

Consanguinity and Hereditary Hearing Loss in Qatar

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Key Words

Hereditary hearing loss · Consanguinity · Genes · Qatar

Abstract

Qatar is a sovereign state located on the Eastern coast of the Arabian Peninsula in the Persian Gulf. Its native population consists of 3 major subgroups: people of Arabian origin or Bedouins, those from an Eastern or Persian ancestry and individuals with African admixture. Historically, all types of consanguineous marriages have been and still are common in the Qatari population, particularly among first and double-first cousins. Thus, there is a higher risk for most inherited diseases including hereditary hearing loss (HHL). In particular, a hearing loss prevalence of 5.2% has been reported in Qatar, with parental consanguinity being more common among affected individuals as compared with unaffected ones. Our recent molecular results confirm a high homogeneity and level of inbreeding in Qatari HHL patients. Among all HHL genes, *GJB2*, the major player worldwide, accounts for a minor proportion of cases and at least 3 additional genes have been found to be mutated in Qatari patients. Interestingly, one gene, *BDP1*, has been described to cause

HHL only in this country. These results point towards an unexpected level of genetic heterogeneity despite the high level of inbreeding. This review provides an up-to-date picture of HHL in Qatar and of the impact of consanguinity on this disease.

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Introduction

Qatar is an independent nation located on the Arabian Peninsula in the Middle East. It is a small country, approximately 11,606 km², with a land border with the Kingdom of Saudi Arabia in the South and the surrounding sea bordering Bahrain, Iran and the United Arab Emirates. Qatar is flat and rocky, with low hills and sand dunes in the West and the South. Throughout the centuries, its arid climate has resulted in only temporary settlements, mainly by the nomadic tribes of the Arabian Peninsula, with some small coastline villages. Fishing and pearling were the main source of income for Qatar until the oil explorations of 1930s and its subsequent export starting in the late 1940s. With the country's rapid in-

crease in economic activities over the past decade, there has been a boom of a largely male expatriate workforce to Qatar. The latest census indicates a population of 2.0 millions, of which only 25% are Qatari citizens (see webpage of Qatar Statistics Authority, available at: <http://www.qsa.gov.qa/eng/PopulationStructure.htm>). The vast majority of inhabitants live in the capital Doha and its suburb, approximately 25% reside in rural areas. The official religion of the country is Islam and the official language is Arabic, although English is widely spoken.

A recent study on the structure of the Qatari population [1] revealed 3 clear genetic subgroups: consistent with Arabian origin or Bedouins (Q1), with an Eastern or Persian ancestry (Q2) and individuals with African admixture (Q3). The extent of linkage disequilibrium was found to be greater than that of African populations, and runs of homozygosity in some individuals reflect substantial consanguinity. These molecular findings confirm previous epidemiological studies showing that, in the Qatari population, there is a rate of consanguinity of 51% in the present generation with a coefficient of inbreeding of 0.023724 [2]. Very recently, data on whole exome sequencing of 100 individuals representing the 3 major genetic subgroups of the Qatari population (Q1, Q2 and Q3) have been reported [3]. By this approach, Rodriguez-Flores et al. [3] identified 37 variants in 33 genes with effects on 36 clinically significant Mendelian diseases, including variants not present in the 1000 Genomes Project [<http://www.1000genomes.org/>] and high-frequency variants when compared to the 1000 Genomes Project populations. Several of these Mendelian variants were specific of one Qatari subgroup, and they were further confirmed in an independent population of 386 Qatari individuals [3]. All these findings support the basic assumption of Qatar's population structure with 3 major subgroups.

Consanguinity in Qatar and Its Role in Disease Prevalence

All types of consanguineous marriages have been very common in the country in the past, particularly those of first and double-first cousins. Thus, the current generation shows a higher risk for most hereditary diseases, including cancer, mental disorders, heart diseases, gastrointestinal disorders, hypertension, diabetes mellitus, hereditary hearing loss (HHL) and schizophrenia [2, 4]. Moreover, a recent survey on Qatari people born between 1946 and 1991 has reported that 22% of all participants

were offspring of a consanguine relationship (between cousins) and another 15% were offspring of an affine relationship (with parents belonging to the same tribe) [5]. Also evaluating the type of relationships in the current generation, this survey has reported that 35% of the participants were in a consanguineous relationship (first-cousin marriage), while 9% were only in an affine relationship and 56% were not married to a blood relative according to their own account [5].

