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Research Article

Evidence for Central Asian Origin of the p.Val27Ile Variant in the *GJB2* Gene

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The mutations in the *GJB2* gene are the most common cause of nonsyndromic hearing impairment and they are associated with the population's ethnic background. The p.Val27Ile is frequent in both Asia and America. In this retrospective study, we report the findings from the *GJB2* screening and the audiological exams conducted on 125 Mexican mestizo patients with non-syndromic hearing impairment; they were treated at the Instituto Nacional de Rehabilitacion in Mexico City. The most frequent audiometric findings were bilateral, symmetrical, and profound hearing impairment. The allele frequencies in the *GJB2* screening were p.Val27Ile 15%, other mutations 5%, and wild type 80%. We found no correlation between *GJB2* genotype and auditory phenotype. The high allele frequency of p.Val27Ile was a very interesting finding. Our research suggests that p.Val27Ile arose in an ancient common ancestor who lived in Altai Republic and then the polymorphism was brought to America by its first inhabitants, the Amerindians. These results enhance our understanding of the peopling of the America, which remains unresolved.

1. Introduction

The gap junction $\beta 2$ gene (*GJB2* [MIM*121011]) (Online Mendelian Inheritance in Man (OMIM), http://www.omim.org/), encoded to the protein connexin 26. Mutations in this gene are the most common cause of hereditary nonsyndromic hearing impairment, causing up to 50% of autosomal recessive cases [1, 2] and up to 37% of unknown cause [3]. Also, although infrequently, mutations in this gene cause genetic syndromes that affect hearing and skin [4, 5].

The frequency of *GJB2 variants* has been associated with ethnic background. The most frequent pathogenic mutations are c.35delG (p.Gly12ValfsTer1) in Caucasian Europeans [6], c.167delT (p.Leu56ArgfsTer26) in Ashkenazi Jews [7], c.427C>T (p.R143W) in Africans from Ghana [8], c.74G>A (p.W24X) in Indians and Romanies [9, 10], c.109G>A (p.V37Ile) in East Asians [11], and c.235delC (p.L79CfsX3) in East Asians (Japanese, Koreans, and Chinese), Mongolians (Central Asia), and southern Altaians (South Siberia) [12–16]. The high carrier frequencies (0.7 to 16%) of each of these pathogenic mutations among the populations in which they are endemic suggest that there may be some evolutionary advantage to being a carrier of these mutations [17].

The most frequent polymorphic variants are c.79G>A (p.Val27Ile) and c.341G>A (p.Glu114Gly); these are most frequent in East Asian populations [12–14, 18].

The p.Val27Ile polymorphism has been reported as the most common variant of *GJB2* gene in several studies [12–16, 18–25]. It occurs in the first transmembrane domain of connexin-26 and it involves the conversion of a valine codon (evolutionarily conserved), to an isoleucine codon (Val27Ile). It is considered a polymorphism because it appears with similar frequency both in people with normal hearing (PNH) and in people with hearing impairment (PHI) [15, 16, 18, 20, 23, 26].

The highest allele frequencies (AFs) of p.Val27Ile are found in the Asian populations (up to 41%) [12–16, 18, 24, 27], followed by the American populations (up to 27%), [19–23, 25, 28–31] (Table 1; Figure 1). The p.Val27Ile polymorphism seems to be rare or absent in European and African populations [26, 32].

Table 1: Geographic distribution of the polymorphism p.Val27Ile in the *GJB2*.

Populations	ChrNH *n* (AFs)	ChrHI *n* (AFs)	References
Asians:			
Koreans	192 (41%)	200 (40%)	Kim et al., [18] Park et al., [13]
Japanese		192 (39%)	Abe et al., [12]
Chinese		4126 (25%)	Dai et al., [14]
Mongolians	434 (30%)	1068 (26%)	Tekin et al., [15]
Turkish		308 (2.3%)	Tekin et al., [27]
Siberians:			
Southern Altaians (Altai Republic)	260 (19%)	60 (28%)	Posukh et al., [16]
Russian ethnic group (Altai Republic)		0 (0%)	Posukh et al., [16]
Yakuts (Sakha [Yakutia])	340 (10.5%)[a]	88 (3.4%)	Barashkov et al., [24]
Americans:			
East Greenlanders		90 (3.3%)	Homøe et al., [28]
Mexican-Americans (South California USA)	200 (24%)	42 (19%)	Shimmenti et al., [20]
Hispanic (USA).		242 (11.5%)	Pandya et al., [19]
American Caucasians (USA).		1176 (0.34%)	Pandya et al., [19]
Mexican mestizos		250 (15%)	This study
Mexicans (unspecified ethnicity)		152 (24%)	Arenas-Sordo et al., [22]
Brazilians (Belém Pará, amazon region)	800 (12%)	154 (15.5%)	Castro et al., [23]
Brazilians (Sao Paulo) "white" (majority)		600 (1%)	Batissoco et al., [29]
Colombians		224 (8%)	Tamayo et al., [21]
Ecuadorian mestizos	222 (27%)[b]		Paz-y-Miño et al., [25]
Chileans		162 (4.9%)	Arancibia et al., [30]
Argentineans		92 (1%)	Dalamón et al., [31]

