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LARGE DELETIONS IN VLGR1 CAUSES ASCHER SYNDROME TYPE IIC IN MALE AND FEMALE PATIENTS IN A FAMILY OF TABRIZ – IRAN

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ABSTRACT

Ascher syndrome is a genetically and clinically heterogeneous disease. Tuesday clinical phenotype of the syndrome, including USH1, USH2, USH3 be caused by mutations in ten different genes. Ascher syndrome type IIC (USH2C) with mild to severe hearing loss, Retinopigmentosa and normal vestibular function characterized. Previous reports of mutations in VLGR1 this phenotype is shown in 5 families. In this study, we evaluated the deaf person is a family-Tabrizi 9, 7 person who participated in this project. Five patients had a phenotype consistent with Ascher syndrome, but two other people who were non-syndromic deafness, had this haplotype. We have identified a new mutation in VLGR1 this family. This mutation is a large deletion G.371657-507673del and contains 84 exons and 85 and is likely to change the format. In the family described a male with USH2C first mutation was identified in VLGR1.

KEYWORDS: Ascher syndrome type IIC (USH2C), Tabriz, Iran, gene VLGR1.

INTRODUCTION

Usher syndrome is a relatively rare genetic disorder caused by a mutation in any one of at least 11 genes resulting in a combination of hearing loss and visual impairment and is a leading cause of deafblindness. Usher syndrome is incurable at present.

Other names for Usher syndrome include **Hallgren syndrome**, **Usher-Hallgren syndrome**, **retinitis pigmentosa-dysacusis syndrome**, and **dystrophia retinae dysacusis syndrome**.[1]

Characteristics

This syndrome is characterized by hearing loss and a gradual visual impairment. The hearing loss is caused by a defective inner ear, whereas the vision loss results from retinitis pigmentosa (RP), a degeneration of the retinal cells. Usually, the rod cells of the retina are affected first, leading to early night blindness and the gradual loss of peripheral vision. In other cases, early degeneration of the cone cells in the macula occurs, leading to a loss of central acuity. In some cases, the foveal vision is spared, leading to "doughnut vision"; central and peripheral vision are intact, but an annulus exists around the central region in which vision is impaired.

Usher syndrome has three clinical subtypes, denoted as I, II and III.[2] People with Usher I are born profoundly deaf and begin to lose their vision in the first decade of life. They also exhibit balance difficulties and learn to walk slowly as children, due to problems in their vestibular system. People with Usher II are not born deaf, but do have hearing loss. They do not seem to have noticeable problems with balance; they also begin to lose their vision later (in the second decade of life) and may preserve some vision even into middle age. People with Usher syndrome III are not born deaf, but experience a gradual loss of their hearing and vision; they may or may not have balance difficulties.

Usher syndrome is a variable condition; the degree of severity is not tightly linked to whether it is Usher I, II, or III. For example, someone with type III may be unaffected in childhood, but go on to develop a profound hearing loss and a very significant loss of sight by early to midadulthood. Similarly, someone with type I, who is therefore profoundly deaf from birth, may keep good central vision until the sixth decade of life, or even beyond. People with type II, who have useful hearing with a hearing aid, can experience a wide range of severity of the RP. Some may maintain good reading vision into their 60s, while others cannot see to read while still in their 40s.

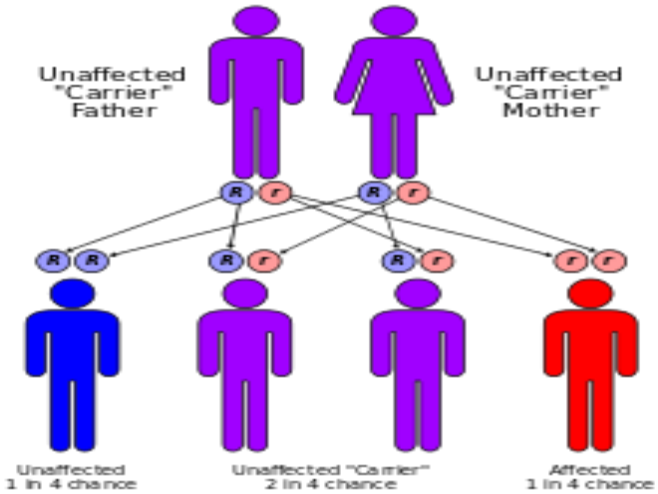
Usher syndrome I and II are associated with a mutation in any one of six or three different genes, respectively, whereas only one mutation has been linked with Usher III. Since Usher syndrome is inherited in an autosomal recessive pattern, both males and females are equally likely to inherit it. Consanguinity of the parents is a risk factor. Children of parents who both are carriers of the same mutation have a one-fourth chance of inheriting the condition and children of such parents who are unaffected have a one-half chance of being carriers. Children of parents where only one parent is a carrier have a no chance of having the disease,

but have a one-half chance of being a carrier. First recognized in the 19th century, Usher syndrome was the first condition to demonstrate that phenotypes could be inherited in tandem; deafness and blindness are inherited together, but not separately. Animal models of this human disease (such as knockout mice and zebrafish) have been developed recently to study the effects of these gene mutations and to test potential cures for Usher syndrome.

