
Variation of studied genes

Studied genes have been registered in the NCBI under the accession numbers as shown in the table (1). All of the compared sequences do not show 100% similarity (Table, 1). In the current study, the comparison was made with the first 100 Blast, then selected the genes with various mutations to clarifying all mutations.

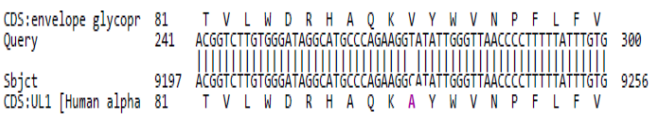
Table 1. Nucleotides sequencing data for studied genes

Genes	Query Length	Accession number	Compatible with	Identity %
UL1	675	PV780005.1	MN401203.1	99.85
UL22	2517	PV780004.1	OR771680.1	99.92
UL27	2715	PV780003.1	MG999898.1	99.78

Although UL1-Glycoprotein-gL (PV780005.1) was more similar to different sequences (99.85%), gL differed from all sequences resulting (Figure, 2) C-to-T substitution (C272T). Specifically, gL had a unique amino acid change (Table, 2) from Alanine (A) to Valine (V) (A91V).



A



B

Figure 2. Alignment of UL1 gene, A. nucleotide sequences B. amino acid sequences

Table 2. Nucleotide and amino acid differences of studied genes

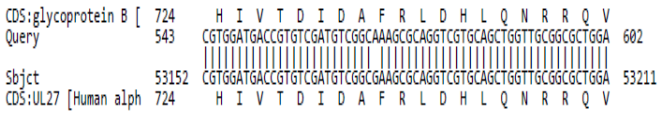
Genes	Nucleotide			Amino acid	
	Change	Position	Mutation	Change	Position
UL1	C→T	272	Missense	Alanine → Valine	91
UL22	C→T	100	Silent		
	A→G	1667	Missense	Valine → Alanine	555
	G→T	2163	Missense	Proline → Threonine	720
UL27	G→A	568	Silent		
	G→A	1687	Silent		
	C→T	1798	Silent		
	G→A	1851	Silent		
	G→A	2002	Silent		
	G→T	2566	Silent		
	G→T	2480	Missense	Threonine → Lysine	827
	T→G	2486	Missense	Asparagine → Proline	829
	T→G	2487			
	C→G	2532	Missense	Alanine → Proline	844
	G→A	2688	Missense	Arginine → Cysteine	896

UL22-Glycoprotein-gH sequences showed the 44 nucleotide sequence changes ; 41 of which with few frequency appeared in a few references sequences were absolutely conserved in PV780004.1 and many

reference sequences. There were three unique substitutions: one of which C100T without causing any amino acid change (Table, 2), two substitutions revealed amino acid variations; A1667G resulting in an amino acid change (V555A) from Valine (V) to Alanine (A) and G2163T resulting in an amino acid change (P720T) from Proline (P) to Threonine (T) (Figure, 3).

Figure 3. Alignment of UL22 gene amino acid sequences

Comparison of the UL27-Glycoprotein-gB sequence showed that it had the most variation in nucleotide sequence, gB sequence revealed a 59 substitutions; 48 of which with few frequency appeared in a few references sequences (as KX265035.1 in which substitution G2540A resulting in an amino acid change from Proline (P) to Lucine (L) were absolutely conserved in PV780003.1 and many reference sequences. There were eleven unique substitutions: six of which without causing any amino acid change (Table, 2), including substitutions; G568A, G1687A, C1798T, G1851A, G2002A and G2566T (Figure, 4). Moreover, there were five substitutions showed four amino acid changes; G2480T resulting in an amino acid change (T827K) from Threonine (T) to Lysine (K), the double substitutions T2486G and T2487G resulting in an amino acid change (N829P) from Asparagine (N) to Proline (P), also substitution C2532G resulting in an amino acid change (A844P) from Alanine (A) to Proline (P), furthermore, substitution G2688A resulting in an amino acid change (R896C) from Arginine (R) to Cysteine (C) (Figure, 4).



