HHS Public Access

Author manuscript

Ann Hum Genet. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Ann Hum Genet. 2016 November ; 80(6): 327–331. doi:10.1111/ahg.12177.

Targeted Resequencing of Deafness Genes Reveals a Founder *MYO15A* Variant in Northeastern Brazil

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Abstract

Identifying the genetic etiology in a person with hearing loss (HL) is challenging due to the extreme genetic heterogeneity in HL and the population specific variability. In this study, after excluding *GJB2* variants, targeted resequencing of 180 deafness-related genes revealed the causative variants in 11 of 19 (58%) Brazilian probands with autosomal recessive HL. Identified pathogenic variants were in *MYO15A* (10 families) and *CLDN14* (1 family). Remarkably, the *MYO15A* p.(Val1400Met) variant was identified in 8 families from the city of Monte Santo in the Northeast region of Brazil. Haplotype analysis of this variant was consistent with a single founder. No other cases with this variant were detected among 105 simplex cases from other cities of Northeastern Brazil, suggesting that this variant is confined to a geographical region. This study suggests that it is feasible to develop population-specific screening for deafness variants once causative variants are identified in different geographical groups.

Keywords

Founder; gene; hearing loss; targeted resequencing

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Conflict of Interest

Authors declare that there is no conflict of interest to report.

INTRODUCTION

Evidence of the genetic etiology of HL in Brazil has been demonstrated by a number of independent studies (Pfeilsticker et al., 2004; Piatto et al., 2004; Bernardes et al., 2006; de Oliveira et al., 2007; Christiani et al., 2007; Batissoco et al., 2009; Cordeiro-Silva et al., 2011; Motta et al., 2012; Castro et al., 2013; Manzoli et al., 2013; Ramos et al., 2013; Melo et al., 2014; Moreira et al., 2015). Most studies present data representative of Brazil's Southeast region, while few studies show genetic HL data from the North and Northeast regions. According to these studies, variants in the DFNB1 locus [*GJB2* (MIM 121011) and *GJB6* (MIM 604418) genes] explain the etiology of HL in 1% to 18.2% of subjects analyzed; *GJB2* c.35delG (rs80338939) is the most frequent (10.8%) pathogenic variant (Melo et al., 2014).

Brazil is the largest country in South America and the fifth most populous country world-wide (Philander, 2012). Its population is mainly the product of admixture between Europeans, Africans and Amerindians. The proportions of each vary between regions. In the Southern and Southeastern Brazil, Europeans make up the majority of the ancestry, while in the Northeastern and Northern populations, it is Africans and Amerindians, respectively (Salzano & Freire-Maia, 1970).

Hereditary HL is extremely heterogeneous and it is well established that the frequency of HL genes and variants varies across populations (Duman & Tekin, 2012). For example, pathogenic variants in *GJB2* gene are an uncommon cause of HL in Africans (Kabahuma et al., 2011), but very common in populations of European origin (Gasparini et al., 2000). As only about 20% of HL is caused by variants in the DFNB1 locus in Brazil (Melo et al., 2014), it is very important to broaden the scope of tested genes, identify other variants, and establish a panel with the genes causing most of the HL in Brazil. Next-generation sequencing (NGS) is one of the most powerful tools for investigating a large number of DNA regions simultaneously. NGS has made the identi?cation of causative genes easier, even for small families and diseases with extensive locus and allelic heterogeneity (Duman & Tekin, 2012; Atik et al., 2015).

Previous studies of HL in Brazil have focused on traditional gene discovery methods (Martins et al., 2013; Dantas et al., 2014; Rosenberg et al., 2015; Svidnicki et al., 2015); the aim of this study was to identify pathogenic variants underlying HL in subjects from Brazil employing NGS techniques.

MATERIALS AND METHODS

Subjects

This study was approved by the local Institutional Review Board at the University of Miami (USA), the Ethics Committee of Federal University of Bahia – UFBA (Brazil) and the Hospital de Clínicas de Porto Alegre (Brazil). Informed consent was obtained from all participants and, in the case of a minor, from parents.

Fifteen reportedly unrelated probands from Monte Santo, Bahia (BA) (Northeast), one from Salvador, Bahia (Northeast) and three from Porto Alegre, Rio Grande do Sul (RS) (South), with a family history consistent with autosomal recessive nonsyndromic sensorineural HL (NSHL) (i.e., multiplex) were included. All probands were derived from a larger cohort prescreened for *GJB2* variants, (*GJB6*-13S1830), (*GJB6*-D13S1854) and m.1555A>G variant in the *MTRNR1* (MIM 561000) gene. Only the probands negative for these variants were included in this study. In addition, 105 probands from different towns of Northeastern Brazil not including Monte Santo without a family history of NSHL (i.e., simplex) and were negative for *GJB2* mutations were included only to screen for the most common mutation identified in the multiplex probands (Figure S1).