HHL in Qatar

HHL is a common genetic disorder accounting for at least 60% of all prelingual deafness cases in children worldwide. Most cases (70%) are nonsyndromic and are not associated with other signs or symptoms, while the remaining 30% are syndromic presenting other symptoms and/or signs. The most common pattern of inheritance for nonsyndromic HHL (NSHHL) is autosomal recessive (DFNB), which accounts for 75–85% of all cases. Another 15–25% of the cases are inherited in an autosomal dominant (DFNA) pattern, while the remaining 1–2% are X-linked (DFNX) or mitochondrial disorders (<http://hereditaryhearingloss.org/>). Members of the connexin family, in particular gene *GJB2* encoding connexin 26, play a major role in the recessive form of NSHHL [6–8]. According to the hereditaryhearingloss.org home page, more than 140 NSHHL loci have been mapped, and approximately 65 genes have been identified. Based on the type of gene product, these genes can be categorized into several groups, such as those encoding proteins involved in the structure and function of hair cells, the auditory nerve and virtually every structural element of the inner ear.

As regards HHL in Qatar, a hearing loss prevalence of 5.2% has been reported with parental consanguinity being more common among affected individuals as compared with unaffected ones (60.5 vs. 25.3%) [9]. Moreover, hearing deficiencies have been reported to be one of the most frequent causes (8.2%) of school failure in Qatar [10].

Very recently, we had the opportunity to verify the overall amount of molecular kinship, a way of looking at similarities among individuals, using data from high-density SNPs arrays coming from 36 individuals belonging to 6 HHL families from Qatar, whose pedigrees are shown in figure 1. We merged our dataset of Qatari samples with that containing all Human Genome Diversity Project populations (<http://www.hagsc.org/hgdp/>

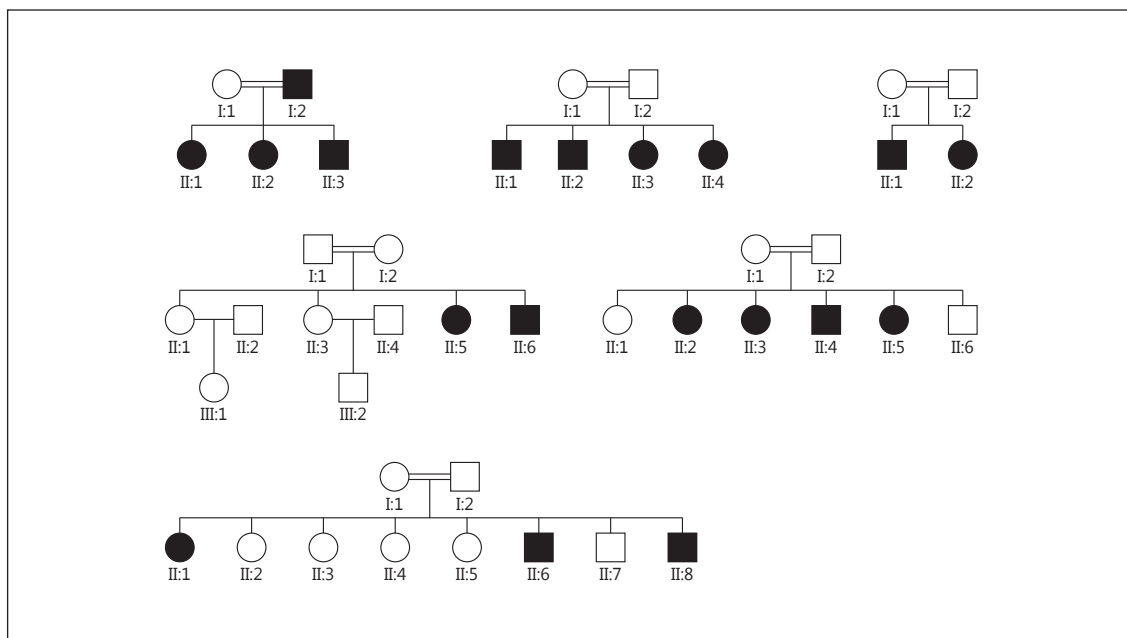


Fig. 1. Pedigrees of 6 Qatari consanguineous families affected by HHL. Filled symbols represent affected individuals. Double bars indicate consanguinity of the family.