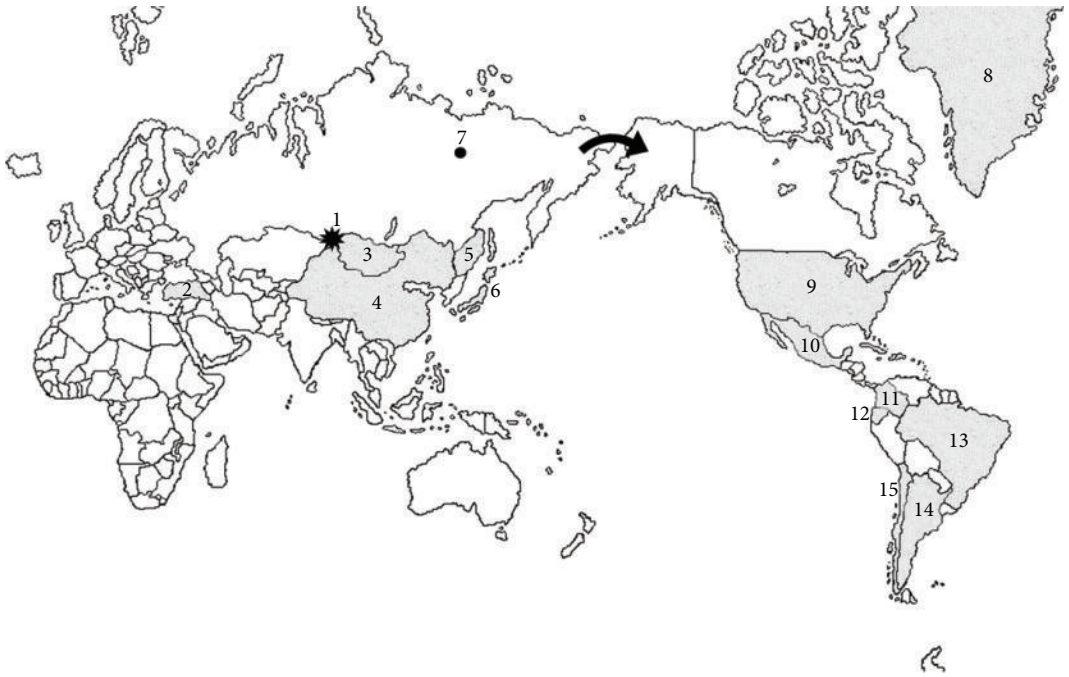
AFs = allele frequencies; ChrNH = chromosomes of normal hearing persons; Chr HI = chromosomes of patients with hearing impairment.
[a]Relatives of persons with *GJB2* homozygous mutation IVS1+1G>A.
[b]Chromosomes of normal hearing persons; chromosomes of patients with hearing impairment and chromosomes of relatives of persons with hearing impairment.

The second most frequent polymorphism of *GJB2* is p.Glu114Gly; it occurs almost exclusively in the Asian continent (in the same regions as p.Val27Ile) and its highest AFs are found in East Asia: Koreans and Chinese 17% [13, 14, 18] and Japanese 13% [12] followed by Mongolians and Altaian ethnic group 11% in Central Asia [15, 16].

The p.Val27Ile polymorphism can be found alone or together with other polymorphisms, most commonly in cis haplotype with p.Glu114Gly. In Asia, the haplotype p.(Val27Ile; p.Glu114Gly) accounts for 30–50% of the cases of p.Val27Ile and almost 100% of the cases of p.Glu114Gly [14–16, 18]. The p.Val27Ile and p.Glu114Gly polymorphisms seem to be tightly linked, and this has been proposed as haplotype tagging SNPs [18]. In America this haplotype is rare or absent [19–23, 25, 30, 31].

This research was conducted in mestizo patients, born in Mexico, a country located in North America with a population of 112 million according to the 2010 census (Instituto Nacional de Estadística y Geografía [INEGI], Mexico, 2010. Censo de Población y Vivienda 2010, http://cuentame.inegi.org.mx), of them, 93% were mestizos, (resulting from post-Columbian admixture between Amerindians, Spaniards, and Africans, principally) [33]. The origin of the nuclear DNA from current Mexican mestizo population has been estimated to be 55.3% Amerindian (Native American), 42.2% European, 3.3% African, and 1.2% East Asian (Philippines). With variations among geographic regions, in the North the highest ancestral contribution is European, while in the Central and South the highest ancestral contribution is Amerindian [34].

The main purpose of this retrospective study was to analyze the results of the allele frequency (AF) of p.Val27Ile on *GJB2* screens and its possible correlation with auditory phenotype in the 125 Mexican mestizo patients with non-syndromic hearing impairment and to propose our two hypotheses about p.Val27Ile origin: first, that p.Val27Ile arose in an Asian ancient common ancestor and second, that this Asian ancient common ancestor lived in the Altai Republic. Also, we will try to elucidate why p.Val27Ile is frequent in Asia and America and why p.Glu114Gly is almost absent in America.



(1) Altai Republic (Siberia)
(2) Turkey
(3) Mongolia
(4) China
(5) Korea
(6) Japan
(7) Yakutia (Siberia)
(8) Greenland
(9) United States of America
(10) Mexico
(11) Colombia
(12) Ecuador
(13) Brazil
(14) Argentina
(15) Chile

Figure 1: Geographic distribution of the p.Val27Ile polymorphism in the *GJB2* gene (http://commons.wikimedia.org/wiki/File:PLANISFERIO). The image was modified.

2. Materials and Methods

2.1. Clinical Genetic Evaluation. The information was taken from the patients' medical files. In this retrospective study we included 125 Mexican mestizo patients with nonsyndromic hearing impairment who were treated at the Instituto Nacional de Rehabilitación in Mexico City. We excluded patients with potentially adverse hearing factors such as premature birth, low birth-weight, perinatal asphyxia, jaundice, intrauterine infections (e.g., toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex (TORCH)), postnatal viral and bacterial infections, and exposure to ototoxic drugs, and those patients with signs and/or symptoms that suggested syndromic hearing impairment [35, 36].