History

Usher syndrome is named after the Scottish ophthalmologist Charles Usher, who examined the pathology and transmission of this illness in 1914 on the basis of 69 cases.[3] However, it was first described in 1858 by Albrecht von Gräfe, a pioneer of modern ophthalmology.[4] He reported the case of a deaf patient with retinitis pigmentosa, who had two brothers with the same symptoms. Three years later, one of his students, Richard Liebreich, examined the population of Berlin for disease pattern of deafness with retinitis pigmentosa.[5] Liebreich noted Usher syndrome to be recessive, since the cases of blind-deafness combinations occurred particularly in the siblings of blood-related marriages or in families with patients in different generations. His observations supplied the first proofs for the coupled transmission of blindness and deafness, since no isolated cases of either could be found in the family trees.

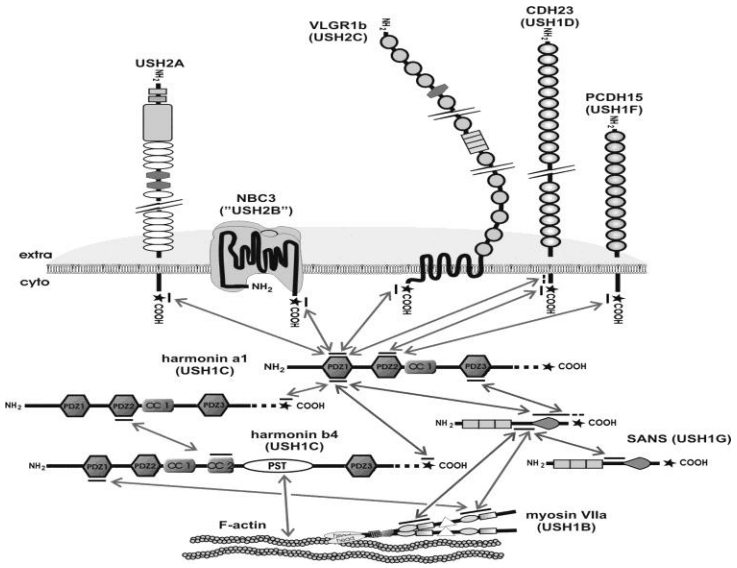
Symptoms and subtypes



Usher syndrome is inherited in an autosomal recessive pattern. The genes implicated in Usher syndrome are described below.

Usher syndrome is responsible for the majority of deaf-blindness.[6] The word *syndrome* means that multiple symptoms occur together, in this case, deafness and blindness. It occurs

in roughly 1 person in 23,000 in the United States,[7] 1 in 28,000 in Norway[8] and 1 in 12,500 in Germany.[9] People with Usher syndrome represent roughly one-sixth of people with retinitis pigmentosa.[2]



Usher syndrome is inherited in an autosomal recessive pattern. "Recessive" means both parents must contribute an appropriate gene for the syndrome to appear and "autosomal" means the gene is not carried on one of the sex chromosomes (X or Y), but rather on one of the 22 other pairs. (See the article on human genetics for more details.).

The progressive blindness of Usher syndrome results from retinitis pigmentosa.[10][11] The photoreceptor cells usually start to degenerate from the outer periphery to the center of the retina, including the macula. The degeneration is usually first noticed as night blindness (nyctalopia); peripheral vision is gradually lost, restricting the visual field (tunnel vision), which generally progresses to complete blindness. The qualifier 'pigmentosa' reflects the fact that clumps of pigment may be visible by an ophthalmoscope in advanced stages of degeneration.[2]

Although Usher syndrome has been classified clinically in several ways,[12][11][13] the prevailing approach is to classify it into three clinical sub-types called Usher I, II and III in order of decreasing severity of deafness.[10] Usher I and II are the more common forms; the fraction of people with Usher III is significant only in a few specific areas, such as Finland[14] and Birmingham.[15] As described below, these clinical subtypes may be further subdivided by the particular gene mutated; people with Usher I and II may have any one of six and three

genes mutated, respectively, whereas only one gene has been associated with Usher III. The function of these genes is still poorly understood. The hearing impairment associated with Usher syndrome is better understood: damaged hair cells in the cochlea of the inner ear inhibit electrical impulses from reaching the brain.

Usher syndrome I

People with Usher I are usually born deaf and often have difficulties in maintaining their balance owing to problems in the vestibular system. Babies with Usher I are usually slow to develop motor skills such as walking. Worldwide, the estimated prevalence of Usher syndrome type I is 3 to 6 per 100,000 people in the general population.