DNA sequencing and bioinformatics analysis

Genomic DNA was extracted from peripheral blood leucocytes using standard methods.

The Agilent SureSelect target capture system was used for a custom capture panel which contains all exons, 5' UTRs and 3' UTRs of 180 known/candidate syndromic and non-syndromic deafness genes. Subsequently the Illumina HiSeq 2000 was used for the targeted resequencing (Tekin et al., 2016).

Bioinformatics pipeline including variant calling and filtering was performed by using our previously published protocol (Yan et al., 2016). PolyPhen2, SIFT and MutationTaster2 used for *in silico* analysis (Adzhubei et al., 2010; Kumar et al., 2009; Schwarz et al., 2014). Conservation of variants across species was evaluated by PhastCons and GERP (Siepel et al., 2005; Davydov et al., 2010). Finally American College of Medical Genetics and Genomics (ACMG) 2015 guidelines were used for the variant interpretation (Richards et al., 2015).

Confirmation and segregation of the identified variants was evaluated by using Sanger sequencing in the available family members of all families.

RESULTS

An average of 99%, 87%, 63% of the targeted bases were covered at 10X, 50X and 100X reads, respectively. We identified pathogenic variants in 11 out of 19 multiplex families in following genes: *MYO15A* (MIM 602666) and *CLDN14* (MIM 602666) (Table 1; Table S1). Remarkably the *MYO15A* p.(Val1400Met) variant was identified in eight of the families from the Northeast region of Brazil. In six families, affected individuals were homozygous for this variant and in two families, affected individuals were heterozygous for this variant and the p.(Arg2728Cys) variant (Figure S2). Two other *MYO15A* c.9319G>T and c.7636C>T variants were identified in two families. After screening 105 simplex cases from Brazil, no additional probands with *MYO15A* p.(Val1400Met) variant were identified.

Subjects who were homozygous for the *MYO15A* p.(Val1400Met) variant have prelingual, nonprogressive, bilateral and profound sensorineural hearing loss.

Inspection of the targeted resequencing data demonstrated that a 34.8 kb (chr17:18034837-18069628; hg19) haplotype was associated with the *MYO15A* p.

(Val1400Met) variant in all Brazilian families (Table S2). This haplotype was observed in three chromosomes from Northeastern Brazil that did not have the p.(Val1400Met) variant. Sixteen of these chromosomes shared a common haplotype in this population. A previously reported family with the same p.(Val1400Met) variant from Turkey (Cengiz et al., 2010) was also evaluated. This family did not have the same haplotype as the Brazilian families and instead was found to have the most common haplotype that was observed in both Brazilian and Turkish control chromosomes (Table S2).

Among the non-*MYO15A* families, we identified a homozygous pathogenic variant in *CLDN14* in a family from Porto Alegre.

DISCUSSION

Despite the extreme genetic heterogeneity of autosomal recessive NSHL, *MYO15A* is one of the most common genes for HL after *GJB2* in several ethnicities (Bademci et al., 2015). Here we show that variants in *MYO15A* are a common cause of HL in Monte Santo, Brazil and they occur in Southern Brazil. A few other studies have identified *MYO15A* variants in the HL population in Brazil (Svidnicki et al., 2015; Lezirovitz et al., 2008).

Monte Santo is a city localized in Northeast Brazil, 183.7 miles from Salvador, the Bahia state capital. Its population has been estimated at 54,733 (IBGE, 2010). Only a few HL studies have focused on the Northeast region of Brazil (Manzoli et al., 2013; Melo et al., 2014); our data greatly expands what is known about the genetics of HL in this region and facilitates diagnostic etiology in this region. The variant p.(Val1400Met) in *MYO15A* is the most frequently identified. This variant has not been previously reported in Brazilian studies, but was identified in one family from Turkey (Cengiz et al., 2010). In this study we showed that the haplotypes associated with the p.(Val1400Met) variant are different in the Brazilian and Turkish populations, suggesting that either this variant arose at least two times in history (the more likely explanation) or that it is a very old mutation.

It has been observed that in Monte Santo, there is an increased incidence of several autosomal recessive genetic disorders (such as Mucopolysaccharidosis type VI and Phenylketonuria), probably due to relative endogamy and isolation (Costa-Motta et al., 2011). All Mucopolysaccharidosis type VI (MPS VI) patients from Monte Santo have the same variant. Genealogy information and haplotype analysis confirmed that all Mucopolysaccharidosis type VI (MPS VI) patients from Monte Santo have the same origin (Costa-Motta et al., 2011). Here we show that all subjects from Monte Santo with HL caused by *MYO15A* p.(Val1400Met) pathogenic variant have the same haplotype associated with this variant. Thereby, because of the highly endogamous nature of the Monte Santo population (Acosta et al., 2013) and haplotype results, it is most likely that this variant was inherited from a common founder.