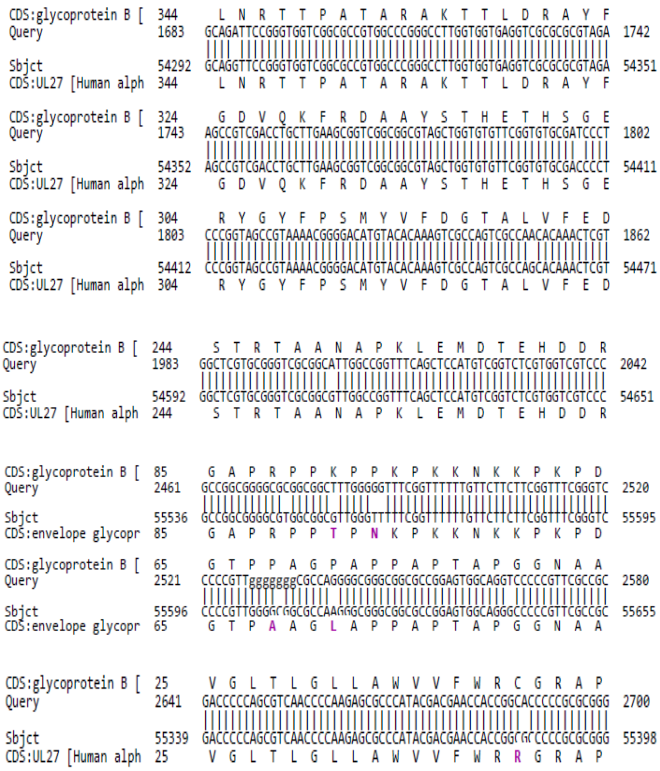


Figure 4. Alignment of UL27 gene amino acid sequences

Discussion

Viral glycoproteins play a key role in virion adhesion to various cellular receptors, virus entry occurs through the union of the viral envelope with the cell membrane or through endocytosis (Madavaraju et al., 2020). Viral glycoproteins gB, gD, gH, and gL play essential roles in the fusion of the viral envelope with cellular membranes and development of cell to cell fusion of neighboring infected cells (Connolly et al., 2011). However, Avitabile et al.(2009) showed that the Interaction between gB and gH/gL does not necessarily require gD . Most amino acid differences between studied sequence and different sequences located at gB because of the length of the gene.

HSV-1 gB is a 904-amino-acid residues long , which structurally composed of a spike-like ectodomain, a membrane proximal region (MPR), a transmembrane domain (TMD), and a cytoplasmic tail domain (CTD) (Fontana et al., 2017). The MPR is a hydrophobic region and situated between the ectodomain and the TMD (Madavaraju et al., 2020). The ectodomain has a trimeric crystal structure, with five structural domains (I-V) (Heldwein et al., 2006), where Domain II is hypothesized to interact with gH/gL during the

fusion process. (Atanasiu et al., 2010).

In present study, gB aa sequences (Table, 2) revealed that most of the aa differences were located within CTD of gB (T827K, N829P, A844P and R896C), and this region may play a role in restricting fusion activity and these mutations will relaxation this restriction.

It was previously believed that only the gB's ectodomain was actively involved in the fusion reaction, while recent research has confirmed that the adjacent MPR, TMD, and CTD regions also play a pivotal role (amino acids 730 to 904) in regulating the fusion reaction (Cooper and Heldwein, 2015; Fontana et al., 2017). The gB CTD acts as a clamp like structure which stabilizes the ectodomain in a pre-fusion form. Mutations in CTD cause the clamp to destabilize, leading to mutant viruses with Hyper-fusogenicity to forming multinucleated cells (syncytia) (Silverman et al., 2012). Mutations that delete the terminal 28 amino acids of gB or those result in changes in a single amino acid near the carboxyl terminus of gB can lead to virally stimulated extensive cell fusion, Because they change the extracellular conformation of glycoprotein B. (Foster et al., 2001, Muggeridge, 2000). In the MBR region, a set of specific amino acid residues may facilitate the attachment of the virus to the host cell membrane, while another set of amino acids in this region may shields and isolates the fusion loops during the fusion reaction. Both MPR and TMD regions are essential for enabling lipid mixing and formation of the fusion pore at the initiation of the fusion reaction. The amino acids in TMD region are highly stable among different alphaherpesviruses (Atanasiu et al., 2010b).

HSV-1 gH, is an 838aa glycoprotein encoded by the UL22 gene. It is a type I glycoprotein which consists of several domains, including a signal peptide, a large ectodomain, transmembrane domain, and cytoplasmic domain.