Usher syndrome type I can be caused by mutations in any one of several different genes: *CDH23*, *MYO7A*, *PCDH15*, *USH1C* and *USH1G*. These genes function in the development and maintenance of inner ear structures such as hair cells (stereocilia), which transmit sound and motion signals to the brain. Alterations in these genes can cause an inability to maintain balance (vestibular dysfunction) and hearing loss. The genes also play a role in the development and stability of the retina by influencing the structure and function of both the rod photoreceptor cells and supporting cells called the retinal pigmented epithelium. Mutations that affect the normal function of these genes can result in retinitis pigmentosa and resultant vision loss.

Type I has been found to be more common in people of Ashkenazi Jewish ancestry (central and eastern European) and in the French-Acadian populations (Louisiana).

Usher syndrome II

People with Usher II are generally hard-of-hearing rather than deaf and their hearing does not degrade over time; moreover, they generally have a normal vestibular system. Usher syndrome type II occurs at least as frequently as type I, but because type II may be underdiagnosed or more difficult to detect, it could be up to three times as common as type I. Usher syndrome type II may be caused by mutations in any of three different genes: *USH2A*, *GPR98* and *DFNB31*. The protein encoded by the *USH2A* gene, usherin, is located in the supportive tissue in the inner ear and retina. Usherin is critical for the proper development and maintenance of these structures, which may help explain its role in hearing and vision loss. The location and function of the other two proteins are not yet known.

Usher syndrome III

By contrast, people with Usher III experience a 'progressive' loss of hearing and roughly half have vestibular dysfunction. The frequency of Usher syndrome type III is highest in the Finnish population, but it has been noted rarely in a few other ethnic groups.

Mutations in only one gene, *CLRN1*, have been linked to Usher syndrome type III. *CLRN1* encodes clarin-1, a protein important for the development and maintenance of the inner ear and retina. However, the protein's function in these structures and how its mutation causes hearing and vision loss, is still poorly understood.

Differential diagnosis

Since Usher syndrome is incurable at present, it is helpful to diagnose children well before they develop the characteristic night blindness. Some preliminary studies have suggested as many as 10% of congenitally deaf children may have Usher syndrome.[1] However, a misdiagnosis can have bad consequences.

The simplest approach to diagnosing Usher syndrome is to test for the characteristic chromosomal mutations. An alternative approach is electroretinography, although this is often disfavored for children, since its discomfort can also make the results unreliable.[1] Parental consanguinity is a significant factor in diagnosis. Usher syndrome I may be indicated if the child is profoundly deaf from birth and especially slow in walking.

Thirteen other syndromes may exhibit signs similar to Usher syndrome, including Alport syndrome, Alstrom syndrome, Bardet-Biedl syndrome, Cockayne syndrome, spondyloepiphyseal dysplasia congenita, Flynn-Aird syndrome, Friedreich ataxia, Hurler syndrome (MPS-1), Kearns-Sayre syndrome (CPEO), Norrie syndrome, osteopetrosis (Albers-Schonberg disease), Refsum's disease (phytanic acid storage disease) and Zellweger syndrome (cerebrohepatorenal syndrome).

Genes associated with Usher syndrome

Table 1: Genes linked to Usher syndrome

Type	Freq[16]	Gene locus	Gene	Protein	Function	Size (AA)	UniProt	OMIM
USH1B	39–55%	11q13.5	*MYO7A*	Myosin VIIA	Motor protein	2215	Q13402	276900
USH1C	6–7%	11p15.1-p14	*USH1C*	Harmonin	PDZ-domain protein	552	Q9Y6N9	276904

USH1D	19–35%	10q21-q22	*CDH23*	Cadherin 23	Cell adhesion	3354	Q9H251	601067
USH1E	rare	21q21	?	?	?	?	?	602097
USH1F	11–19%	10q11.2-q21	*PCDH15*	Protocadherin 15	Cell adhesion	1955	Q96QU1	602083
USH1G	7%	17q24-q25	*USH1G*	SANS	Scaffold protein	461	Q495M9	606943
USH2A	80%	1q41	*USH2A*	Usherin	Transmembrane linkage	5202	O75445	276901
USH2C	15%	5q14.3-q21.1	*GPR98*	VLGR1b	Very large GPCR	6307	Q8WXG9	605472
USH2D	5%	9q32-q34	*DFNB31*	Whirlin	PDZ-domain protein	907	Q9P202	611383
USH3A	100%	3q21-q25	*CLRN1*	Clarin-1	Synaptic shaping	232	P58418	276902

Several genes have been associated with Usher syndrome using linkage analysis of patient families (Table 1) and DNA sequencing of the identified loci.[17][18] A mutation in any one of these genes is likely to result in Usher syndrome. The clinical subtypes Usher I and II are associated with mutations in any one of six (*USH1B-G*) and three (*USH2A*, *C-D*) genes, respectively, whereas only one gene, *USH3A*, has been linked to Usher III so far. Two other genes, *USH1A* and *USH2B*, were initially associated with Usher syndrome, but *USH2B* has not been verified and *USH1A* was incorrectly determined and does not exist.[19] Research in this area is ongoing.