In addition to *MYO15A,* we identified a *CLDN14* pathogenic variant in a family from Porto Alegre. More samples with deafness gene panels need to be studied in different geographical regions of Brazil to catalogue all pathogenic variants.

In conclusion we present novel information regarding causative genes involved in the etiology of HL in Brazil. Our results show that a *MYO15A* variant is a common cause of HL in a Northeastern Brazilian town.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This study was supported by the National Institutes of Health/National Institute on Deafness and Other Communication Disorders to Xuezhong Liu (R01DC05575, R01DC01246, and R01DC012115) and to Mustafa Tekin (R01DC09645 and R01DC012836). This work was supported by CNPq, the National Council for Scientific and Technological Development Brazil to Gabrielle Novais Manzoli. Contributions - Study design: Gabrielle N. Manzoli, Guney Bademci, Angelina X. Acosta, Têmis M. Félix, Danniel S. Dias Da Silva, Ibis Menendez, Demet Tekin, Kiyoko Abe-Sandes, Xue Zhong Liu, Mustafa Tekin; Data collection: Gabrielle N. Manzoli, Têmis M. Félix, Danniel S. Dias Da Silva, Ibis Menendez, Mustafa Tekin; Contribution of new reagents or analytical tools: Guney Bademci, Susan H. Blanton, Xue Zhong Liu, Mustafa Tekin; Data analysis: Gabrielle N. Manzoli, Guney Bademci, Isalis Sanchez-Pena, F.Basak Cengiz, Joseph Foster II, Demet Tekin, Susan H. Blanton, Xue Zhong Liu, Mustafa Tekin; Manuscript preparation: Gabrielle N. Manzoli, Guney Bademci, Angelina X. Acosta, Têmis M. Félix, Isalis Sanchez-Pena, F.Basak Cengiz, Ibis Menendez, Joseph Foster II, Demet Tekin, Susan H. Blanton, Kiyoko Abe-Sandes, Xue Zhong Liu, Mustafa Tekin

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Table 1

Summary of pathogenic variants identified in this study.

Family ID	Family origin	Genotype	cDNA	Protein	NM_Transcript	Gene	Reference	ACMG
1923	Monte Santo - BA	Homozygous	c.4198G>A	p.(Val1400Met)	NM_016239.3	*MYO15A*	Cengiz et al., 2010	LP
1940	Monte Santo - BA	Homozygous	c.4198G>A	p.(Val1400Met)	NM_016239.3	*MYO15A*	Cengiz et al., 2010	LP
1926	Monte Santo - BA	Homozygous	c.4198G>A	p.(Val1400Met)	NM_016239.3	*MYO15A*	Cengiz et al., 2010	LP
1939	Monte Santo - BA	Homozygous	c.4198G>A	p.(Val1400Met)	NM_016239.3	*MYO15A*	Cengiz et al., 2010	LP
1950	Monte Santo - BA	Homozygous	c.4198G>A	p.(Val1400Met)	NM_016239.3	*MYO15A*	Cengiz et al., 2010	LP
1927	Monte Santo - BA	Homozygous	c.4198G>A	p.(Val1400Met)	NM_016239.3	*MYO15A*	Cengiz et al., 2010	LP
2191	Monte Santo - BA	Heterozygous	c.4198G>A	p.(Val1400Met)	NM_016239.3	*MYO15A*	Cengiz et al., 2010	LP
		Heterozygous	c.8182C>T	p.(Arg2728Cys)	NM_016239.3	*MYO15A*	This study	LP
1931	Monte Santo - BA	Heterozygous	c.4198G>A	p.(Val1400Met)	NM_016239.3	*MYO15A*	Cengiz et al., 2010	LP
		Heterozygous	c.8182C>T	p.(Arg2728Cys)	NM_016239.3	*MYO15A*	This study	LP
1504	Porto Alegre - RS	Homozygous	c.9319G>T	p.(Glu3107*)	NM_016239.3	*MYO15A*	This study	P
1500	Porto Alegre - RS	Heterozygous	c.7636C>T	p.(Gln2546*)	NM_016239.3	*MYO15A*	This study	LP
		Heterozygous	c.9319G>T	p.(Glu3107*)	NM_016239.3	*MYO15A*	This study	LP
1502	Porto Alegre - RS	Homozygous	c.291C>A	p.(Cys97*)	NM_001146077.1	*CLDN14*	This study	LP

BA: Bahia, **RS**: Rio Grande do Sul, **LP**: Likely Pathogenic, **P**: Pathogenic, **ACMG:** American College of Medical Genetics guideline (Richards et al., 2015)