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Original Article

Investigation of *GJB2* and *SLC26A4* genes related to pendred syndrome genetic deafness patients

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ABSTRACT

Deafness can occur due to damage to the ear, especially the inner ear. In other cases, the cause is a heterogeneous genetic abnormality and is caused by the changes that occur in the genes involved in the hearing process. Mutations in *GJB2* and *SLC26A4* genes are one of the most important causes of deafness in the world, which causes syndromic and non-syndromic hereditary hearing loss. The purpose of this study is to investigate *GJB2* and *SLC26A4* genes related to genetic syndromes of deafness and bioinformatic analysis at the genome and proteome level and to evaluate and compare the expression of these genes in different tissues of the human body. For this purpose, tools related to bioinformatics analysis such as UCSC and OMIM databases were used. One of the common genetic syndromes caused by mutations in these genes is pendred syndrome. The clinical symptoms of this disease are weight gain, constipation, dry skin, and hair, decreased energy, sleepiness, bulging belly, decreased body temperature, and slow growth. This disease does not currently have a specific treatment, so it is very important and fundamental to investigate the genetic factors affecting this disease. The results of this research showed that the transfer of potassium, sodium, and chlorine ions as well as the mutation in the *SLC26A4* gene, which is responsible for the synthesis of pendrin protein, is very effective in the occurrence of pendred syndrome. To diagnose pendred syndrome more accurately, molecular methods should be used in genetic tests. The results of comparing the expression profiles of these two genes showed that the difference in the expression of these two genes is very high and, in general, the expression of the *SLC26A4* gene in the body is very low. Because people with hearing loss have other problems including damage to other parts of the body such as the heart, kidneys, or eyes. Knowing the genetic cause in these cases allows the doctor to be aware of problems in other systems as well.

1. Introduction

Deafness is one of the most common neurological diseases. More than 50% of deafness cases have a genetic origin. Pendred syndrome is a genetic and hereditary disorder

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that occurs as a result of defects in the function of the *SLC26A4* gene. The pattern of this disease is autosomal recessive [1-4]. This syndrome is one of the syndromes associated with hearing loss and usually causes profound hearing loss, with an estimated prevalence of 1 in 14,500. This disease is caused by the thyroid hormone not working properly. It's most important symptom is hearing loss. In this disease, a person has hearing loss since birth, and the thyroid gland is enlarged and causing goiter. Goiter usually appears at the age of eight, but in some cases, it has been observed at birth [5]. As mentioned, the *SLC26A4* gene encodes the pendrin protein. This protein is the cause of pendred syndrome. Pendrin protein is the transporter of sulfate inside and outside the cell, as well as the transporter of iodide and chloride in membrane cells [3, 6, 7]. Since potassium, sodium, and chlorine ions are very important for hearing, a defect in the *SLC26A4* gene causes disruption in the transmission of sound waves to the brain and reduces the sense of hearing. Due to the lack of genetic research and gene therapy in this field, hearing aids and cochlear implants are currently used as effective treatment methods for children with this disorder (Figure 1). Other clinical symptoms of Pendred syndrome are weight gain, constipation, dry skin and hair, decreased energy, sleepiness, bulging belly, low body temperature, low growth, and mental retardation.

Research has shown that more than 150 gene loci are involved in deafness and more than 1200 different mutations in the human genome are involved in deafness [8]. According to the statistics of the World Health Organization, around 360 million people around the world have mild to severe deafness, and 1 out of every 1000 children born is deaf. Some environmental factors can cause hearing loss. Hearing loss in babies is due to "environmental" reasons, such as the mother's infection during pregnancy and complications after birth. In some cases, environmental genetic effects work together and cause hearing loss. Deafness has high heterogeneity, and in different clinical conditions, different genes play a role in the occurrence of this disease. *GJB2* and *SLC26A4* genes are common deafness genes and account for 40% of genetic deafness patients [8, 9]. The purpose of this study is to investigate GJB2 and *SLC26A4* genes related to genetic syndromes of deafness and bioinformatic analysis at the genome and proteome level and to evaluate and compare the expression of these genes in different tissues of the human body.

