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Commentary

Correspondence regarding Ballana et al., "Mitochondrial 12S rRNA gene mutations affect RNA secondary structure and lead to variable penetrance in hearing impairment"

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Abstract

Ballana et al. [E. Ballana, E. Morales, R. Rabionet, B. Montserrat, M. Ventayol, O. Bravo, P. Gasparini, X. Estivill, Mitochondrial 12S rRNA gene mutations affect RNA secondary structure and lead to variable penetrance in hearing impairment, Biochem. Biophys. Res. Commun. 341 (2006) 950–957] detected a T1291C mutation segregating in a Cuban pedigree with hearing impairment. They interpreted it as probably pathogenic, based on family history, RNA conformation prediction and its absence in a control group of 95 Spanish subjects. We screened a sample of 203 deaf subjects and 300 hearing controls (110 "European-Brazilians" and 190 "African-Brazilians") for the mitochondrial mutations A1555G and T1291C. Five deaf subjects had the T1291C substitution, three isolated cases and two familial cases. In the latter, deafness was paternally inherited or segregated with the A1555G mutation. This doesn't support the hypothesis of T1291C mutation being pathogenic. Two "African-Brazilian" controls also had the T1291C substitution. Six of the seven T1291C-carriers (five deaf and two controls) had mitochondrial DNA of African origin, belonging to macrohaplogroup L1/L2. Therefore, these data point to T1291C substitution as most probably an African non-pathogenic polymorphism.

Keywords: T1291C; A1555G; Nonsyndromic hearing loss; Sensorineural hearing impairment; Mitochondrial DNA; 12S rRNA gene

Ballana et al. [1] analyzed the mtDNA 12S rRNA gene in a cohort of 443 families with hearing impairment and detected the T1291C mutation in all maternally related individuals of a Cuban pedigree. They concluded that the mitochondrial mutation T1291C was probably pathogenic, causing hearing loss, based on segregation analysis in the Cuban family, RNA conformation prediction, and the absence of this mutation in a control group of 95 hearing subjects. Since 1998, we have been investigating genetic causes of deafness in the Brazilian population [2]. We have already screened a sample of 203 deaf subjects and 300 unrelated hearing controls, 110 classified as "European-Brazilians," and 190 as "African-Brazilians," for the mitochondrial mutations A1555G and T1291C (the restriction test developed by Estivill et al. [3] detects both mutations). Five deaf individuals had the T1291C substitution. Three were isolated cases of deafness. In one familial case, the A1555G mutation was found to segregate with deafness. In the other family, the propositus' father, and paternal grandmother and great-grandmother presented deafness. Therefore, familial data do not support T1291C as the cause of deafness in these patients. Among the 300 unrelated hearing controls, this mutation was found in two individuals of the "African-Brazilian" group. The T1291C mutation was in homoplasmy in all carriers.

The Brazilian population represents a complex admixture of ethnic groups. South American Indians, Portuguese

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T1291C              GCCUAUAUACCGCCAUCUUCAGCAAACCCUGAUGAAGGCCA-CAAAGUAAGCGCAAGUAC
H. Sapiens          GCCUAUAUACCGCCAUCUUCAGCAAACCCUGAUGAAGGCUA-CAAAGUAAGCGCAAGUAC
Gorilla gorilla     GCCUAUAUACCGCCAUCUUCAGCAAACCCUGAUGAAGGCCA-CAAAGUAAGCACAAGUAC
Pongo pygmaeus      GCCUAUAUACCGCCAUCUUCAGCAAACCCUGAUGAAGGCCA-CGAAGUAAGCGCAAACAC
Pan paniscus        GCCUAUAUACCGCCAUCUUCAGCAAACCCUGAUGAAGGUUA-CAAAGUAAGCGCAAGUAC
Pan troglodytes     GCCUAUAUACCGCCAUCUUCAGCAAACCCUGAUGAAGGUUA-CAAAGUAAGCACAAGUAC
Panthera tigres     GCCUAUAUACCGCCAUCUUCAGCAAACCCUAAAA-AGGAAGAAAA-GUAAGCACAAGUAU
Bassaricyon gabbii  GUCUAUAUACCGCCAUCUUCAGCAAACCCUUAAA-AGGAACAAAA-GUAAGCACAAUAAU
Mirounga leonina    GUCUAUAUACCGCCAUCUUCAGCAAACCCUUAAA-AGGAAUAGAA-GUAAGCACAAUAAU
Equus caballus      GCCUAUAUACCGCCAUCUUCAGCAAACCCUAAACAAGGUACCGAA-GUAAGCACAAAUAU
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Fig. 1. Alignment analysis of the 12S rRNA in different species. The position 1291 is boxed.

settlers, and African slaves contributed to its gene pool, and during the last hundred years the country received other immigrants [4]. Mitochondrial haplogroup analysis showed that all five deaf subjects and one of the two hearing controls with the T1291C mutation belong to the macrohaplogroup L1/L2, indicating an African origin of their mtDNA.

The frequency of 1.05% (2/190) of T1291C in the "African-Brazilian" control samples indicates that it is most likely polymorphic in the African population. The Cuban family reported by Ballana et al. might also have some African genetic background since Cuba has received an important African migration. According to Klein [5], "On the eve of the Haitian rebellion of 1791, Cuba was already well on its way to emerging as the major slave island in the Caribbean". May be a Spanish control sample was not suitable in this case.

Alignment analysis shows that the 1291 position of the mitochondrial genome is not conserved between species (Fig. 1). In addition, the C is present in the wild-type sequence of the apes *Gorilla gorilla* (GI 51127246) and *Pongo pygmaeus* (GI 511227239), supporting the hypothesis that the T1291C substitution might be a non-pathogenic polymorphism.

Therefore, our data point to T1291C substitution as most probably an African non-pathogenic polymorphism.

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