2.2. Family Data. This information was taken from the patient's pedigree; we only included patients whose pedigree went back at least three generations and whose place of origin, as well as their four grandparents, was Mexico and the region was specified, that is, North, Central, or South. Patients with foreign ancestry were excluded.

The families with at least two affected members were considered to be multiplex or familial; the families with only one affected member were considered to be simplex or sporadic.

2.3. Audiologic Analysis. Audiometric data was extracted from copies of available pure-tone audiometries. Pure-tone averages (PTA4) were determined by calculating the mean of tested thresholds at 500, 1000, 2000, and 4000 Hertz and were used for the analysis of the degree of hearing impairment. The degree of hearing impairment was defined by the PTA4 in the better ear; 21–40 dB, mild; 41–70 dB, moderate; 71–95 dB, severe; >95 dB, profound [35].

2.4. Molecular Testing. Informed consent form was obtained from all the patients. The patient's peripheral blood samples were drawn at the Instituto Nacional de Rehabilitación in Mexico City. The DNA testing was performed by the laboratory of Arti Pandya, M.D., Department of Human and Molecular Genetics, Virginia Commonwealth University, Richmond, Virginia, USA. DNA samples from all patients were screened for mutations in exon 1 and 2 of the *GJB2* by cycle sequencing [19, 37].

2.5. Statistical Analysis. The SPSS17 statistical package was used for the analysis (SPSS Inc., Chicago, IL, USA). We analyzed the frequency and percent distribution, and we calculated the minimum and maximum and mean. Finally, we analyzed for correlation between *GJB2* genotypes

Table 2: Alleles found in the *GJB2* screening in 250 chromosomes of Mexican mestizo patients with nonsyndromic hearing impairment.

Alleles	Homozygous	Heterozygous	Total of chromosomes	Allele frequencies
c.79G>A (p.Val27Ile)	4	29	37	15%
Wild type	79	42	200	80%
Recessive mutation	0	13	13	5%
Total	83	84	250	100%

Table 3: *GJB2* genotype by degree of hearing impairment in the better ear in 125 Mexican mestizo patients with nonsyndromic hearing impairment.

Genotype	Degree of hearing impairment *n* (%)				Total by genotype
	Mild	Moderate	Severe	Profound	
p.Val27Ile/wild type	2 (6.9)	8 (27.5)	6 (20.6)	13 (45)	29 (100)
p.Val27Ile/p.Val27Ile		2 (50)	1 (25)	1 (25)	4 (100)
Mutation[a]/wild type		2 (15)	2 (15)	9 (70)	13 (100)
Wild type/wild type	5 (6.3)	22 (28)	23 (29)	29 (37)	79 (100)
Total by degree	7 (5.6)	34 (27.2)	32 (25.6)	52 (41.6)	125 (100)

[a]Recessive.

and the other qualitative data using the χ^2 test, with a level of minimum confidence interval of 95%.

3. Results

The sampling consisted of 125 Mexican mestizo patients, of them 69 (55%) were females and 56 (45%) were males, with ages varying from 3 to 69 years old (mean 22.41 years). Eighty-seven patients (69%) came from 57 families, considered multiplex or familial, and 38 (31%) came from 38 families considered to be simplex or sporadic. All the patients and their four grandparents' place of origin was Central or South Mexico and they did not refer any foreign ancestor. The hearing impairment findings were bilateral 96.8% (121 out of 125), unilateral 3.2% (4 out of 125), symmetrical 85.1% (97 out of 114), and asymmetrical 14.9% (7 out of 114).

The allele frequency of p.Val27Ile was 15%, both when we included all the patients and when we included only the 95 unrelated patients. The alleles found in the *GJB2* screening of all the patients are shown in Table 2. The *GJB2* genotypes by degree of hearing impairment are shown in Table 3. We found no correlation between *GJB2* genotype and auditory phenotype (degree, unilateral-bilateral, and symmetrical-asymmetrical hearing impairment) or with any other qualitative variables (multiplex-simplex family structure and gender); in all cases we found χ^2, $P > 0.05$.

4. Discussion

It is important to mention that this is the study with the highest sampling of Mexican patients with familial nonsyndromic hearing impairment and the first study in Mexican mestizo patients, who have been screened for *GJB2*. The most interesting finding in this sampling was the high AF of p.Val27Ile polymorphism, being 15%, which supports the high AFs previously reported in American populations (Table 1): Ecuadorians, Mexicans (unspecified ethnicity), Mexican Americans in Southern California, and Hispanics in the United States, Brazilians from Belém Pará in the Amazon region, Colombians, Chileans, and East Greenlanders all who have AFs of 3.4–27% (Table 1) [19–23, 25, 29, 30]. The high AFs of p.Val27Ile reported in these populations (Table 1), which also have high percentages of autosomal Native American DNA 19–55% [34, 38–40] coupled with the low AFs of p.Val27Ile, ranging from 0.34 to 1% in American Caucasian populations: in the United States, Brazil (Sao Paulo), and Argentina [19, 29, 31, 41], support that in American populations p.Val27Ile is associated with their Amerindian origin, as it has been proposed in Brazil [23].