2. Materials and methods

First, the sequences of GJB2 (NM_004004.6) and *SLC26A4* (NM_000441.2) genes were obtained from the NCBI database. The lengths of these proteins were 226 and 780 amino acids, respectively. The exact location of these genes was then determined using the UCSC database. The three-dimensional structure of the proteins and drawing of a diagram of Ramachandran were determined using the MBC database, and the molecular weight and isoelectric point of the proteins were determined using the ProtScale database. Then, Cell comparison of GJB2 and *SLC26A4* genes and expression of these genes were examined by Human Protein Atlas OMIM database.

Fig. 1. Goiter associated with deafness and use of hearing aids and cochlear implants for children

3. Results

3.1. Analysis of genes related to deafness

The *GJB2* gene is located on chromosome number 13 and at position 13q12.11. It has 2 exons and 226 amino acids. This gene has a row of six consecutive G nucleotides at the position of nucleotides 30-35, which is prone to slippage in replication, which results in the premature termination codon in exon number 2. The most common type of mutation is the deletion of a nucleotide at the 30delG and 35delG position, which is the main cause of much hereditary and non-syndromic deafness

(autosomal recessive in the DFNB1 locus and autosomal dominant in the DFNA3 locus). A single mutation in this gene, c.35delG, accounts for more than 60% of hereditary deafness in Northern European countries. Research has shown that the prevalence of the 35delG mutation is higher in the white population [10].

The *GJB2* gene provides direct intracellular communication and allows the passive release of molecules up to 1 kDa including nutrients, metabolites (glucose), ions (calcium and potassium), and secondary messengers such as (IP3, and cAMP)[11].

GJB2 gene encodes connexin 26 protein. Connexin 26 (CX26) is one of the main proteins involved in potassium (K^+) homeostasis in the cochlea. CX26 is found in supporting cells, fibrocytes of the spiral ligament, and cells of the spiral limbus. If the CX26 protein is not enough, the potassium level in the inner ear will be too high, causing hearing damage [11]. It has suggested that deafness associated with CX26 mutations is caused not only by reduced potassium recirculation in the inner ear but also by abnormalities in the exchange of other metabolites through the cochlear cleft [12].

It has showed that CX26 and CX43 subunits are involved in the migration of neurons to the cerebral cortex, and the reduction of CX26 and CX43 at the points of contact between radial fibers and migrating neurons leads to neurological disorders in the cerebral cortex [13].

The *GJB6* gene encoding connexin 30 (CX30) is located near the *GJB2* gene. The proteins obtained from these two genes (*GJB2* and *GJB6*) are members of the gap junction protein family. This group includes 22 different genes that facilitate the transport of small molecules and ions between cells. Mutations in these two genes cause different degrees of deafness [14].

The *SLC26A4* gene is located on chromosome number 7 and at position 7q22.3. This gene is in the Solute carriers (SLC) group, which contains 433 different genes. It has 21 exons and 780 amino acids. This gene encodes the protein pendrin, which is an anion transporter (chlorine and iodine ions). More than 300 mutations have been identified in this gene. A defect in this gene disrupts the function of the ear, thyroid, and kidney [15].

Table 1. Genes sequence results of *GJB2*, and *SLC26A4*

Name	*GJB2*	*SLC26A4*
Approved name	gap junction protein beta 2	solute carrier family 26 member 4
ORGANISM	Homo sapiens (Human)	Homo sapiens (Human)
Accession number nucleotide	NM_004004.6	NM_000441.2
Accession number protein	NP_003995.2	NP_000432.1
Gene ID	2706	5172
Chromosome	13	7
Cytogenetic location	13q12.11	7q22.3
Chromosome location bp	20187470-20192938	107660828-107717809
nucleotide length	2290 bp	4737 bp
protein length	226aa	780aa
Molecular weight (Da)	26215.07	85723.07
Isoelectric point	9.11	6.04
Total Exon	2	21

3.2. Investigating the role of molecular biology and cell in the GJB2 gene

The *GJB2* gene plays a role in identical protein binding and causes cell communication, cell signaling, sound perception, and gap junction assembly in biological processes. Also, this gene plays an active role in the cellular components of the endoplasmic reticulum-Golgi intermediate compartment, membrane, plasma membrane, gap junction, connexin complex, and cell junction [16-20].

