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Investigating the Genetic Characteristics of Cochlear Implant Candidates with Hearing Impairment

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Abstract

Background: Hearing loss, especially at a young age, has severe personal and social consequences for a person and brings enormous costs to the treatment system. Considering the vital role of genetics in hearing loss, genetics research creates a suitable platform for progress in the treatment of these patients, so we decided to conduct a study with the aim of early diagnosis and even before symptoms appear in order to reduce possible complications.

Aim: In this study early diagnosis of hearing loss and even before symptoms appear in order to reduce possible complications.

Methods: Based on the history and phenotype and examination of the medical records of 1249 patients who are candidates for cochlear implantation, genetic testing among the patients suspected of non-syndromic genetic hearing loss, a request for genetic testing of stage one or two or both was made and according to the willingness of the families and their cooperation A total of 138 genetic tests were performed and subjected to genetic analysis.

Results: Among 138 tested cases, 71 women and 67 men, NSHL inheritance autosomal recessive pattern was 84/78% and autosomal dominant, 5/07 which is very close to previous studies. There were genetic mutations in the Gjb2 gene in ten cases of patients. Ninety-one patients were negative for GJB2 involvement and were candidates for WES, but unfortunately, many families refused to perform the test due to the cost of this test. Seven patients underwent WES, and several genetic mutations were identified in the thesis. WES was performed for 34 patients according to the investigations carried out directly.

Conclusion: Iranian society has played an essential role in improving our understanding of the genes involved in proper hearing functioning and how these genes' variants cause hearing loss. Researchers have worked tirelessly to solve the genetic mystery of hearing loss in Iran, which has been very successful. However, more work is still needed.

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Introduction

Hearing loss (HL) is a widespread sensorineural disorder that affects approximately 466 million people globally (1). It can be caused by various environmental factors such as drugs, infections, or injury and can range from mild to profound, impacting

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one or both ears (2). The disorder can be congenital or occur later in life and is due mainly to genetic factors in over 60% of cases in developed countries (3). Non-syndromic hearing loss (NSHL) makes up two-thirds of congenital cases, with the remaining third being syndromic forms of HL. NSHL can be inherited in various ways, including autosomal recessive (75-80%), autosomal dominant (20-25%), X-linked, or in rare cases, mitochondrial inheritance (4-6). Over 400 genetic disorders have been linked to hearing loss, with more than 120 deafness-specific genes identified. The most common syndromes include Pain, Wardenberg, BOR, and Usher (7). In Iran, hearing loss is the second most common disorder after mental retardation, affecting 1 in 166 people. Over the past 30 years, several HL-related genes have been identified in Iranian families. Next-generation sequencing has dramatically improved the genetic screening of disorders with high genetic and allelic heterogeneity, such as hearing loss, by allowing for the simultaneous identification of hundreds of genes in several patients. Exome sequencing has become the preferred method for studying families with Mendelian traits and has led to the discovery of over 32 new NSHL genes (8). Most cases of congenital hearing loss (80%) are caused by membrane abnormalities in the inner ear, while the remaining 20% are associated with bony labyrinth abnormalities (9). Cochlear implantation response in patients is affected by various factors, including age, duration of hearing loss, and the degree of residual hearing. In conclusion, early molecular diagnosis can help reduce hearing loss's socio-economic and psychological impact on affected individuals and their families. Genetic identification of patients is crucial for providing helpful information such as disease type, inheritance mode, and prognosis (9, 10). Considering the importance of inner ear abnormalities and genetic characteristics in the results of cochlear implantation, as well as the lack of a study to investigate the prevalence of genes involved in bone abnormalities, in this study, the children who were candidates for cochlear implantation at the Cochlear Implant Center of Loghman Hakim Hospital examine the genetic profile and also examine the clinical information of the patients that was available in the archived files (11).

Methods

Type of study

This study was a descriptive investigation of patients with hearing loss who were referred to the Cochlear Implant Center of Loghman Hakim Hospital until 1400.