Aiming to elucidate the origin of p.Val27Ile, we propose as a first hypothesis, that p.Val27Ile arose in an Asian ancient common ancestor. Our arguments are as follows: first, p.Val27Ile seems to be associated to Amerindian origin, and the general consensus is that the Amerindians were the first inhabitants of the American continent and that they came from the Asian continent [42, 43]. Second, the geographic distribution of p.Val27Ile is practically confined to Asia: (specifically East and Central Asia and South and East Siberia) [12–16, 18, 24] and several countries of America (Table 1; Figure 1) [19–23, 25, 28, 30]. Third, p.Val27Ile shows up more frequently in Asia than in America, and this descending gradient could be due to the geographic distance [42, 44], between Asia and America; the founder serial effect from Asia to America; the genetic drift, favored by the isolation [45] of the American continent for over 10,000 years (~500 generations, with each generation of 20 years) followed by a drastic reduction in the Native American population, due mostly to epidemic diseases (bottleneck effect) during the colonization by Europe ~500 years ago and also due to post-Columbian admixture [44–48]. The second and the third arguments contradict the possibility that the high frequency of p.Val27Ile is due to multiple mutational events.

Assuming that our first hypothesis about the Asian ancient common ancestor is true, then we would like to propose a second hypothesis; this to argue that the common

ancestor's place of origin was the Altai Mountains, probably Altai Republic, inhabited ~45,000 years ago [49], and considered a region of great evolutionary importance located right in the center of Asia, in South Siberia bordering with Mongolia, China, and Kazakhstan (Official portal Altai Republic: Government: welcoming letter of the Head of the Altai Republic, http://www.eng.altai-republic.ru/modules.php?op=modload&name=Sections&file=index&req=viewarticle&artid=6&page=1). Our first argument is that Altai Republic has been proposed as the possible homeland for the ancestry of the Native Americans, which is supported by the presence of mitochondrial DNA type X both in the Altaians and the Native Americans [50, 51].

Our second argument is that in the Altaian ethnic group (Mongoloids) that lives in southern Altai Republic, p.Val27Ile has a high AF (28%), but it is absent in the Russian ethnic group (Caucasians) [16], which suggests that in Asian populations p.Val27Ile is associated to Mongoloid origin (Altaian ethnic group). Our third argument is that the high-resolution analysis of the Y chromosome haplogroup has revealed that southern Altaians and Native Americans share a common paternal ancestor, who lived in the South of Altai ~22,000 years ago (Upper Paleolithic/Last Glacial Maximum) and his descendants diverged into southern Altaians and Native Americans ~13,400 years ago, which coincides with the initial settlement of the American continent [43, 51–55]. We suspect that p.Val27Ile also arose in this common ancestor or in one of his male descendants (before the divergence into southern Altaians and Native Americans), and it was brought to America by some of the Native Americans, who must have left Altai Republic in the first migratory wave according to the Greenberg three-migration model [56], who after crossing the eastern Beringia, they arrived in Alaska [57] from there and with serial founder effect, in the millennia after, they have spread p.Val27Ile in America. In East Asia, p.Val27Ile may have dispersed through gene flow and emigrations facilitated by Altai's shared borders with Mongolia and China, from there, p.Val27Ile could have spread to Korea and then to Japan.

Even though Korea has the highest AF in the world (41%), we do not believe it to be the place of origin for p.Val27Ile, since as far as we know Korea has had no migrations that support the current geographical distribution of p.Val27Ile.

In regards to the p.Val27Ile distribution in Central Asia, we find it interesting that Turkey has a low AF (2.3%), although it is known that the Turkish were ancient inhabitants of Central Asia, from there they migrated to Turkey ~1000 years ago. This low frequency could be due to the many ethnically distinct populations that immigrated into Turkey from the Paleolithic Era, mainly during the past 10,000 years [27, 58, 59].

To prove that p.Val27Ile comes from a common ancestor will be difficult, since we are dealing with an ancient variant. In these cases the polymorphisms, even the closer ones, could be different, even in populations with the same origin [58, 60–62]. This could be the case with p.Val27Ile and p.Glu114Gly which has been found frequently in cis haplotype and tightly linked in Asian populations [14–16, 18] while in Americans p.Glu114Gly is almost absent [19–23, 25, 28, 30, 31], which is supported by the present study (we did not find any case). We believe there are two probable reasons why p.Glu114Gly is almost absent in Americans: first, perhaps p.Glu114Gly was not brought to America by the first immigrants, because the polymorphism had not yet arisen when they left Altai or because they were not carriers of this polymorphism (founder effect). Second, p.Glu114Gly came to America, but was reversed by natural evolution, or maybe p.Glu114Gly carriers were eliminated by natural selection.

To estimate the biological age and clarify the origin of p.Val27Ile and p.Glu114Gly, it would be very useful that the researchers of population genetics screen for *GJB2* in ancient human remains found in the regions where p.Val27Ile and/or p.Glu114Gly occur in the highest frequencies, including "Naia," the most ancient (almost complete) human skeleton of America, recently discovered in Yucatán Peninsula, México [57].

If Altai Republic is confirmed as the origin place of p.Val27Ile we propose to use p.Val27Ile as tagging SNP of southern Altaian and Amerindian origins. And we propose p (Val27Ile; Glu114Gly) as haplotype tagging SNP of southern Altaian origin.

In case that p.Val27Ile have been arisen ~22,000 years ago (1,100 generations), this will be the oldest *GJB2* variant, since it has been estimated that the c.35delG mutation arose 10,000–14,000 years ago [60–62], the c.235delC mutation arose 11,500 years ago [63], and the p.W24X mutation arose 7,880 years ago [10]. It is worth mentioning that these two mutations, c.35delG and c.235delC, also arose in the Upper Paleolithic, and it has been suggested that (c.235delC) could have arisen in the Lake Baikal area [58] or in the Altai-Sayan region [16, 64].

