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Genetic heterogeneity of congenital hearing impairment in Algerians from the Ghardaïa province

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ABSTRACT

Background: Consanguinity rate is high in Algeria, and the population is thus at high risk for genetic diseases transmitted on an autosomal recessive mode. Inherited congenital hearing impairment (HI) is a highly heterogeneous disorder, which affects approximately 1 in 800 Algerian newborns. Several hundreds of genes responsible for deafness have been reported among which more than one hundred are responsible for isolated deafness, of which 19 have already been reported to be involved in the Algerian population. This study focuses on patients from the Ghardaïa province, an ethnically and geographically isolated region of Southern Algeria that has the highest consanguinity rate in the country (56%).

Methods: Eleven families, with at least two related members experiencing moderate to profound congenital HI, were recruited and screened for mutations in known HI genes.

Results: A preliminary screening for common mutations in *GJB2* and *GJB6* identified the prevalent *GJB2*:c.35delG mutation in four families. Targeted exome sequencing further identified the causal mutations in the remaining seven families: *CIB2*:c.97C > T; p.(Arg33*), *MYO7A*:c.470 + 1G > A; p.(?), and *SLC26A4*:c.410C > T; p.(Ser137Leu) biallelic mutations in two families each, and a *TECTA*:c.2743 A > G; p.(Ile915Val) monoallelic mutation in the only family with autosomal dominant transmission of the HI. Of note, the missense mutations of *SLC26A4* and *TECTA* had not been previously reported.

Conclusion: These results further substantiate the genetic heterogeneity of HI, even in reportedly isolated populations. However, several families may harbor the same mutations as a result of a long history of marriages between relatives. This study has important implications for the HI molecular diagnosis strategy, and to develop genetic counseling for families originating from the Ghardaïa province of Algeria.

1. Introduction

Maghrebian populations of North African countries are a mixture of Berbers, Arabs, and Europeans [1,2]. They form distinct human groups that can differ by the territory, language, local customs, and traditions [3,4]. This contributes to the high rate of consanguinity and endogamy, which is a major contributing factor to the manifestation of autosomal recessive disorders, such as congenital (prelingual) hearing impairment (HI) [5,6]. Algeria and Tunisia show the highest prevalence of consanguinity (20–29%) among Maghrebian countries [7]. To date, more than 100 different causal mutations in a total of 32 HI genes have been reported in North Africa [8]. Mutations of *GJB2* are the most frequently involved in Algeria (48%) [9], Tunisia (39%) [10], and Morocco (37%) [11]. In addition, some recurrent mutations, such as the founder mutations *LRTOMT*: c.208C > T and *SLC26A4*:c.1334 T > G, are most prevalent in Morocco and Tunisia, respectively [8]. In Algeria, 37 different causal mutations have already been identified in a total of 18 genes different from *GJB2*, in keeping with the genetic heterogeneity