Glycoprotein L (gL), is an 224aa encoded by the UL1 gene. It is composed of a signal peptide but without transmembrane domain. Due to the lacking of the transmembrane domain in gL , it cannot independently associating with membranes. gL is noncovalently associated with the N-terminal part of the gH ectodomain and depending on interaction with gH for incorporation into virions in herpesviruses in general (Eisenberg et al., 2012). gL is strictly required for gH processing and function (Vallbracht et al., 2017). Consequently, an essential partnership of mutual dependence occurs between gL and gH . They are obligately complexed to each other to form a stable heterodimeric protein complex, where gH acting as the anchor and gL as a chaperone to ensure gH's proper folding and trafficking to incorporated within the viral envelope (Heldwein, 2016). The herpesvirus core fusion machinery is composed of gB and the heterodimeric gH/gL complex. These three components are conserved throughout the Herpesviridae (Atanasiu et al., 2010a).

In the current study, comparison of gL aa sequences with reference sequences revealed that these proteins were highly conserved (Figure, 6). There were only one unique aa change A91V. While, two aa changes (V555A and P720T) were located within gH sequences.

gH ectodomain consists of three distinct domains : N-terminal H1 and H2, and C-terminal H3 . H1, the Membrane-distal domain is the least-conserved domain. It consists of subdomains H1A and H1B, connected by a 20-amino-acid linker and it interacts with the gL protein (Jha et al., 2016). H2 moderately conserved across herpesviruses , and thought to be involved with translating the diverse signals received by H1 into a common message for activating of gB . H3 is the most highly conserved of the three domains, which is essential for transmitting the fusion signal from gH/gL to the viral fusion protein, gB (Cooper and Heldwein, 2015). gH ectodomain receives this signal through H1 domain and transmits it to the H3 through the H2 domain, which then translates the signal to the cytoplasmic tail of gH (Cooper and Heldwein, 2015). After receiving the message gH's cytoplasmic tail acts as a wedge and splits the gB's CTD clamp restrain in the cytoplasmic tail (Rogalin and Heldwein, 2015).

Mutational studies indicate that gH cytoplasmic tail is essential for regulating the fusion process and for activation of gB. Truncation or insertions within the gH cytoplasmic tail affect the ability of gH to reach the gB CTD and inhibit fusion efficiency (Rogalin and Heldwein, 2015; Cooper et al., 2018).The gH cytoplasmic tail influences gB via "inside-out signaling" on the gB CTD region, where the gH

cytoplasmic tail interacts with the gB CTD clamp, destabilizing it and releasing the gB ectodomain from its restrained state. Short HSV1 gH cytoplasmic tail ,which consisting of only 14 amino acid residues, making it a convenient part for mutagenic analysis (Harman et al., 2002).

In the current study the mutations of studied sequence were not in gH cytoplasmic tail. Further deletion of HSV-1 CTD, however, significantly reduced fusion activity, suggesting a regulatory role of the gH CTD (Rogalin and Heldwein, 2015; Vallbracht et al., 2018). The α-helical nature of gH-(626–644) amino acids are important for membrane interaction and that the aromatic residues, tryptophan and tyrosine, are critical for induction of fusion (Galdiero et al., 2008). The conserved residues were predicted to map to the same face of an α-helix and three (A651, S652, G665 in HSV-1) were crucial for gH function in HSV-1. This suggests that the gH TM has an intrinsic property to specifically interact with membrane components such as lipids or (viral glyco-) proteins as a prerequisite for triggering membrane fusion (Harman et al., 2002; Vallbracht et al., 2018).

The carboxyl terminus of gH has been shown to be important for virus-induced cell fusion (Melancon et al., 2005). Therefore, the observed change in aa P720T may lead to altered virus entry kinetics. The A91V amino acid change in gL within the gL domain was known to interact with gH and may affect gH/gL cell surface expression, cell fusion, and virus entry.

Conclusion

The current study conclude that gB aa sequences revealed that most of the aa differences were located within CTD of gB (T827K, N829P, A844P and R896C), and this region may play a role in restricting fusion activity and these mutations will relaxation this restriction. In gH observed change in aa P720T may lead to altered virus entry kinetics. Also, A91V amino acid change in gL within the gL domain was known to interact with gH and may affect gH/gL cell surface expression, cell fusion, and virus entry.

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