Why does p.Val27Ile have high AFs in people with normal hearing in Asia and in America? Maybe it is a selectively neutral variant, but we believe that is unlikely since there are also some facts that suggest that p.Val27Ile could give an heterozygous advantage, as happens with some autosomal recessive mutations [42, 52]. The facts are as follows: the first fact is that p.Val27Ile is a polymorphism in *GJB2*, a gene involved in the embrionary development of the epidermal barrier, and postnatally in its functioning [65]. The epidermis is the layer of the skin that is exposed to the environment and p.Val27Ile apparently arose in the Last Glacial Maximum (LGM), at which time there was extreme cold. For this reason, we suspect that this polymorphism could increase the individual's resistance to the cold and environmental inhospitality by modifying the epidermal barrier, as has been reported in some autosomal, recessive, pathogenic, mutations of *GJB2* (c.35delG, p.R143W and c.101T>C (p.Met34Thr)), in which it has been found that the epidermis had thickened. It has been suggested that this confers a greater resistance to trauma, bacterial infection, and insect bites [17, 66, 67]. The second fact is that c.235delC, the *GJB2* mutation that most frequently causes autosomal recessive hearing impairment (MIM*121011) in Asia has a frequency of 3.4–13.9% [12–14], far below the 35% of autosomal recessive hearing impairment caused by c35deG in southern Europe [6]; even when we are talking about two ancient mutations that could be considered contemporaneous [60–62, 64] and its carrier frequencies are

remarkably similar [17]. This makes us suspect that perhaps p.Val27Ile has some protecting effect against the emergence of *GJB2* pathogenic mutations in cis configuration with this polymorphism; which is supported by the very low frequency of this kind of haplotype (p.Val27Ile; pathogenic mutation) [14, 29, 59]. The third fact is that p.Val27Ile seems to be capable of compensating for the decreased activity of p.Glu114Gly in heterotypic hemichannels of *GJB2* (compound by p.Val27Ile and p.Glu114Gly), as have been demonstrated by *in vitro* tests [67]. Further studies are needed to expand knowledge on the role of p.Val27Ile in the epidermal barrier, hearing function, and the protecting effect against the emergence of *GJB2*'s pathogenic mutations.

5. Conclusions

We found no correlation between *GJB2* genotype and auditory phenotype. The high allele frequency of p.Val27Ile was a very interesting finding and we based on the AF of p.Val27Ile, its geographic distribution, genetics, and historical evidences supported by documents, we propose that p.Val27Ile arose in Asia in Altai Republic in an ancient common ancestor and then it was spread to East Asia and America. The polymorphism p.Val27Ile could be the oldest variant of *GJB2* and may have arisen during the LGM and perhaps confers greater resistance to the cold and protects against the emergence of pathogenic mutations in *GJB2*. This is currently the most common *GJB2* variant. It can be found alone or frequently in haplotype with p.Glu114Gly and it could be very useful as tagging SNP or haplotype tagging SNPs to identify people of Native American and southern Altaian origins. The p.Val27Ile polymorphism could help establish the genetic connection between the southern Altaians and the Native Americans; this could be of great importance for the field of population genetics in solving the place of origin of the first inhabitants of the American continent, which remains unresolved.

Limitations of this research: Native American patients were not available to us. We did not undertake biological exams to determine the function, the biological age, and the origin of p.Val27Ile. The frequency of p.Val27Ile has not been reported in studies of *GJB2* conducted in most countries throughout the world. Furthermore, the vast majority of the studies do not specify the ethnicity of the population included.

Scope of this study: to make a proposal on where, when, and why p.Val27Ile arose and we invite other researchers to help confirm or reject our hypotheses.

Conflict of Interests

The authors declare no conflict of interests.

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References

[1] P. Gasparini, X. Estivill, V. Volpini et al., "Linkage of DFNB1 to non-syndromic neurosensory autosomal-recessive deafness in Mediterranean families," *European Journal of Human Genetics*, vol. 5, no. 2, pp. 83–88, 1997.

[2] F. Denoyelle, D. Weil, M. A. Maw et al., "Prelingual deafness: high prevalence of a 30delG mutation in the connexin 26 gene," *Human Molecular Genetics*, vol. 6, no. 12, pp. 2173–2177, 1997.

[3] X. Estivill, P. Fortina, S. Surrey et al., "Connexin-26 mutations in sporadic and inherited sensorineural deafness," *The Lancet*, vol. 351, no. 9100, pp. 394–398, 1998.

[4] D. P. Kelsell, W.-L. Di, and M. J. Houseman, "Connexin mutations in skin disease and hearing loss," *American Journal of Human Genetics*, vol. 68, no. 3, pp. 559–568, 2001.

[5] J. R. Lee and T. W. White, "Connexin-26 mutations in deafness and skin disease," *Expert Reviews in Molecular Medicine*, vol. 11, p. e35, 2009.

[6] L. Zelante, P. Gasparini, X. Estivill et al., "Connexin26 mutations associated with the most common form of non-syndromic neurosensory autosomal recessive deafness (DFNB1) in Mediterraneans," *Human Molecular Genetics*, vol. 6, no. 9, pp. 1605–1609, 1997.