Using interaction analysis techniques, the identified gene products could be shown to interact with one another in one or more larger protein complexes. If one of the components is missing, this protein complex cannot fulfill its function in the living cell and it probably comes to the degeneration the same. The function of this protein complex has been suggested to participate in the signal transduction or in the cell adhesion of sensory cells.[18]

Prospects for gene therapy

Since Usher syndrome results from the loss of a gene, gene therapy that adds the proper protein back ("gene replacement") may alleviate it, provided the added protein becomes functional. Recent studies of mouse models have shown one form of the disease—that associated with a mutation in myosin VIIa—can be alleviated by replacing the mutant gene using a lentivirus.[20] However, some of the mutated genes associated with Usher syndrome encode very large proteins—most notably, the *USH2A* and *GPR98* proteins, which have roughly 6000 amino-acid residues. Gene replacement therapy for such large proteins may be difficult.

Individual cases

A 31-year-old woman with Usher syndrome, Rebecca Alexander, was profiled in *Marie Claire* in November 2007.[21] After graduating from the University of Michigan with excellent marks, Alexander went on to Columbia University, where she earned two master's degrees in public health and clinical social work. Rebecca is an active member of her community, working with various charities in NYC. Rebecca's dedication as an active member of her community was most notably recognized when she was selected as a "Community Hero" to run with the Olympic Torch for the 1996 Atlanta Olympic Games in honor of her volunteer work for Project Open Hand, a nonprofit organization delivering meals to people living with HIV/AIDS in the San Francisco Bay area. Rebecca received her psychodynamic psychotherapy training through the American Institute of Psychoanalysis. She currently works in private practice specializing in the treatment of mood and anxiety disorders, eating disorders, addictions, disability and trauma. While currently facilitating group seminars for the Foundation Fighting Blindness during national conferences, Rebecca is also in the process of launching the Usher III Initiative, a nonprofit organization dedicated to science and research that seeks to find a cure for Usher III. Rebecca teaches indoor cycling/spin classes with a strong following at select gyms in New York City. She was featured on NBC's Today Show on March 20, 2009 which has been nominated for an Emmy award in September 2010. She is the sister of NBC News National Correspondent Peter Alexander. Rebecca appeared again on the Today Show in September 2014 with her brother and discussed her experiences with the disease and her recently released book "Not Fade Away: A Memoir of Senses Lost and Found".

Christine "Coco" Roschaert[22] Born in Ottawa, ON on 5 January 1980. Christine is a well-known person with Usher syndrome. She has published video blogs at YouTube,[23] and recently was the kick-off speaker for the Deaf Awareness Week at the University of Vermont.[24] In 2006, she graduated with a degree in Communication Sciences from Gallaudet University; there, she was a hunger striker in the 2006 protest organized by the Gallaudet United Now Movement.[25] Roschaert is now in Nigeria founding the first deafblind program in that country.

A web-community, UsherLife,[26] of people with Usher syndrome was founded on 1 February 2005 by Nick Sturley. Although centered on Great Britain, it offers resources to all people with Usher syndrome. The organization is hosting regular get-togethers in England, such as

the Usher Hood Pub in Nottingham[27] and a trip to Brighton pier.[28] Other people with Usher syndrome have posted videos about their lives and condition on YouTube, most notably Ginny Paja-Nyholm.[29] In October 2007, Candice, a mom living in Texas, began blogging about her two daughters, Jasmine and Rebecca; Rebecca has Usher syndrome I.[30]

Catherine Fischer has written a well-received autobiography of growing up with Usher syndrome in Louisiana, entitled *Orchid of the Bayou*.[31] Similarly, Vendon Wright has written two books describing his life with Usher syndrome, *I was blind but now I can see*[32] and *Through my eyes*.[33] Louise Boardman has also written a short book called *My son has Usher's Syndrome*.[34]

Christian Markovic is an artist living with Usher syndrome, runs a company, Fuzzy Wuzzy Designs.[35]

Spencer Tracy's son **John** was a well-known person with Usher syndrome who lived a full life.[36] The John Tracy Clinic was founded in 1942 by his mother Louise to offer free help to parents of hearing-impaired infants and preschool children.[1]

Jacob Desormeaux son of horse-racing jockey Kent Desormeaux, has Usher syndrome. Jacob was born deaf and is progressively going blind. Kent dedicated his race in the Belmont Stakes, which would give him and his horse Big Brown the Triple Crown, to his son Jacob. The family has started an organization to raise funds and awareness of the disease. Usher syndrome is disproportionately common among the Cajuns of south Louisiana, such as Desormeaux and Fischer, because of a genetic mutation among early French Acadian settlers in Nova Scotia.

DNA helix co-discoverer and Nobel laureate **James D. Watson** has homozygous *USH1B* mutations, according to his published genome.[37] It is not clear why he did not develop the syndrome. This lack of genetic penetrance argues that expression of the phenotype of Usher syndrome may be more complex than originally assumed.