A census sampling method was used, and 1299 candidates for cochlear implantation were examined. The hearing loss patients were divided into two categories: genetic and non-genetic, which further included two sub-categories: syndromic and non-syndromic. To be included in the study, patients had to meet specific criteria, such as referral to the Cochlear Transplantation Center of Loghman hakim Hospital for cochlear implantation and no history of meningitis, neonatal jaundice, labyrinthitis, or exposure to teratogenic substances. On the other hand, exclusion criteria included infection, perinatal problems, or exposure to teratogenic substances. The study began with genetic counseling for patients who were candidates for cochlear implantation. Patients suspected of non-syndromic genetic hearing loss were then subjected to genetic sequence examination with the opinion of a genetic specialist. This examination was divided into three stages, two of which were performed in Iran. It involved a blood serum sample test based on the patient's history, a file review by a geneticist, and an examination of all cochlear implant patient files from the last ten years in the hospital transplant department archives.

Statistical

After collecting information through a questionnaire, a geneticist analyzed the exome

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sequencing test results to investigate the relationship between genetic sequences and inner ear anomalies. The gene sequence was first investigated and then confirmed through a separate experiment. Finally, the geneticist analyzed the significant relationship between the genetic changes of the two syndromic and non-syndromic groups.

Results

In this study, the records of 1299 patients were analyzed, and 50 were excluded due to lacking information. Out of the remaining 1249, 1004 had not any history of hearing loss, 47 had a positive history, and 198 had an unknown status. The anomaly index results showed that 1086 patients had negative history, 122 had a positive history, and 41 had an unknown status. These patients were then contacted and asked to undergo a genetic test. Out of 138 participants who consented to the test, seven were found to have non-syndromic hearing loss caused by autosomal dominant inheritance, 117 had non-syndromic hearing loss resulting from the autosomal recessive inheritance, 6 had a combination of dominant and recessive autosomal inheritance leading to non-syndromic hearing loss, and one individual had non-syndromic hearing loss due to a combination of dominant autosomal, recessive autosomal, and recessive sex-linked inheritance patterns. After undergoing genetic evaluations (GJB2 gene test and WES test), it was found that 10 had mutations in the GJB2 gene, while 109 had no mutations (86 had the GJB2 gene test and 20 had the WES test). Three patients were tested for deletion mutations in the mitochondrial genome or the presence of mutations in the NF2 gene and received negative results. Out of the 91 patients who received negative results for the GJB2 gene test, 7 underwent the WES test, and 5 of them had mutations in genes like MYH14, MYO3A, CEP78, USH2A, GPSM2, COL4A4, MYO15A, POU4F3, COL4A6, PCDH15, CDH23, MYO1A, and TECTA. The results of the WES test were negative for the other two patients. Additionally, 34 patients underwent the WES test directly, and 14 had pathogenic mutations in genes like SYNE4, PTPN11, PEX6, TECTA, MYOT, LOXHD1, MYO1A, MYO7A, CLIC5, MYO15A, PCDH15, MYH14 and EPS8L2, CDC14A, TRIOBP, TJP2, and WFS1 (Table 1).

Table 1. List of these mutations

Gender	Pt. num	InherItance pattern	Genetic analysis	Result
Male	1	AD	WES	Het (c.583C>T / N) in PAX6
Female	2	AD	WES	Het (p.R708R/N) in WFS1
Female	3	AR	GJB2	Negative
Male	4	AR	GJB2	Negative
Male	5	AR	GJB2	Negative
Male	6	AR	WES	Negative
Male	7	AR	GJB2	Het (p.lys188fs/N)
Male	8	AR	WES	Negative
Male	9	AR	GJB2	Negative
Male	10	AR	GJB2	Negative
Male	11	AR	GJB2	Negative
Male	12	AR	WES	Negative
Male	13	AR	GJB2	Negative
Male	14	AR	GJB2	Negative