[7] R. J. Morell, H. J. Kim, L. J. Hood et al., "Mutations in the connexin 26 gene (*GJB2*) among Ashkenazi jews with non-syndromic recessive deafness," *The New England Journal of Medicine*, vol. 339, no. 21, pp. 1500–1505, 1998.

[8] C. Hamelmann, G. K. Amedofu, K. Albrecht et al., "Pattern of connexin 26 (GJB2) mutations causing sensorineural hearing impairment in Ghana," *Human Mutation*, vol. 18, no. 1, pp. 84–85, 2001.

[9] G. Minárik, V. Ferák, E. Feráková, A. Ficek, H. Poláková, and L. Kádasi, "High frequency of *GJB2* mutation W24X among Slovak Romany (Gypsy) patients with non-syndromic hearing loss (NSHL)," *General Physiology and Biophysics*, vol. 22, no. 4, pp. 549–556, 2003.

[10] M. RamShankar, S. Girirajan, O. Dagan et al., "Contribution of connexin26 (GJB2) mutations and founder effect to non-syndromic hearing loss in India," *Journal of Medical Genetics*, vol. 40, no. 5, article e68, 2003.

[11] D. K. Chan, I. Schrijver, and K. W. Chang, "Connexin-26-associated deafness: phenotypic variability and progression of hearing loss," *Genetics in Medicine*, vol. 12, no. 3, pp. 174–181, 2010.

[12] S. Abe, S.-I. Usami, H. Shinkawa, P. M. Kelley, and W. J. Kimberling, "Prevalent connexin 26 gene (*GJB2*) mutations in Japanese," *Journal of Medical Genetics*, vol. 37, no. 1, pp. 41–43, 2000.

[13] H.-J. Park, S. Houn Hahn, Y.-M. Chun, K. Park, and H.-N. Kim, "Connexin26 mutations associated with nonsyndromic hearing loss," *Laryngoscope*, vol. 110, no. 9, pp. 1535–1538, 2000.

[14] P. Dai, F. Yu, B. Han et al., "*GJB2* mutation spectrum in 2063 Chinese patients with nonsyndromic hearing impairment," *Journal of Translational Medicine*, vol. 7, article 26, 2009.

[15] M. Tekin, X.-J. Xia, R. Erdenetungalag et al., "GJB2 mutations in mongolia: complex alleles, low frequency, and reduced fitness of the deaf," *Annals of Human Genetics*, vol. 74, no. 2, pp. 155–164, 2010.

[16] O. Posukh, N. Pallarez-Ruiz, V. Tadinova, L. Osipova, M. Claustres, and A.-F. Roux, "First molecular screening of deafness in the Altai republic population," *BMC Medical Genetics*, vol. 6, article 12, 2005.

[17] D. K. Chan and K. W. Chang, "GJB2-associated hearing loss: systematic review of worldwide prevalence, genotype, and auditory phenotype," *The Laryngoscope*, vol. 124, no. 2, pp. E34–E53, 2014.

[18] H.-J. Kim, C.-H. Park, K.-O. Lee et al., "Sequence variations and haplotypes of the *GJB2* gene revealed by resequencing of 192 chromosomes from the general population in Korea," *Clinical and Experimental Otorhinolaryngology*, vol. 3, no. 2, pp. 65–69, 2010.

[19] A. Pandya, K. S. Arnos, X. J. Xia et al., "Frequency and distribution of GJB2 (connexin 26) and GJB6 (connexin 30) mutations in a large North American repository of deaf probands," *Genetics in Medicine*, vol. 5, no. 4, pp. 295–303, 2003.

[20] L. A. Shimmenti, A. Martínez, and M. Telatar, "Infant hearing loss and connexin testing in a diverse population," *Genetics in Medicine*, vol. 10, no. 7, pp. 517–524, 2008.

[21] M. L. Tamayo, M. Olarte, N. Gelvez et al., "Molecular studies in the GJB2 gene (Cx26) among a deaf population from Bogotá, Colombia: results of a screening program," *International Journal of Pediatric Otorhinolaryngology*, vol. 73, no. 1, pp. 97–101, 2009.

[22] M. L. Arenas-Sordo, I. Menendez, E. Hernández-Zamora et al., "Unique spectrum of *GJB2* mutations in Mexico," *International Journal of Pediatric Otorhinolaryngology*, vol. 76, no. 11, pp. 1678–1680, 2012.

[23] L. S. Castro, A. N. Marinho, E. M. Rodrigues, G. C. Marques, T. A. Carvalho, and S. E. Santos dos, "A study of GJB2 and delGJB6-D13S1830 mutations in Brazilian non- syndromic deaf children from the Amazon region," *Brazilian Journal of Otorhinolaryngology*, vol. 79, pp. 95–99, 2013.

[24] N. A. Barashkov, F. M. Teryutin, V. G. Pshennikova et al., "Age-relate hearing impairment (ARHI) associated with GJB2 single mutation IVS1 + 1G > A in the Yakut population isolate in Easter Siberia," *PLoS ONE*, vol. 9, no. 6, Article ID e100848, 2014.

[25] C. Paz-y-Miño, D. Beaty, A. López-Cortés, and I. Proaño, "Frequency of GJB2 and del(GJB6-D13S1830) mutations among an Ecuadorian mestizo population," *International Journal of Pediatric Otorhinolaryngology*, vol. 78, no. 10, pp. 1648–1654, 2014.

[26] P. M. Kelley, D. J. Harris, B. C. Comer et al., "Novel mutations in the connexin 26 gene (GJB2) that cause autosomal recessive (DFNB1) hearing loss," *The American Journal of Human Genetics*, vol. 62, no. 4, pp. 792–799, 1998.