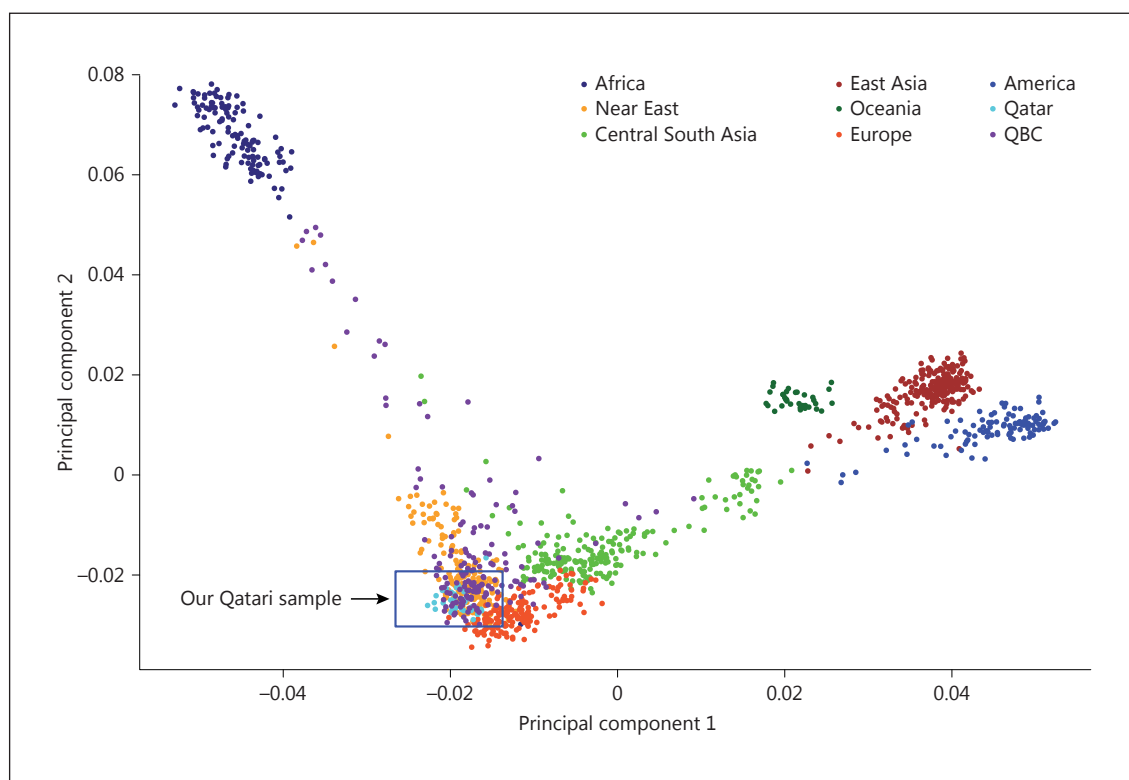


Fig. 2. PCA analysis on the merged dataset; the 156 Qatari samples from the public dataset (QBC) are in violet, our 36 Qatari individuals (Qatar) are in cyan. The variance of each axis is reported. The different populations are named according to their geographic location.

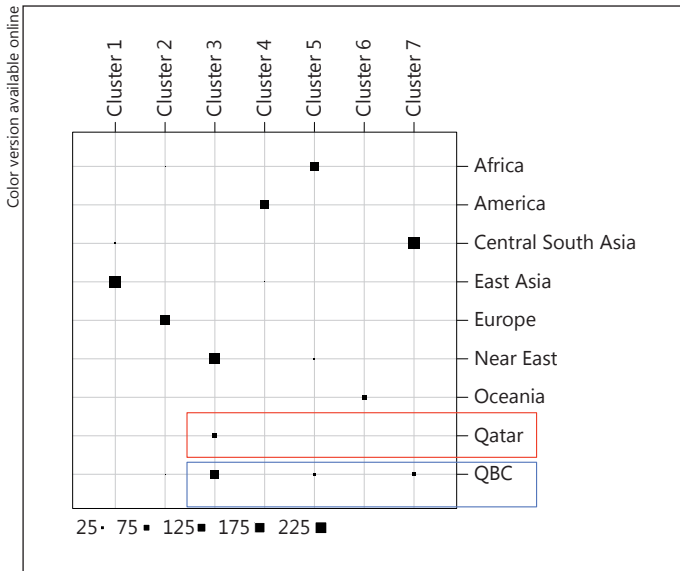


Fig. 3. Membership of all HHL individuals from each geographic region of origin in relation to each of the 7 genetic clusters inferred by DAPC and *k*-means algorithm (clusters 1–7). The size of the square is proportional to the number of individuals present in each cluster.