3.3. Investigating the role of molecular biology and cell in the *SLC26A4* gene

The molecular function of the *SLC26A4* gene is in the form of chloride channel activity, bicarbonate, chloride, iodide, sulfate, and oxalate transmembrane transporter activity, and secondary active sulfate transmembrane transporter activity [21-23]. Also, the *SLC26A4* gene plays a role in biological processes such as ion transport (sulfate, mineral anions, bicarbonate, iodide,

and oxalate), regulation of pH, especially intracellular pH, regulation of membrane potential, transmembrane transport (anion, chloride, and sulfate), regulation of protein localization and sensory perception of the sound [24-27]. Research has also shown that the *SLC26A4* gene is an integral part of the membrane and is actively present in the plasma membrane and extracellular exosome [28-30].

3.4. Three-dimensional structure

Molecular homologation modeling using the SWISS-MODEL server in Expasy resulted in a three-dimensional structure of *GJB2* and *SLC26A4* proteins based on sample 1a02 with the highest similarity (Figure 2). The estimation of protein quality was determined according to the QMEANDisCo Global scale. QMEANDisCo global score [31] is the average per-residue QMEANDisCo score which has been found to correlate well with The Local Distance Difference Test (lDDT) score [32]. The provided error estimate is based on QMEANDisCo global scores estimated for a large set of models and represents the root mean squared difference (i.e. standard deviation) between QMEANDisCo global score and lDDT (the ground truth). As the reliability of the prediction depends on model size, the provided error estimate is calculated based on models of similar size to the input. The value of QMEANDisCo Global for the *GJB2* gene is equal to 0.71±0.05 and for the *SLC26A4* gene is equal to 0.45±0.05.

According to the QMEAN z-scores, it was found that there is a good match between the model structure and the experimental structures of the same size. Figures 3 and 4 show different QMEAN z-scores, which include QMEAN, C-beta interactions, and interactions between all atoms, solvation, and torsion, for *GJB2* and *SLC26A4* genes. Then Ramachandran diagram related to *GJB2* and *SLC26A4* proteins was determined to determine the energy level and stability in terms of two angles φ and ψ in proteins. Considering that in *GJB2* protein the percentage of amino acids in Ramachandran favoured was 94.65% and in *SLC26A4* protein the percentage of amino acids of Ramachandran favoured was 93.33%, Therefore, the proposed model is suitable for three-dimensional structure for proteins (Figure 5).

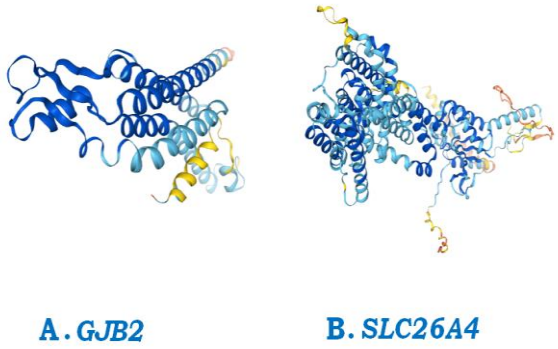

Fig 2. A) Three-dimensional structure of *GJB2* protein. B) Three-dimensional structure of *SLC26A4* protein.

3.5. Gene expression analysis

Figures 6 and 7 show the analysis of *GJB2* and *SLC26A4* gene expression in different body organs. The expression profile for the *GJB2* gene showed that this gene has high expression in most organs and is not expressed only in the eye and connective and soft tissue. As shown in the figure, the *SLC26A4* gene is expressed only in endocrine tissues and is not expressed in other organs. According to the comparison of the expression profile of these two genes, we find that the difference in the expression of these two genes is very high and in general, the expression of the *SLC26A4* gene in the body is very low. The study of gene expression by microarray expression data also confirmed these findings.