[27] M. Tekin, T. Duman, G. Boğoçlu et al., "Spectrum of GJB2 mutations in Turkey comprises both Caucasian and Oriental variants: roles of parental consanguinity and assortative mating," *Human Mutation*, vol. 21, no. 5, pp. 552–553, 2003.

[28] P. Homøe, A. Koch, N. D. Rendtorff et al., "*GJB2* (Connexin-26) mutations are not frequent among hearing impaired patients in east Greenland," *International Journal of Audiology*, vol. 51, no. 6, pp. 433–436, 2012.

[29] A. C. Batissoco, R. S. Abreu-Silva, M. C. C. Braga et al., "Prevalence of *GJB2* (connexin-26) and *GJB6* (connexin-30) mutations in a cohort of 300 Brazilian hearing-impaired individuals: implications for diagnosis and genetic counseling," *Ear & Hearing*, vol. 30, no. 1, pp. 1–7, 2009.

[30] M. Arancibia, R. Ramírez, C. Farfán, M. Acuña, and L. Cifuentes, "Frequency of the 35delG mutation of GJB2 (connexin 26) in a sample of deaf school children in Santiago," *Revista de Otorrinolaringología y Cirugía de Cabeza y Cuello*, vol. 72, pp. 7–14, 2012.

[31] V. Dalamón, A. Béhèran, F. Diamante, N. Pallares, V. Diamante, and A. B. Elgoyhen, "Prevalence of *GJB2* mutations and the del(GJB6-D13S1830) in Argentinean non-syndromic deaf patients," *Hearing Research*, vol. 207, no. 1-2, pp. 43–49, 2005.

[32] J. Samanich, C. Lowes, R. Burk et al., "Mutations in *GJB2*, *GJB6*, and mitochondrial DNA are rare in African American and Caribbean Hispanic individuals with hearing impairment," *American Journal of Medical Genetics A*, vol. 143, no. 8, pp. 830–838, 2007.

[33] G. Martínez-Cortés, J. Salazar-Flores, J. Haro-Guerrero et al., "Maternal admixture and population structure in Mexican-Mestizos based on mtDNA haplogroups," *American Journal of Physical Anthropology*, vol. 151, no. 4, pp. 526–537, 2013.

[34] B. Z. González-Sobrino, I. Silva-Zolessi, and L. Sebastián-Medina, "Estampas de Historia y Genética en México," in *Miradas sin rendición. Imaginario y presencia del universo indígena*, S. Oria-Probert, Ed., pp. 52–56, Fideicomiso para la organización de la conmemoración del Bicentenario de la Independencia Nacional y Centenario de la Revolución Mexicana, Mexico City, Mexico, 1st edition, 2010.

[35] A. Martini, M. Mazzoli, D. Stephens, and A. Read, *Definitions Protocols and Guidelines in Genetic Hearing Impairment*, Whurr Publisher, London, UK, 2001.

[36] C. F. Martínez-Cruz, A. Poblano, and L. A. Fernández-Carrocera, "Risk factors associated with sensorineural hearing loss in infants at the neonatal intensive care unit: 15-year experience at the National Institute of Perinatology (Mexico City)," *Archives of Medical Research*, vol. 39, no. 7, pp. 686–694, 2008.

[37] D. Gordon, C. Abajian, and P. Green, "Consed: a graphical tool for sequence finishing," *Genome Research*, vol. 8, no. 3, pp. 195–202, 1998.

[38] R. Cruz-Coke and R. S. Moreno, "Genetic epidemiology of single gene defects in Chile," *Journal of Medical Genetics*, vol. 31, no. 9, pp. 702–706, 1994.

[39] L. Gómez-Pérez, M. A. Alfonso-Sánchez, A. M. Pérez-Miranda et al., "Genetic admixture estimates by Alu elements in Afro-Colombian and Mestizo populations from Antioquia, Colombia," *Annals of Human Biology*, vol. 37, no. 4, pp. 488–500, 2010.

[40] S. D. Pena, G. di Pietro, M. Fuchshuber-Moraes et al., "The genomic ancestry of individuals from different geographical regions of Brazil is more uniform than expected," *PLoS ONE*, vol. 6, no. 2, Article ID e17063, 2011.

[41] D. Corach, O. Lao, C. Bobillo et al., "Inferring continental ancestry of argentineans from autosomal, Y-chromosomal and mitochondrial DNA," *Annals of Human Genetics*, vol. 74, no. 1, pp. 65–76, 2010.

[42] L. L. Cavalli-Sforza, *Genes pueblos y lenguas*, Crítica, Barcelona, Spain, 2010.

[43] U. A. Perego, N. Angerhofer, M. Pala et al., "The initial peopling of the Americas: a growing number of founding mitochondrial

genomes from Beringia," *Genome Research*, vol. 20, no. 9, pp. 1174–1179, 2010.

[44] S. Wang, C. M. Lewis, M. Jakobsson et al., "Genetic variation and population structure in native Americans," *PLoS Genetics*, vol. 3, no. 11, article e185, 2007.

[45] L. L. Cavalli-Sforza and F. Cavalli-Sforza, *Quienes somos? Historia de la diversidad humana*, Crítica, Barcelona, Spain, 1994.

[46] M. Livi-Bacci, *Historia Mínima de la Población Mundial*, Ariel, Barcelona, Spain, 1990.

[47] H. F. Dobyns, "Disease transfer at contact," *Annual Review of Anthropology*, vol. 22, pp. 273–291, 1993.

