

ONLINE MUTATION REPORT

Maternally inherited non-syndromic hearing impairment in a Spanish family with the 7510T>C mutation in the mitochondrial tRNA^{Ser(UCN)} gene

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Inherited hearing impairment is a highly heterogeneous group of disorders.^{1,2} In a majority of cases (about 70%), the hearing loss is non-syndromic, that is, it is not associated with any other clinical feature. It can be transmitted following autosomal (recessive or dominant), X linked, or maternal inheritance patterns. In the nuclear genome, more than 70 loci have been reported to be involved in non-syndromic hearing impairment, and 27 genes have been isolated from their critical intervals.² In addition, a number of different mutations in several genes of the mitochondrial genome are responsible for hearing impairment.^{3,4} Some of these mutations result in a variety of additional clinical features in diverse organs. Mitochondrial syndromic hearing loss includes Kearns-Sayre syndrome (MIM 530000), MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MIM 540000), MERRF (myoclonus epilepsy and ragged red fibres; MIM 545000), and MIDD (maternally inherited diabetes mellitus and deafness; MIM 520000).³⁻⁵ In other cases, intrafamilial and interfamilial phenotypic variation is observed, a mutation causing syndromic or non-syndromic hearing impairment in different patients. This is the case for the 7445A>G mutation, causing hearing loss and palmoplantar keratoderma,⁶⁻¹⁰ and for 7472insC, responsible for hearing loss and neurological disorders (myoclonus epilepsy, ataxia, and cognitive impairment).¹¹⁻¹⁴ Finally, other mutations have been associated so far only with hearing loss. These include mutations 7510T>C¹⁵ and 7511T>C¹⁶ in the tRNA^{Ser(UCN)} gene, and 1095T>C¹⁷ and 1555A>G¹⁸ in the gene for the 12S rRNA. This last mutation is responsible for a dual phenotype, since it also

confers increased susceptibility to the ototoxic action of aminoglycoside antibiotics.¹⁸

Most of the mutations causing maternally inherited non-syndromic hearing loss have been described in a small number of families from several countries. The only exception is 1555A>G, which seems to be more frequent than the others,¹⁹⁻²² although its real prevalence remains to be determined in most populations. Remarkably, in Spain it may account for about 15-20% of all familial cases of non-syndromic hearing loss, irrespective of their mode of inheritance and age of onset^{23,24} (unpublished results). The prevalence of other mitochondrial mutations causing hearing loss in the Spanish population is unknown. We investigated the prevalence of the 7510T>C and 1095T>C mutations in the Spanish population, and here we report the genetic and clinical characterisation of a Spanish family with non-syndromic postlingual hearing loss, which includes 26 confirmed carriers of the 7510T>C mutation.

MATERIAL AND METHODS

One hundred and forty-eight unrelated Spanish families with non-syndromic sensorineural hearing loss were enrolled in the study. In all of these families, the pattern of inheritance of the hearing loss was consistent with maternal transmission. After getting informed consent, peripheral blood samples were obtained from all participating family members. DNA extraction was performed by standard procedures. At least one patient from each of these 148 families was tested for the presence of the mitochondrial 1555A>G mutation, the result

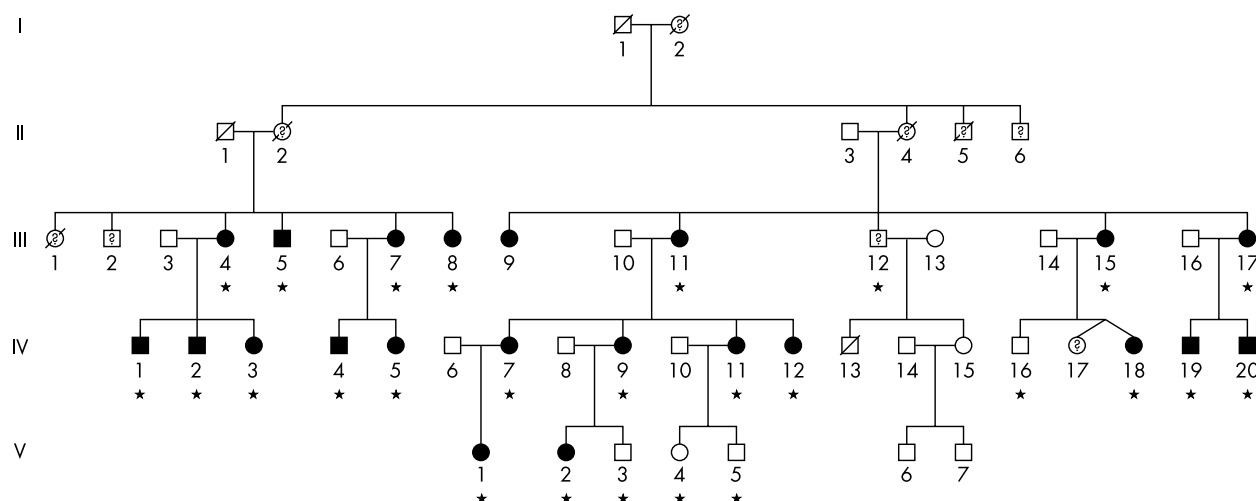


Figure 1 Pedigree of the Spanish family S258. Asterisks indicate confirmed carriers of the 7510T>C mutation. A question mark inside a symbol is used to represent subjects whose clinical status could not be ascertained.