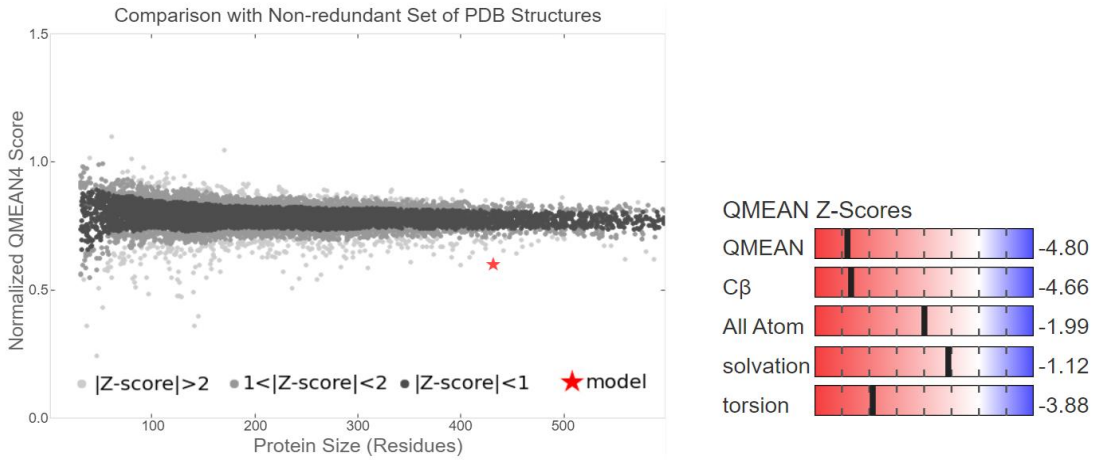

Fig. 3. Plot showing the QMEAN value and Z-score for the *GJB2* gene

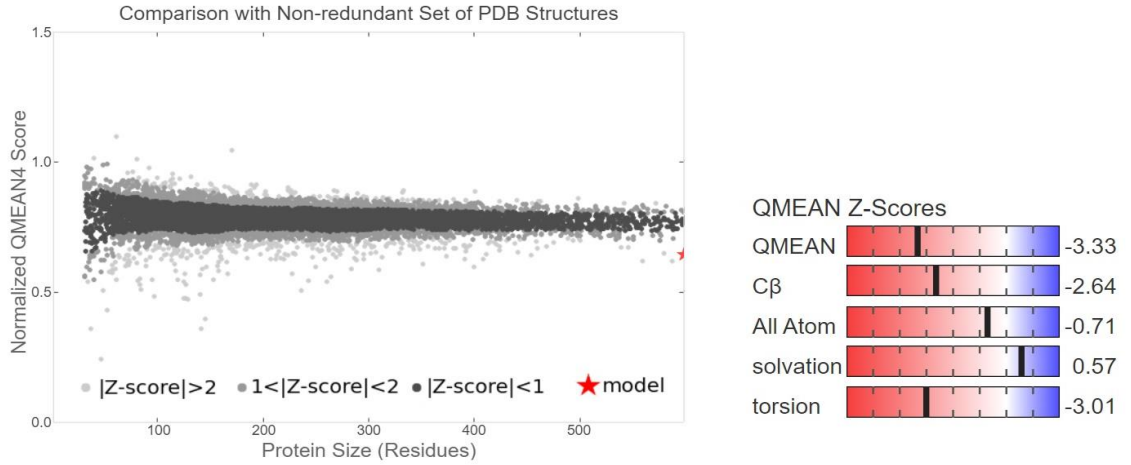

Fig. 4. Plot showing the QMEAN value and Z-score for the *SLC26A4* gene

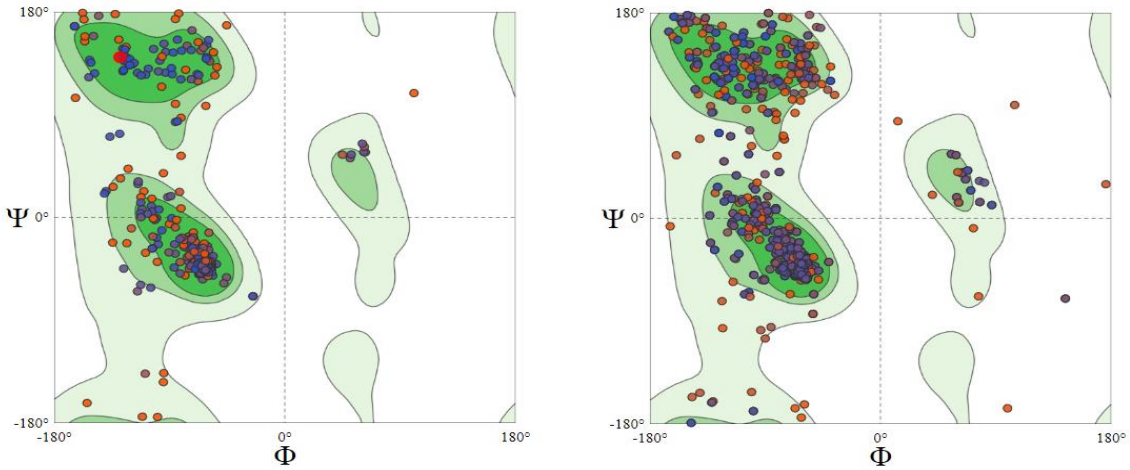

Fig. 5. The *GJB2* protein Ramachandran diagram (The right side), The *SLC26A4 protein* Ramachandran diagram (left side)