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Male	15	AR	GJB2 / WES	No mutation was found in the GJB2 gene. Targeted NGS result: the individual is homozygous for c.9437A>C mutation in MYO15A gene.
Male	16	AR	GJB2	Het (c.487A>G/N)
Male	17	AR	GJB2	Negative
Male	18	AR	WES	Negative
Male	19	AR	GJB2	He is homozygous for c.35delG(p.G12>vfs) mutation in GJB2 gene.
Male	20	AR	GJB2	Negative
Male	21	AD	WES	Heterozygote nonsense variant(c.1126C>T) in CDC14A gene
Male	22	AR	WES	Negative
Male	23	AR	GJB2	Negative
Male	24	AD	WES	Heterozygote for c.4-11 dup CCGGTGCG (P.G5Rfs26) mutation in TJP2 gene
Male	25	AR	WES	Negative
Male	26	AR	GJB2	Negative
Male	27	AR	GJB2	Negative
Male	28	AR	GJB2	Negative
Male	29	AR	WES	SYNE4 gene (c.563_564 ins GA)
Male	30	AR	GJB2	Negative
Male	31	AR	GJB2	Negative
Male	32	AR	GJB2	Negative
Male	33	AR	WES	PEX6 (c.231 C>A)(p.Ser77Arg)
Male	34	AR	GJB2	c.35 del G (p.Gly 12 Valfs) hemozygote
Male	35	AR	GJB2	Negative
Male	36	AR	WES	Negative
Male	37	unknown	GJB2	Negative
Male	38	AR	GJB2	Negative
Male	39	AR	GJB2	Negative
Male	40	AR/AD	WES	MYO7A(AD/AR),MYO1A(AD),CLIC5(AR) ,MYO15A(AR)
Male	41	AR	GJB2	Negative
Male	42	AR	GJB2	Negative
Male	43	AD	WES	Heterozygote for c.4130 T>C(P.F13775) mutation in ESP8L2 gene
Male	44	AR	GJB2	Negative
Male	45	AR	GJB2	Negative
Male	46	AR	GJB2	Negative
Male	47	AR	GJB2	Negative
Male	48	AR	GJB2	Negative
Male	49	AR	GJB2	Negative
Male	50	AR	GJB2	Negative
Male	51	AR	GJB2	Negative
Male	52	AR	GJB2	Negative
Male	53	AR	GJB2 / WES	Negative

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Male	54	AR	GJB2	Negative
Male	55	AR	GJB2	Negative
Male	56	AR	WES	Negative
Male	57	AR	GJB2	Negative
Male	58	unknown	GJB2 / WES	c.236_239 Del TGCA ins AGATCCG heterozygote
Male	59	AR	GJB2	Negative
Male	60	AR	GJB2	Negative
Male	61	AR	GJB2 / WES	Negative
Male	62	AR	Mitochondrial mutation detection	Negative
Male	63	AR	WES	Negative
Male	64	AD	WES	Heterozygote for C1489T Mutation in TRIOBP
Male	65	AR	WES	Negative
Male	66	AR	WES	Negative
Male	67	AR	GJB2	Negative
Female	68	AR	Mitochondrial mutation detection	Negative
Female	69	AR	GJB2	Negative
Female	70	AR	GJB2	Negative
Female	71	AR	GJB2	Negative
Female	72	AR	GJB2	Negative
Female	73	AR	GJB2	Negative
Female	74	AR	GJB2	Negative
Female	75	AR	GJB2	Negative
Female	76	AR	GJB2	Negative
Female	77	AR	WES	Negative
Female	78	AR	GJB2	The 35delG mutation was found to be heterozygous, so it is a carrier
Female	79	AR	GJB2	Negative
Female	80	AR	WES	Negative
Female	81	AR	GJB2	Negative
Female	82	unknown	GJB2	Negative
Female	83	AR	GJB2	Homozygote for c.35 del G(P.G12.Vfs)
Female	84	AR	WES	Negative
Female	85	AR	GJB2	Negative
Female	86	unknown	WES	Negative
Female	87	AR	GJB2	Negative
Female	88	AR	GJB2	The person is heterozygous for c.341A>G(p.E114G) and c.79G>A(p.V27I) mutations in GJB2 gene.
Female	89	AD	WES	MYH14(AD),LOXHD1(AR),PCDH15(AR)
Female	90	AR	WES	TECTA(AR)
Female	91	AR	GJB2	Negative