[48] B. García-Martínez, "La época colonial hasta 1760," in *Nueva Historia mínima de México*, P. Escalante-Gonzalbo, B. García Martínez, L. Jáuregui, J. Zoraida-Vázquez, E. Especkan-Guerra, and J. Garciadiego, Eds., p. 79, Colegio de México, Mexico City, Mexico, 2010.

[49] V. N. Khar'kov, V. A. Stepanov, O. F. Medvedeva et al., "Gene pool differences between Northern and Southern Altaians inferred from the data on Y-chromosomal haplogroups," *Genetika*, vol. 43, no. 5, pp. 675–687, 2007.

[50] I. A. Zakharov, M. V. Derenko, B. A. Maliarchuk, I. K. Dambueva, C. M. Dorzhu, and S. Y. Rychkov, "Mitochondrial DNA variation in the aboriginal populations of the Altai-Baikal region: implications for the genetic history of North Asia and America," *Annals of the New York Academy of Sciences*, vol. 1011, pp. 21–35, 2004.

[51] M. C. Dulik, S. I. Zhadanov, L. P. Osipova et al., "Mitochondrial DNA and Y chromosome variation provides evidence for a recent common ancestry between Native Americans and Indigenous Altaians," *The American Journal of Human Genetics*, vol. 90, no. 3, pp. 229–246, 2012.

[52] L. L. Cavalli-Sforza, P. Menozzi, and A. Piazza, *The History and Geography of Human Genes*, Princeton University Press, Princeton, New Jersey, USA, 1994.

[53] T. Goebel, "Pleistocene human colonization of Siberia and peopling of the Americas: an ecological approach," *Evolutionary Anthropology*, vol. 8, no. 6, pp. 208–227, 1999.

[54] F. R. Santos, A. Pandya, C. Tyler-Smith et al., "The central Siberian origin for native American Y chromosomes," *The American Journal of Human Genetics*, vol. 64, no. 2, pp. 619–628, 1999.

[55] M.-C. Bortolini, F. M. Salzano, M. G. Thomas et al., "Y-chromosome evidence for differing ancient demographic histories in the Americas," *American Journal of Human Genetics*, vol. 73, no. 3, pp. 524–539, 2003.

[56] J. H. Greenberg, *Language in the Americas*, Stanford University Press, Stanford, California, USA, 1987.

[57] J. C. Chatters, D. J. Kennett, Y. Asmerom et al., "Late pleistocene human skeleton and mtDNA link paleoamericans and modern Native Americans," *Science*, vol. 344, no. 6185, pp. 750–754, 2014.

[58] B. Balci, F. Özbaş Gerçeker, S. Aksoy et al., "Identification of an ancestral haplotype of the 35delG mutation in the GJB2 (connexin 26) gene responsible for autosomal recessive non-syndromic hearing loss in families from the Easter Black Sea region in Turkey," *Turkish Journal of Pediatrics*, vol. 47, no. 3, pp. 213–221, 2005.

[59] M. Tekin, G. Boğoçlu, S. T. Arican et al., "Evidence for single origins of 35delG and delE120 mutations in the *GJB2* gene in Anatolia," *Clinical Genetics*, vol. 67, no. 1, pp. 31–37, 2004.

[60] L. Van Laer, P. Coucke, R. F. Mueller et al., "A common founder for the 35delG *GJB2* gene mutation in connexin 26 hearing impairment," *Journal of Medical Genetics*, vol. 38, no. 8, pp. 515–518, 2001.

[61] H. Kokotas, M. Grigoriadou, M. Villamar, A. Giannoulia-Karantana, I. Del Castillo, and M. B. Petersen, "Hypothesizing an ancient greek origin of the GJB2 35delG mutation: can science meet history?" *Genetic Testing and Molecular Biomarkers*, vol. 14, no. 2, pp. 183–187, 2010.

[62] L. U. Dzhelmileva, O. L. Posukh, N. A. Barashkov et al., "Haplotype diversity and reconstruction of ancestral haplotype associated with the c.35delG mutation in the GJB2 (Cx26) gene among the Volgo-Ural populations of Russia," *Acta Naturae*, vol. 3, no. 3, pp. 52–63, 2011.

[63] D. Yan, H.-J. Park, X. M. Ouyang et al., "Evidence of a founder effect for the 235delC mutation of *GJB2* (connexin 26) in East Asians," *Human Genetics*, vol. 114, no. 1, pp. 44–50, 2003.

[64] L. U. Dzhemileva, N. A. Barashkov, O. L. Posukh et al., "Carrier frequency of GJB2 gene mutations c.35delG, c.235delC and c.167delT among the populations of Eurasia," *Journal of Human Genetics*, vol. 55, no. 11, pp. 749–754, 2010.

[65] M. Kretz, K. Maass, and K. Willecke, "Expression and function of connexins in the epidermis, analyzed with transgenic mouse mutants," *European Journal of Cell Biology*, vol. 83, no. 11-12, pp. 647–654, 2004.

[66] J. E. A. Common, W.-L. Di, D. Davies, and D. P. Kelsell, "Further evidence for heterozygote advantage of GJB2 deafness mutations: a link with cell survival," *Journal of Medical Genetics*, vol. 41, no. 7, pp. 573–575, 2004.

[67] S.-Y. Choi, K. Y. Lee, H.-J. Kim et al., "Functional evaluation of GJB2 variants in nonsyndromic hearing loss," *Molecular Medicine*, vol. 17, no. 5-6, pp. 550–556, 2011.