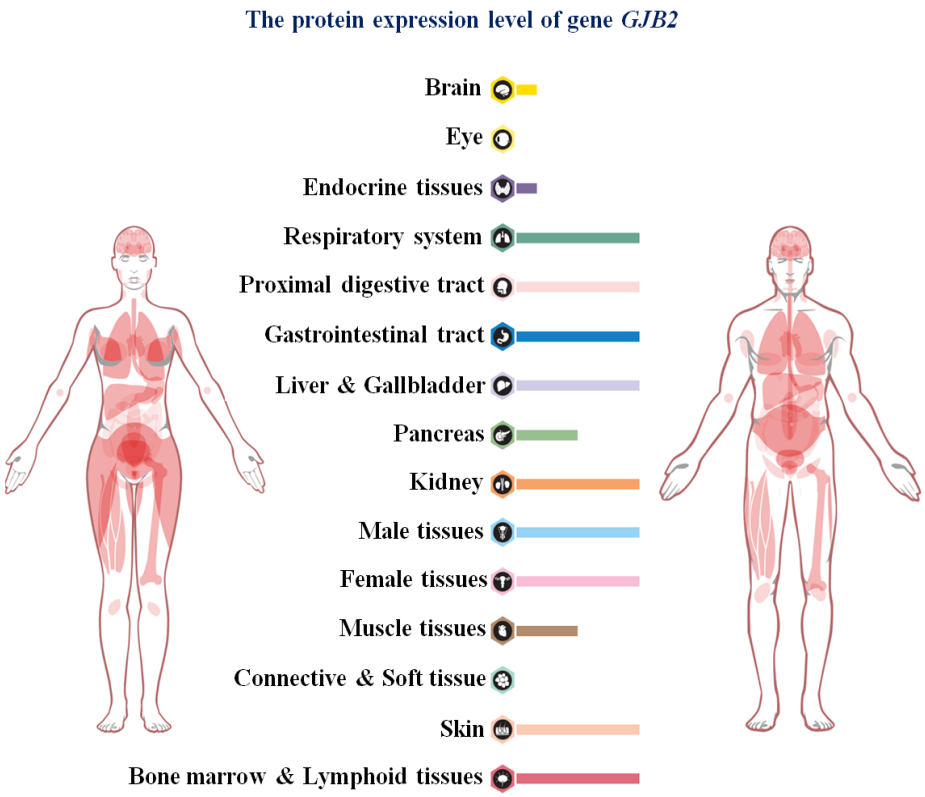

Fig. 6. Expression profile of gene *GJB2* in different organs of the body

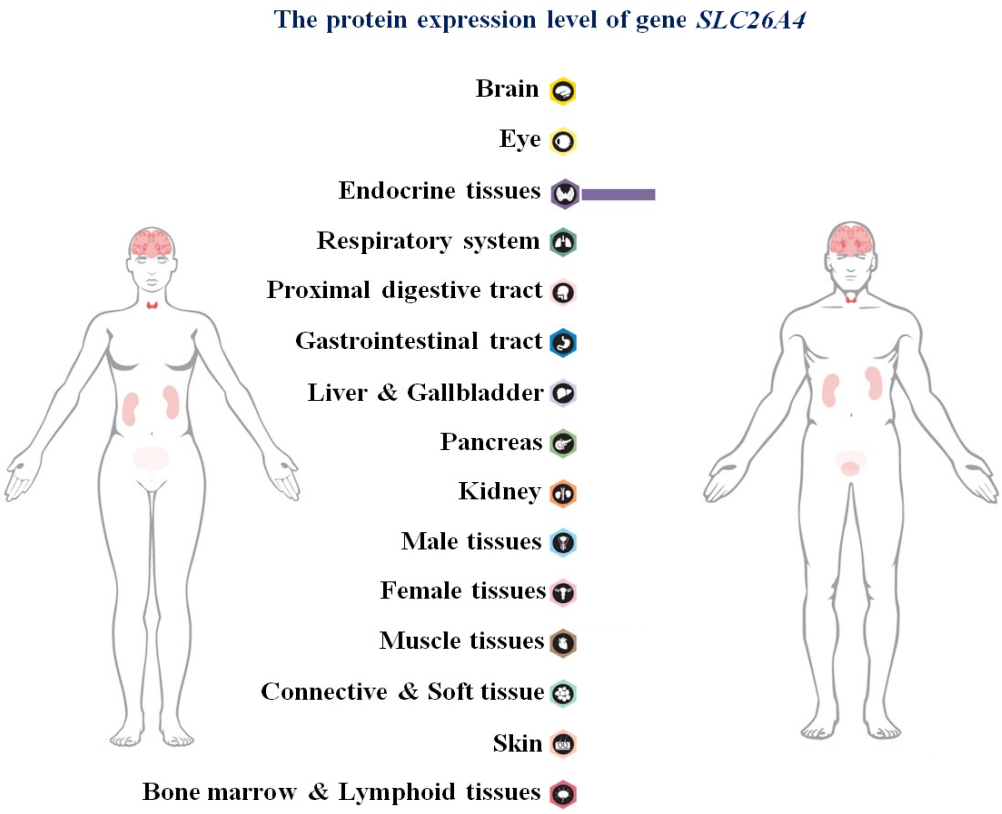

Fig. 7. Expression profile of gene *SLC26A4* in different organs of the body

4. Discussion

Manifestations of hearing are different; it is usually seen as moderate to profound sensor neural hearing loss. Hearing loss is usually diagnosed in the first two years of life and is often symmetrical. Considering the high prevalence of pendred syndrome as the second most common syndrome of deafness and also the frequency of consanguineous marriages, this disease, like any autosomal recessive disease, has a wide prevalence and the possibility of obtaining a molecular diagnosis, and genetic counseling seems essential for families [33]. So far, no significant relationship between the type and severity of goiter with the type of mutation in the *SLC26A4* gene has been reported. Considering the widespread prevalence of goiter disease, its association with deafness alone does not indicate pendred syndrome unless a person with deafness and goiter shows a linkage to the DFNB4 locus. In these cases, it is necessary to perform other complementary thyroid tests such as thyroid function tests and perchlorate discharge tests in these people. Radiological changes of the inner ear and cochlea help to diagnose Pendred syndrome as a valuable diagnostic test, but the non-specificity of this test and the normalization of its findings do not alone determine the diagnosis of Pendred syndrome. Therefore, the totality of these findings indicates the necessity of conducting a molecular test to find the connection between the DFNB4 locus in non-syndromic deaf people [33].

It is worth mentioning that due to the different spectrum of identified mutations, it seems necessary to continue more extensive studies, including the study of the whole gene and studies on syndromic and non-syndromic hereditary deafness families. It is also necessary to evaluate the identified changes by DNA sequencing. This case is very effective for identifying other mutations of this locus in the deaf population. Understanding the genetic causes of deafness has important benefits. This knowledge not only allows doctors to inform families about their chances of having a hearing-impaired child, but it can also influence how people are treated for deafness [34].

5. Conclusion

The research conducted in this study along with the analysis of genes related to hearing in humans emphasizes the necessity of using bioinformatics in treatment. Analyzing data from genome sequencing, gene expression, and investigating mutations or gene variants that can affect the patient's response to a specific drug or change the prognosis of the disease is essential. The collection of these factors, along with the examination of databases and specialized software, has had a remarkable approach in the field of clinical trials and diagnosis and prevention of genetic diseases, which are expected to be used in the stages of gene therapy.

Conflict of Interests

All authors declare no conflict of interest.

Ethics approval and consent to participate

No human or animals were used in the present research.

Consent for publications

All authors read and approved the final manuscript for publication.

Informed Consent

The authors declare not used any patients in this research.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors had equal role in study design, work, statistical analysis and manuscript writing.

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