The Israeli Nalaga'at (do touch) Deaf-blind Acting Ensemble consists of 11 deaf-blind actors, most of whom are diagnosed with Usher syndrome. The theater group has put on several productions and appeared both locally in Israel and abroad in London and Broadway.[38]

Ascher syndrome (USH) is a genetic disorder with autosomal recessive and complex clinical outbreaks of 3 to 6 cases per 100,000 births is.[1] Distinct types of Ascher syndrome (USH1-USH2-USH3) have been identified. All types of deafness and retinitis pigmentosa syndrome characterized. So far, 13 different genetic loci associated with this syndrome have been identified, including 10 genes. At least 5 genes with genes from non-syndromic deafness associated. These genes include: PCDH15, WHRN, CDH23, USH1C, MYO7A.

Ascher syndrome type II, non-progressive congenital deafness is characterized by a more moderate Frequency will occur. Retinitis pigmentosa in the first or second decade of life begins and there is no indication Vestibulary. Three types of Ascher syndrome type II locus with two genes have been identified.

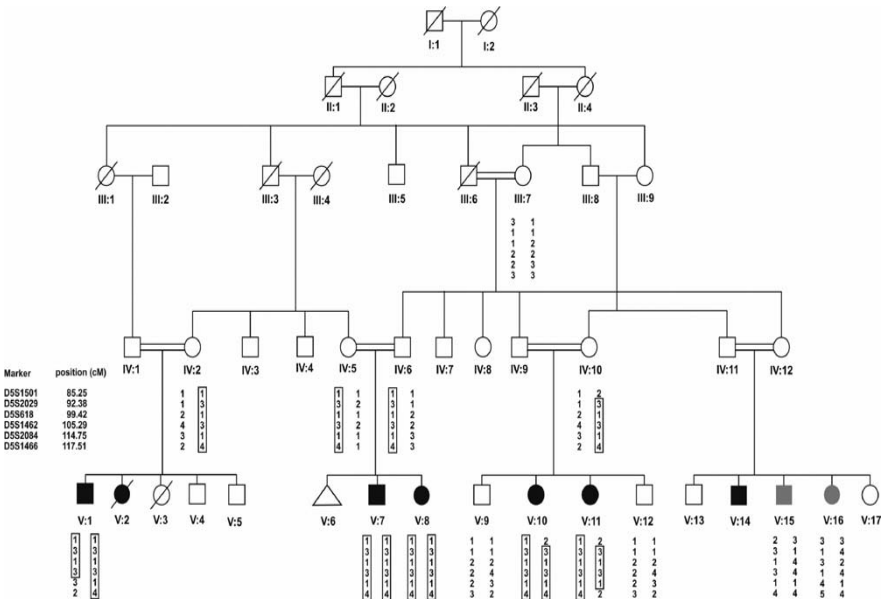


Figure 1: The inheritance pattern of a poplar families with Ascher syndrome IIC: bold signs and symptoms of patients with USH2C hollow showing signs of gray represents the healthy and those with non-syndromic deafness are. On the left to find the candidate markers that have been shown.

In 1998 the three different patient USH2A, as the disease gene on chromosome 1q14 was found to be.[2] In 2000, USH2C on the long arm of chromosome 5 was found in the year 2005, VLGR1 as other genes associated with the disease locus was identified in.[3] VLGR1 gene, a gene is very large size of 605kb. Tuesday isoform mRNA and human VLGR1 identified isoforms of type b is the largest and contains all 90 exons. Isoform a b isoforms of intron 64 starts and contains 26 exons end. isoform c has the same initial codon in exon 31

isoform b, it just is. All three isoforms are involved in the development of the central nervous system. Special function[4] isoforms a and c are unknown. VLGR1 protein molecule is large and is one of the largest known human proteins. The trans-membrane receptor protein to the amine family of seven subfamilies include a VLGR1 belong and have a place proteolysis coupled with protein G (GPS) is. These proteins include various Domain each special function.[5]

MATERIALS AND METHODS

According to Figure 1, 13 individuals participated in this study. Diagnosis is based on clinical examination on 5 individuals with Ascher syndrome (V; 1, V; 7, V; 8, V; 10, V; 11), respectively. Pure tone audiometry (PTA) was performed in sequence ./25,./5,1,2,4,8khz. To search Vesitbulary disorder, Video Alktrvnystagmvgrafy in all patients except V; 1 was performed. To assess ocular abnormalities, according to case, the methods include Optometry, Goldman kinetic Perry meters (slit-lamp biomicroscopy) and electroretinography Fundoscopy a full range cones were used.