Table 1. ROH and level of inbreeding

	Segments/ individual, n (on average)	ROH length/ individual, Mb (on average)	Inbreeding coefficient <i>F</i>
Africa	5	25	0.151
Near East	11	80	0.069
Central South Asia	11	83	0.063
East Asia	4	18	0.099
Oceania	16	59	0.2683
Europe	4	18	0.063
America	30	214	0.27
Qatar	16	160	0.13

files.html). This dataset consists of a total of 142,670 SNPs with a genotyping rate of >0.99 and a minor allele frequency of >0.01 for 1,079 individuals. It was used to evaluate: (1) inbreeding, (2) runs of homozygosity (ROH), and (3) proportions identical by descent (IBD). In addition, this dataset was also combined with that of 156 Qatari individuals described in a previous work [1]. The resulting dataset was then used to perform principal component analysis (PCA) and discriminant analysis of principal components (DAPC) [11]. Both PCA and

DAPC clearly discriminated the 3 subgroups (Q1, Q2 and Q3) of the analyzed Qatari people (fig. 2). In particular, to evaluate genetic spatial variation, PCA was performed in R using the package SNPRelate [12] on the merged dataset. The populations' labels refer to their geographical locations: Africa, Europe, Near East, Central South Asia, East Asia, Oceania, America and Qatar (the 156 Qatari individuals from a previous work [1] were labeled as QBC). The cluster algorithm *k*-mean and the Bayesian information criterion were used to choose the optimal number of clusters as explained in Jombart et al. [11].

Different to what is known from previous studies showing the presence of 3 distinct population subgroups (Q1, Q2 and Q3), DAPC displays that our sample of HHL cases is quite homogeneous, since all individuals belong to the Q1 subgroup, overlapping also with individuals belonging to the Near Eastern population (Cluster 3; fig. 3). This is an extremely interesting finding, suggesting that the majority of hearing-impaired individuals belong to the Q1 subgroup. Of course we cannot rule out the presence of a bias at the level of recruitment, leading to a selection of only Q1 subgroup patients. However, taking the 'capillary' organization of the Qatari National Health Care system into account, a recruitment bias is quite difficult to be considered.

Moreover, using the same genetic dataset, ROH, inbreeding coefficients and IBD proportions were also estimated for each individual. In particular, because our study population reflects a recent inbreeding, characterized by essentially few opportunities of recombinational events, our analysis focused on long ROH (class C ROH), as has recently been described [13]. The parameters used for estimating ROH were: (a) a SNP density of at least 1 SNP per 50 kb; (b) a ROH minimum length of 1.5 Mb, roughly meaning recent inbreeding [13]; (c) a maximum gap between 2 ROH of 1 Mb, and (d) a sliding window of 5,000 kb to scan each individual genome. Indeed our ROH analysis showed evidence of recent inbreeding, as the degree of genomic homozygosity is quite high compared to that from other Near Eastern populations. However, it is not as high as in other populations which have higher levels of parental relatedness, a small effective population size and are the outcome of both ancient and recent parental relatedness, such as Pima Americans or Maya [14]. The numbers and lengths of ROH in each population are reported in table 1. Moreover, the analysis of the inbreeding coefficient *F* confirms these findings of high consanguinity (table 1).

Table 2. Description of genes involved in HHL, discovered in Qatari families

Gene	Cytogenetic position	Pattern of inheritance in Qatar	Inner hair cell expression	Animal models with hearing phenotype	OMIM No.
<i>LOXHD1</i>	18q21.1	recessive	mechanosensory hair cells	available	613072
<i>BDP1</i>	5q13	recessive	endothelial cells of the stria vascularis capillaries in mesenchyme-derived cells surrounding the extracellular matrix around the cochlear	not available	607012
<i>GJB2</i>	13q11-q12	recessive	multiple cell types	available	121011
<i>MYO15A</i>	17p11.2	recessive	tips of the stereocilia of the cochlear and vestibular hair cells	available	613392

The Genetics of HHL in Qatar

The Role of Connexin Genes

Recently, the first mutational screening of gene *GJB2*, *GJB6* (a deletion) and mitochondrial DNA (an A1555G transition in the 12S rRNA gene) has been carried out in a large cohort of 120 patients from Qatar [15]. The results of the largest collection of Qatari cases described so far demonstrate only a minor role for the *GJB2* gene. Considering the origin(s) of the Qatari population and comparing the present data with those reported for the Saudi Arabian and Iranian populations, the proportion of detected cases involving *GJB2* in our sample is the smallest [16, 17].