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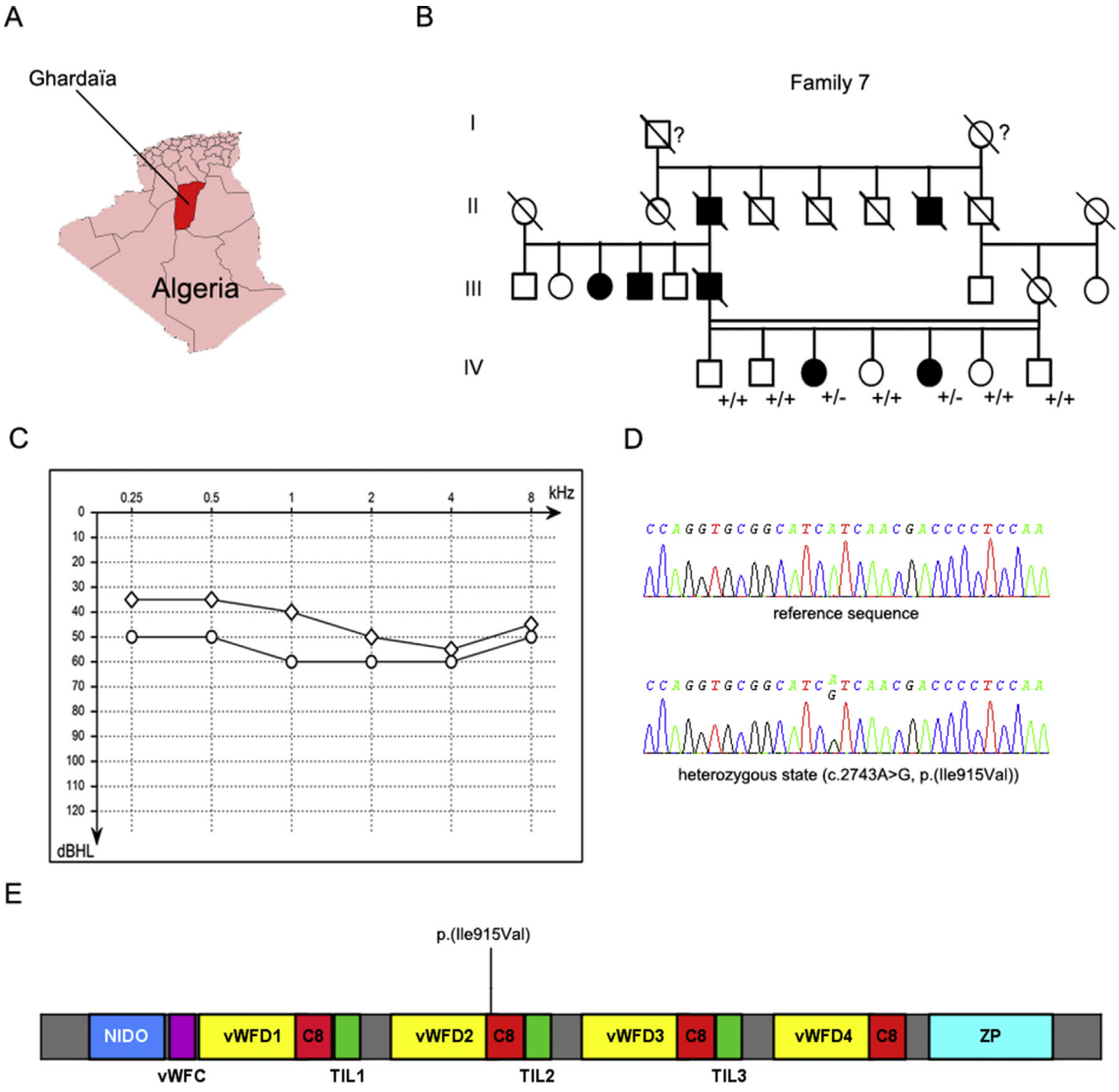

Fig. 1. Pedigree, audiometric curves, and molecular analysis of the HI patients harboring a monoallelic missense mutation of *TECTA*: (A) Map of Algeria showing the province of Ghardaïa (in red). **(B)** Segregation of HI and the *TECTA* mutation in family 7. Black symbols indicate HI individuals. The wild-type (unmutated) and mutated alleles of *TECTA* are denoted + and -, respectively. **(C)** Air-conduction audiometric curves for one patient. Diamonds and circles are for the right and left ears, respectively. Hearing thresholds are expressed in 'decibels Hearing Level' (dBHL) **(D)** DNA sequencing chromatograms of unaffected (upper) and affected (lower) individuals showing the mutation, in the heterozygous state, in the HI patient (arrow). **(E)** Schematic representation of α-tectorin showing the position of the p. Ile915Val missense mutation. Abbreviations: NIDO, nidogen-like domain (blue); vWFC, von Willebrand factor type C domain (purple); vWFD, von Willebrand factor type D domain (yellow); C8, domain containing eight conserved cysteine residues (red); TIL, trypsin inhibitor-like cysteine-rich domain (green); ZP, zona pellucida domain (turquoise). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Genotypes and phenotypes of the HI patients from the Ghardaïa province.

	Consanguinity	Ethnic origin	Type of HI	Gene	Nucleotide change	Amino acid change	Status of affected individuals
Family 1	Yes	Arabic	Profound	*CIB2*	c.97C > T	p.(Arg33*)	Homozygous
Family 2	Yes	Arabic	Profound	*CIB2*	c.97C > T	p.(Arg33*)	Homozygous
Family 3	Yes	Mozabite	Profound	*SLC26A4*	**c.410C > T**	**p.(Ser137Leu)**	Homozygous
Family 4	Yes	Mozabite	Profound	*SLC26A4*	**c.410C > T**	**p.(Ser137Leu)**	Homozygous
Family 5	Yes	Arabic	Profound	*MYO7A*	c.470+1G > A	?	Homozygous
Family 6	Yes	Arabic	Profound	*MYO7A*	c.470+1G > A	?	Homozygous
Family 7	Yes	Arabic	Moderate/severe	*TECTA*	**c.2743A > G**	**p.(Ile915Val)**	Heterozygous
Family 8	Yes	Arabic	Profound	*GJB2*	c.35delG	p.(Gly12Valfs*2)	Homozygous
Family 9	Yes	Arabic	Profound	*GJB2*	c.35delG	p.(Gly12Valfs*2)	Homozygous
Family 10	Yes	Arabic	Profound	*GJB2*	c.35delG	p.(Gly12Valfs*2)	Homozygous
Family 11	Yes	Arabic	Profound	*GJB2*	c.35delG	p.(Gly12Valfs*2)	Homozygous

Novel mutations are indicated in bold.