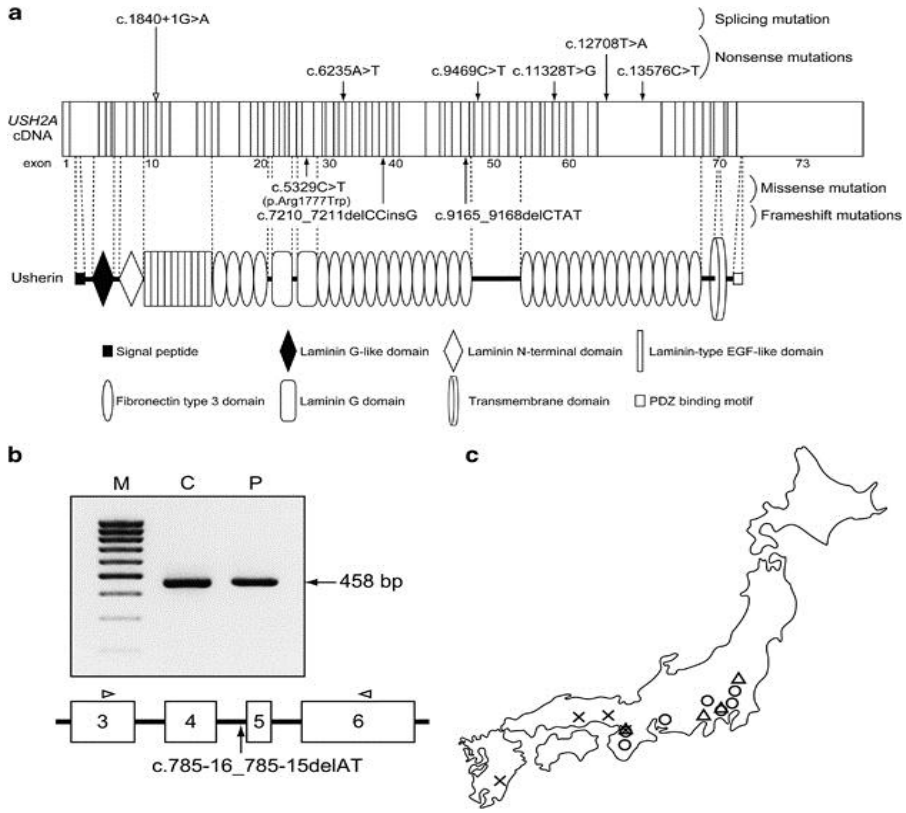


Figure 1: Schematic view of the pattern formed bands in the target gene.

Genetic analysis

Autosomal recessive inheritance and clinical findings on all subjects, SLINK simulations were performed using the Easy Linkage.[6] SLINK scores were above 3.3 Indicative advertisers family enough for linkage analysis was.[7] All genotypes by polymerase chain reaction (PCR) and polyacrylamide gel electrophoresis using standard methods were evaluated. Whole-genome survey by Prevention Gene company is using 400 polymorphic markers throughout the genome-wide Microsattelite are done. Two-point linkage analysis with calculation and multipoint lod score was performed. Fixed parameters for all calculations conjunction with a lod score./001 allele frequency, a level phenocopy 0%, 0% came wt / mt,% 100 for mt / mt applied. Primers for all 90 exons and intron boundaries were designed VLGR1. Moreover, additional primers to detect the removal of fracture interones 83 and 85, were used. Coding exon 1 and exon 2 encodes the GJB2 gene in V; 15 and V; 16 were amplified.

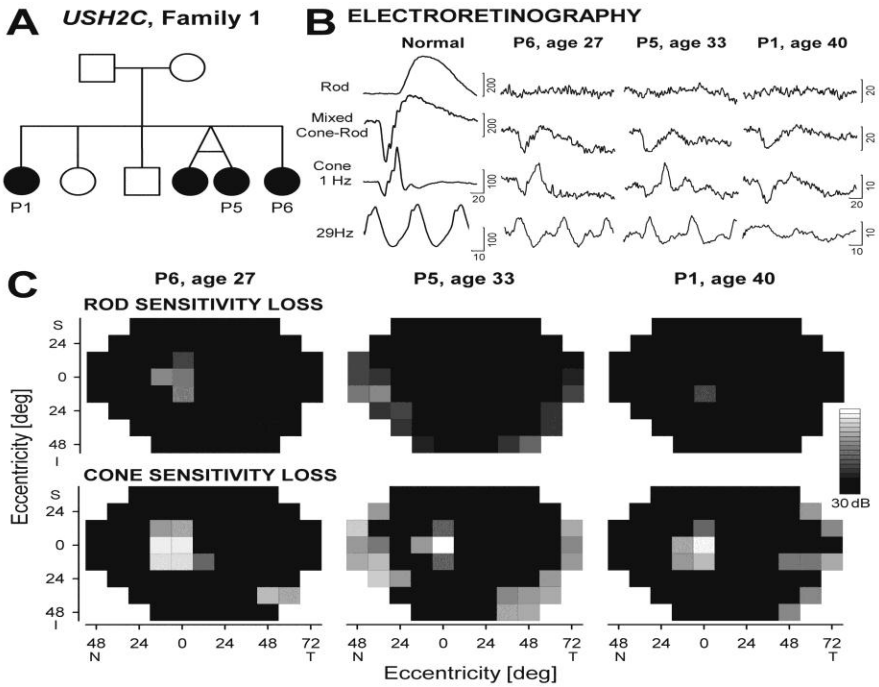


Figure 2: Schematic view of the pattern electroretinography in the target gene.