As a matter of fact, the prevalence of HHL in the Iranian population is estimated 2–3 times higher than that in other parts of the world, with a *GJB2* mutation as the most common genetic cause of NSHHL, with a mean frequency of 18.17–38.3% [18–20]. The discrepancy between studies may be due to differences in inclusion criteria for patients. In all studies, c.35delG was the most common deafness-causing mutation in the Iranian population [19–21], reaching an allele frequency of 40.9%. *GJB6* and the A1555G mutation played virtually no role.

As regards Saudi Arabia, the proportion of cases explained by *GJB2* mutations has been 15.6% in a recent study, with c.35delG being the most common allele. Interestingly, biallelic *GJB2* mutations have not been detected in patients of Arab tribal origins, reflecting the genetic heterogeneity of the Western area of the Kingdom of Saudi Arabia [16]. The data from Qatar are more in agreement with these findings, albeit with an even lower mutation detection rate, and with the c.35delG allele not being the most common mutation.

Regarding other mutations, 5 homozygous cases for the IVS1+1G>A allele have been described [16]. This allele has been reported to be quite frequent in Turkish as well as in Chinese patients [22, 23]. Overall, these findings clearly demonstrate that *GJB2* accounts for a minor proportion of HHL in the Qatari population. This proportion is even lower than that reported for Saudi Arabia but higher when compared to that of the Omani population, in which the role of *GJB2* is negligible [24]. With regard to the *GJB6* gene, no mutations have been found in the cases studied.

The Role of Other Genes

Considering the marginal role of the connexin genes, there was a need to search for other causative HHL genes, and, thus, several attempts have been carried out leading to the identification of some additional genes (see table 2). In particular, using a combined strategy based on both linkage analysis and whole exome sequencing, we identified a new gene and mutation causing hearing loss in the Qatari population [25]. Linkage analysis identified a region of 40 Mb on chromosome 5q13 (LOD score 3.8) for which exome sequencing data revealed a mutation (c.7873 T>G leading to p.*2625Gluext*11) in the *BDP1* gene (B double prime 1; a subunit of RNA polymerase III transcription initiation factor IIIB) in patients from a second-degree consanguineous Qatari family, showing bilateral, postlingual, sensorineural hearing impairment. The mutation disrupts the termination codon of the transcript, resulting in an elongation of the BDP1 protein of 11 residues. This elongation does not contain any known motif and is not conserved across species. Immunohistochemistry studies on the mouse inner ear showed Bdp1 expression within the endothelial cells in the stria vascu-

Table 3. Average Hd in gene *LOXHD1* and average proportion of IBD for each population/geographical region

	Average Hd	Average proportion of IBD
Africa	0.53	0.0056
Near East	0.69	0.0021
Central South Asia	0.65	0.0011
East Asia	0.68	0.0220
Oceania	0.64	0.0108
Europe	0.59	0.0127
America	0.56	0.0373
Qatar	0.71	0.0866

laris as well as in mesenchyme-derived cells surrounding the cochlear duct.

Using a targeted re-sequencing approach based on the analysis of 96 HHL genes (including some candidate genes), two additional families have been further characterized at the molecular level [26]. The first one is a consanguineous family, showing bilateral, early-onset, sensorineural hearing impairment, carrying a novel allele in the *LOXHD1* gene, which segregates in the homozygous state in all affected family members. The *LOXHD1* protein consists entirely of PLAT (polycystin/lipoxygenase/alpha-toxin) domains, it is expressed in the mechanosensory hair cells in the mouse inner ear, and mutations in the gene have already been associated with recessive forms of NSHHL in Iranian people and Ashkenazi Jews [27, 28]. Moreover, in a knockout samba mouse model, the hair cell function is altered and the hair cells eventually degenerate [27]. In the second family, homozygosity (due to consanguinity) for a new deletion/insertion within the *MYO15A* gene has been detected. The patients show bilateral, early-onset, sensorineural hearing loss. It is very well known that mutations in the *MYO15A* gene cause DFNB3 hearing loss in individuals from different populations worldwide (see <http://hereditaryhearingloss.org/>). Interestingly, after this preliminary screening, the analysis of 4 additional families under investigation was completely negative for the presence of mutations in one of the 96 genes included in the hearing loss panel. This finding implies that other yet unknown HHL genes underlie the disease in these Qatari families [26].