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Female	92	AR/AD	GJB2 / WES	Negative in GJB2
Female	93	AR/AD	GJB2 / WES	No mutation was found in the GJB2 gene. WES result as: (AD) MYO3A(AD/AR),MYH14
Female	94	AR	GJB2	Negative
Female	95	AR	WES	Negative
Female	96	AR	GJB2	Negative
Female	97	AR	GJB2	Negative
Female	98	AR	GJB2	Negative
Female	99	AR	GJB2	Negative
Female	100	AR	GJB2	Negative
Female	101	unknown	GJB2	Negative
Female	102	AR	GJB2	Negative
Female	103	AR	GJB2	Negative
Female	104	AR	GJB2	Negative
Female	105	AR/AD	WES	PTPN11(AD)
Female	106	AR	WES	Negative
Female	107	AR	GJB2	Negative
Female	108	AR	WES	Negative
Female	109	AR	GJB2	Negative
Female	110	AR	GJB2	Negative
Female	111	AR	GJB2	Het (c.79G>A/N)
Female	112	AR	GJB2	Negative
Female	113	AR	GJB2	Negative
Female	114	AR	GJB2	Negative
Female	115	AR	GJB2	Negative
Female	116	AR	GJB2	Negative
Female	117	AR	WES	Hom (c.584G>A) in EPS8L2
Female	118	AR	GJB2	Negative
Female	119	AR	GJB2	Negative
Female	120	AR	GJB2	Negative
Male	121	AR	GJB2 / WES	Negative in GJB2
Male		AD	GJB2 / WES	Het (p.C305C/N) in TECTA
Male		AD	GJB2 / WES	Het (splicing) in MYO1A
Male		AD/AR	GJB2 / WES	Het (p.Y2574Y/N) in CDH23
Male		AD/AR	GJB2 / WES	Het (P.N637S/N) in PCDH15
Female	122	AR/AD	WES	MYOT(AD),LOXHD1(AR)
Female	123	AR	GJB2 / WES	No mutation was found in the GJB2 gene. WES result as: (AR)COL4A4(AD/AR),GPSM2(AR),USH2A(AR),CEP78
Female	124	AR	GJB2	Negative
Female	125	AR	GJB2	Negative
Female	126	AR	GJB2	Negative
Female	127	AR	GJB2	Negative
Female	128	AR	GJB2	Negative

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Female	129	AR	GJB2	Het (c.164-4G>A / N)
Female	130	unknown	GJB2	Negative
Female	131	AR/AD	WES	Negative
Female	132	unknown	WES	Negative
Female	133	AR	NF2 / WES	Negative
Female	134	AR	GJB2	Negative
Female	135	AR	GJB2	Negative
Female	136	AR	GJB2	Negative
Female	137	AR	GJB2	Negative
Female	138	AR	GJB2	Negative
Male		AR	GJB2 / WES	Negative in GJB2
Male	139	AD	GJB2 / WES	Het (c.145T>G/N) in POU4F3
Male		XLR	GJB2 / WES	Hemizygote for c.1359G>T in COL4A6

Discussion

The study involved 138 participants who underwent genetic testing for Non-Syndromic Hearing Loss (NSHL). The results indicated that 5.07% of NSHL cases were due to autosomal dominant inheritance, 84.78% were due to autosomal recessive inheritance, and 4.34% were a combination of autosomal dominant and recessive inheritance. Also, 0.72% of individuals had all three inheritance patterns (autosomal dominant, autosomal recessive, and sex-linked recessive), while 5.07% had an uncertain inheritance pattern. It is similar to previous studies, which have reported autosomal recessive NSHL at a rate of 75-80%, autosomal dominant NSHL at a rate of 20-25%, X-linked NSHL at a rate of 1-2%, and rare cases of mitochondrial NSHL (36). The study found that 51.44% of the 138 individuals or families investigated were women, and 48.56% were men. Following genetic evaluations, which included the GJB2 gene evaluation test and the whole exome sequencing (WES) test, it was determined that ten individuals had mutations in the GJB2 gene. Of the 91 patients who received a negative result for the GJB2 gene evaluation, 7 underwent the WES test, and 5 of them had disease-causing mutations in genes such as MYH14, MYO3A, CEP78, USH2A, GPSM2, COL4A4, MYO15A, POU4F3, COL4A6, PCDH15, CDH23, MYO1A, and TECTA. The WES test was negative for the remaining two patients. Presently, the WES test was requested for 34 individuals, and 14 of them had pathogenic mutations in genes such as SYNE4, PTPN11, PEX6, TECTA, MYOT, LOXHD1, MYO1A, MYO7A, CLIC5, MYO15A, PCDH15, MYH14, EPS8L2, CDC14A, TRIOBP, TJP2, and WFS1. It means that the cause of the disease was determined in 46.36% of the 41 individuals who underwent the WES test. However, it is worth noting that many patients who received a negative result for the GJB2 mutation were unwilling to pay for the WES test due to its high cost, making it challenging to find the disease-causing mutation in these individuals. Previous studies have shown that comprehensive genetic testing for deafness leads to a diagnosis in approximately 50% of patients globally (12).Despite the heterogeneous nature of NSHL, screening for the GJB2 gene has shown an unexpectedly high diagnostic rate. It may be because the GJB2 gene has only one coding exon, making it relatively simple to screen and analyze using direct sequencing or restriction fragment length polymorphism (RFLP) testing. The GJB2 gene variant has been linked to different clinical outcomes, with more than 100 variants reported in ARNSHL. Though caused by a few