Findings

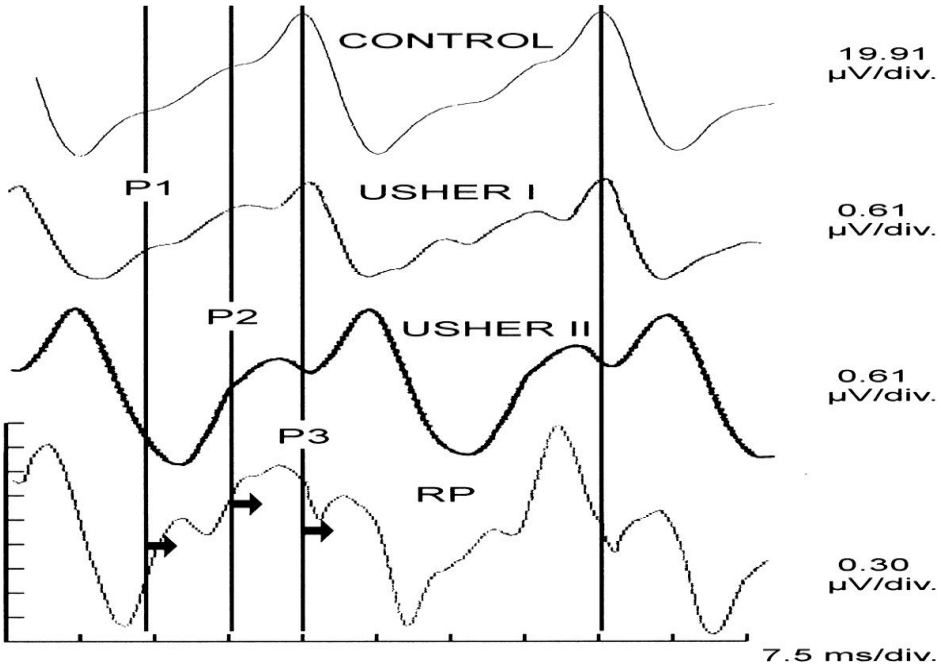
Based on clinical trials, five patients with a phenotype consistent with Ascher syndrome (Women V; 8, V; 10, V; 11) and (Men V; 1, V; 7), respectively. Of V; 2 and V; 14 families were reported as individuals with individual V; 2 feet And one V; 14 did not participate in this study. For the V; 1 (53 years old) audiogram was taken, but no check or balance was eye.

The patient was almost completely blind. Patients V; 15 and V; 16 had a different phenotype. They are not compatible with Ascher syndrome and ocular abnormalities were deaf. Audiometry in all people with Ascher syndrome mild to severe sensory neural hearing loss at all frequencies showed that were associated with increased severity of deafness Frequency. electronistaghemogeraphy for four probands revealed no abnormalities. phondoscopic test pattern in all four patients with retinitis pigmentosa Ascher syndrome showed a possible start in the first or second decade of life.

Table 2: Summary of clinical symptoms in patients with Ascher syndrome type IIC and V; 15 and V; 16 Pical the next hearing.

Person	Genotype	Deafness	Eye examination	ERG	OCT	ENG
V;1	Delete / remove	Moderate - severe	Blind	/	/	/
V;7	Delete / remove	Moderate - severe	Retinitis pigmentosa	Cone cell destruction - cylindrical	Thickening of the retina	36% one-sided weakness left
V;8	Delete / remove	Moderate - severe	Retinitis pigmentosa	/	/	35% one-sided weakness right
V;10	Delete / remove	Moderate - severe	Retinitis pigmentosa	/	/	A right-sided weakness (13%)
V;11	Delete / remove	Moderate - severe	Retinitis pigmentosa	/	/	Natural
V;15	Delete / remove	Severe - deep	Natural	/	/	/
V;16	Delete / remove	Severe - deep	Natural	/	/	/

Using the primers 5'-CCAGAGGGCATATCATGAGTCC-3 'as primers Forward and 3'-GTTGGGCCAGAATGTTAAGG-5 'as Reverse, delete the ones who are causing a fragment of approximately 630bp. PCR products from samples taken from patients, purified and sequenced and remove the front and back fractures in the 371/657 and 507/673 revealed. Remove G.371657-507673del with 136 / 017bp in length and contains 84 exons and 85 and part of 83 and 85 is interones.