Finally, in order to obtain additional data on relatedness and HHL, the level of IBD between pairs was calculated using the procedure implemented in PLINK. We took all SNPs of the genes discovered in previous studies

of hearing loss in Qatari samples [15, 25, 26] and we estimated the haplotype diversity in these genes with respect to other reference populations. The haplotypes were phased using an expectation-maximization procedure implemented in PLINK. The haplotype diversity (Hd) is defined as follows:

$$Hd = \left[\frac{n}{(n-1)} \right] \times \left(1 - \sum_{i=1}^k p_i^2 \right),$$

where n is the sample size, p_i is the frequency of allele i at the haplotype locus. This approach requires a minimum of 2 markers to construct a haplotype. Among all *GJB2*, *MYO15A* and *BDP1* genes, only *LOXHD1* showed enough markers (i.e. 4) to perform this kind of analysis. Therefore, Hd was calculated only for this gene, being quite high (Hd >0.69) and showing little correlation with the previously mentioned genetic homogeneity (table 3). Moreover, in agreement with previous findings, the level of IBD in HHL Qatari families is quite high (table 3), confirming the presence of a homogeneous disease group. These findings reveal an unexpected level of haplotype heterogeneity in this gene.

Age-Related Hearing Loss

As regards the complex form of hearing loss, age-related hearing loss (ARHL or presbycusis) is the most prevalent sensory impairment in the elderly, contributing to a loss of autonomy and being associated with anxiety, depression and cognitive decline. ARHL is currently untreatable and due to the limited potential of available therapies and the large number of people affected, there is an unmet need to develop new preventive strategies and therapeutic approaches. Ageing causes many changes, involving hair cells, cochlear neurons, the stria vascularis and combinations thereof. Twin studies have demonstrated a heritability rate ranging from 40 to 60%. Recently, a genome-wide association study has identified a highly significant SNP located in the *GRM7* gene [29], and additional association studies have confirmed a role for this gene and identified several other interesting genes [30, 31]. Moreover, a few single-gene, late-onset, dominant mutations have also been described, but these are rare, confirming the difficulties in dissecting the molecular basis of ARHL. Furthermore, quite recently, some genes associated with hearing functions, which might also play a role in ARHL, have been identified [32]. Finally, relatively few animal models of hearing impairment

have been associated with ARHL (<http://hearingimpairment.jax.org/index.html>). Almost no data are available so far on genetic and environmental risk factors for ARHL in the Qatari population.

Conclusions

This review provides an up-to-date overview of the genetics of hearing loss in Qatar and the role of consanguinity in this disease. The reported and commented data are taken from the literature as well as from personal research activities we are carrying out to better understand the molecular basis of HHL in this part of the Gulf area. Interestingly, beside the large proportion of consanguineous mating and, in our sample, the presence of a population structure mainly characterized by one group, a large genetic heterogeneity for HHL is now evident. So far, 4 genes (*GJB2*, *LOXHD1*, *MYO15A* and *BDP1*) have been found to be mutated in some Qatari HHL families [24, 25]. Moreover, an interesting allele/haplotype variability

in the *LOXHD1* gene has been also detected in inbred and homogeneous disease groups.

We actually know that additional genes will account for the families not yet characterized further, increasing the large genetic heterogeneity of the disease in this country. Thus, the combination of consanguinity and HHL in Qatar is a good example of how inbreeding could increase an intra-familial clustering of HHL more than a population clustering. Large-scale genotyping with higher density SNPs array and clinical assessments, together with the constitution of genetically homogeneous groups of patients (Q1, Q2 and Q3, respectively), would help in establishing the exact genotype-phenotype correlation. Mutation screening in HHL families from Qatar along with information about their ethnic origin is needed at present, because the Q1 subgroup is, to our knowledge, the most affected and the one with the highest level of inbreeding. The screening will help in genetic counseling and prenatal diagnosis, and thus, in turn, may help to reduce the incidence of hearing loss in this highly consanguineous population.

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