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variants, Autosomal dominant hearing loss is frequently related to skin conditions, including deafness combined with plantar keratoses, deafness accompanied by ichthyosis hystrix-like, and keratitis (13-16). The genetic basis of hereditary hearing loss (HL) varies across different populations, with specific variants identified as the leading cause in different ethnic groups. In the Caucasian population, the c.35delG (p. Gly12Valfs2) variant is the most common cause of HL, with a carrier frequency of 2-4% and an average rate of 1.89% in Europe (17). On the other hand, the c.235delC (p. Leu79Cysfs3) variant is prevalent in East Asian patients. Other variants linked to HL include c.167delT (Leu56Argfs*26) in Ashkenazi Jews and c.427C>T (p. Arg143Trp) in Ghanaians (18). Studies on the genetic basis of HL in Iran began in 2002 with the analysis of the GJB2 gene by Najmabadi et al. They used SSCP, nested, and ARMS-PCR techniques for screening and direct sequencing to detect variants in the gene (17). The incidence of GJB2-related HL in Iran has shown significant variation between ethnic groups, with an overall incidence of 16.5%. The frequency of c.35delG is the highest in the Gilan province in northern Iran, suggesting a founder effect in this region (19, 20). New variants of the GJB2 gene have been reported in the Iranian population, with most being associated with ARNSHL and a few being linked to non-syndromic autosomal dominant hearing loss (21). Identifying the genetic cause of hearing loss in families has become increasingly challenging with the discovery of more genes associated with this condition. Babanjad et al. conducted a study on 144 Iranian negative GJB2families and identified causative variants in 23% of families in ten genes (MYO15A, SLC26A4, ILDR1, TECTA, TMC1, PJVK, LRTOMT, OTOF, MARVELD2, and MYO7A) using linkage analysis and Sanger sequencing. The study highlighted Iran's genetic and allelic heterogeneity, similar to research findings in other countries (22). In 2016, Bademci et al. used ES to screen for known ARNSHL gene variants in 160 families from various countries, including Iran. They discovered pathogenic or possibly pathogenic variants in eight genes in 13 Iranian families (MYO15A, MYO7A, SLC26A4, CDH23, ILDR1, PCDH15, USH1C, and TECTA) (23). In 2021, Mohseni et al. identified eight new candidate genes for autosomal recessive HL (DBH, TOP3A, COX18, USP31, SCP2, and CARMIL1), autosomal dominant AL and X-linked recessive HL (TCF19 and TENM1) in 76 consanguineous Iranian families using ES (18). In 2022, a similar study was conducted in a Pakistani cohort, reporting ADAMTS1, MPDZ, MVD, and SEZ6 as novel candidate genes for ARNSHL (24). Identifying the genes associated with hearing loss is still challenging, particularly for the rare forms of genetic deafness where the causative gene is present in only a limited number of families. Determining these causative variants can be helpful in genetic counseling, risk assessment, and in some cases, choosing the best rehabilitation approach. The recent advent of NGS technology has resulted in a significant increase in the number of known deafness genes and the detection rate of HL in Iran. Despite using Next Generation Sequencing (NGS), detecting Non-Syndromic Hearing Loss (NSHL) is not always accurate due to various factors. These may include technological limitations such as low coverage or a causative variant in an uncovered region. Additionally, Iran's high incidence of consanguineous marriages contributes to internal family heterogeneity. Due to accurate diagnosis and proper genetic counseling, it is crucial to evaluate clinical and molecular data thoroughly (8).

Conclusion

The Iranian population has made significant contributions towards gaining knowledge about the genes responsible for proper

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hearing and the various genetic variations leading to hearing loss. Despite the progress that has been made in unraveling the genetic mystery of hearing loss in Iran, further research is still required.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Ethics

This study has been approved by the ethical committee of sbmu with the code of ethics (IR.SBMU.MSP.REC.1400.172).

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