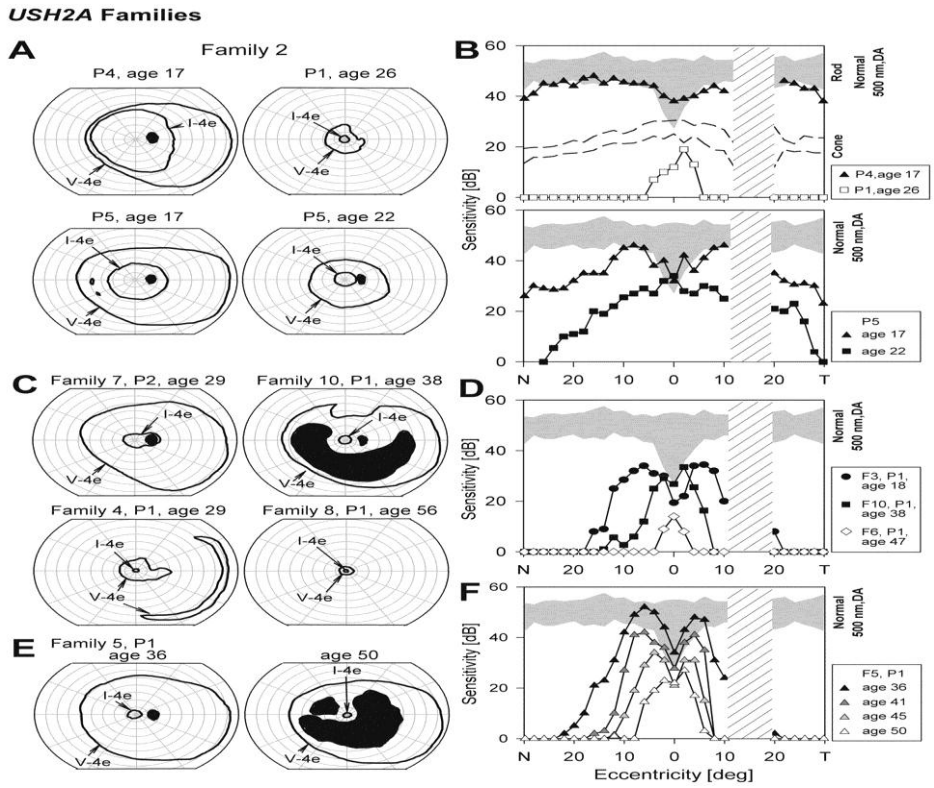
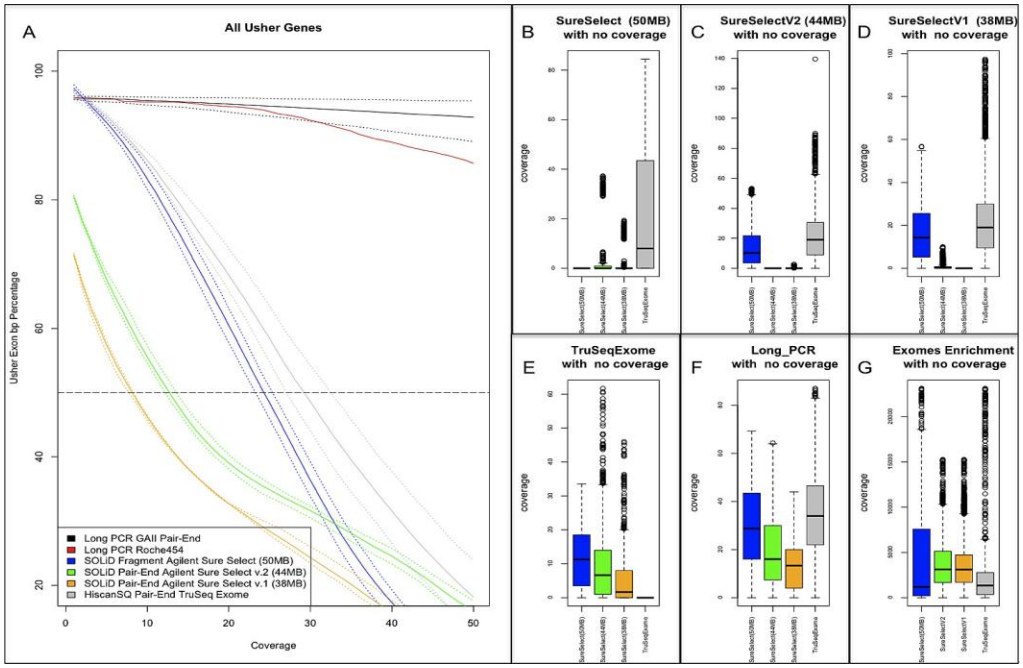


Figure 3: Schematic view of the audio frequency of the target gene in units of dB.



CONCLUSION

We found a large deletion in VLGR1 that might cause a change in the form and appearance of Ascher syndrome type IIC has been in the family. Male patients with USH2C first VLGR1 mutations were identified. This is the first report of a removal VLGR1 USH2C second report VLGR1 molecular mutations in the population of Iran is Tabriz.

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