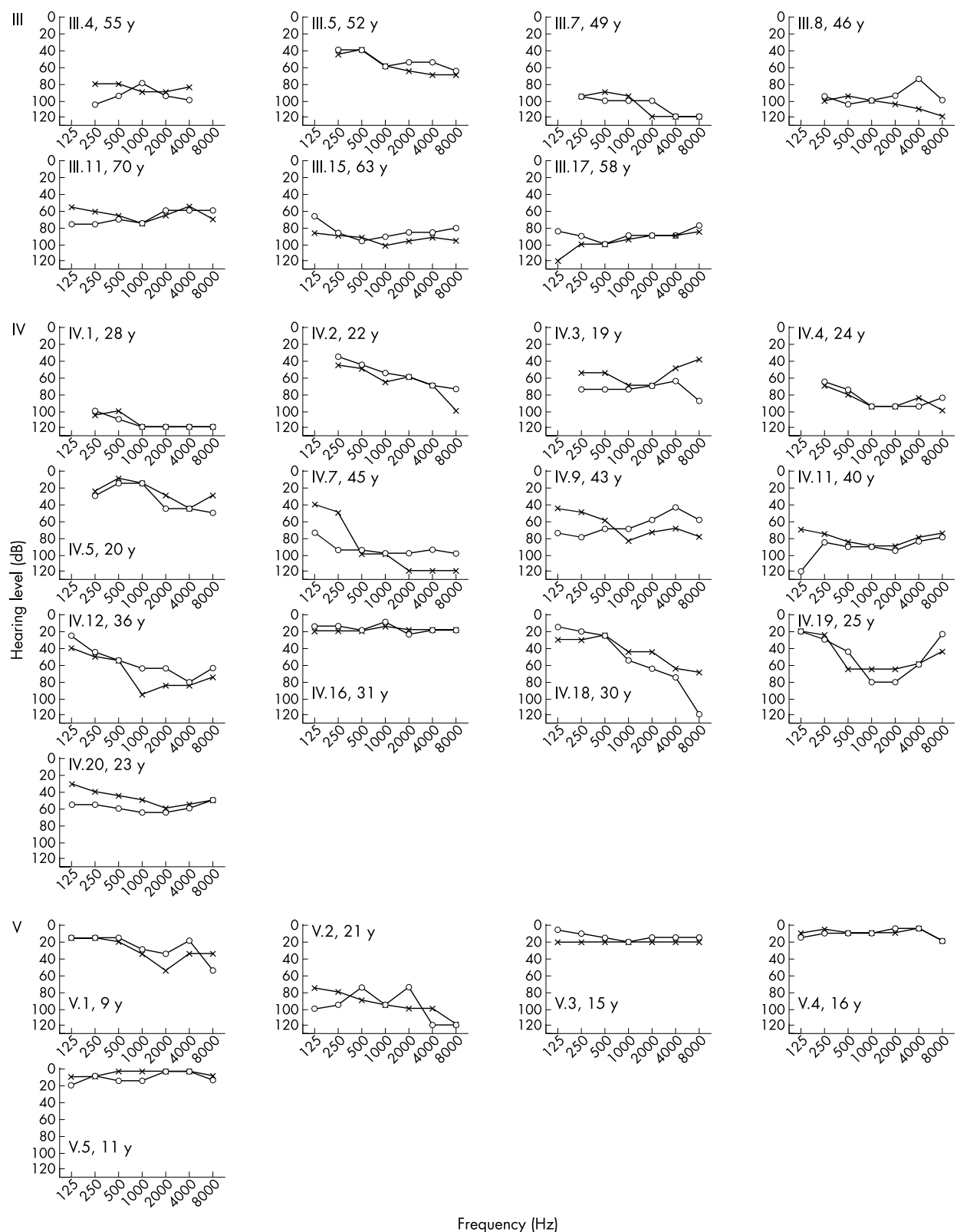


Figure 2 Air conduction audiograms of 25 carriers of the 7510T>C mutation from family S258. All of these audiograms were obtained during this study, and so they represent the most recent record for each subject, whose age is indicated in years (y). Circles, right ear; crosses, left ear.

being positive in 66 families (manuscript in preparation). In the remaining 82 cases, detection of the 1095T>C and 7510T>C mutations was performed by tests that are based on PCR amplification of a DNA fragment containing the

mutation, followed by digestion with a specific restriction endonuclease.¹⁵⁻¹⁷ Mutation 1095T>C was not found in any of these 82 families, but mutation 7510T>C was detected in subject IV.3 in family S258 (fig 1), a result that was confirmed

by DNA sequencing. Subsequently, the presence of the mutation was shown in a total of 26 subjects from this family. In all of them, the mutation was homoplasmic, considering our detection limits (>95% mutant copies). No additional mutation was found in the tRNA^{Ser(UCN)} gene in these patients. We also investigated the 4336A>G mutation in the tRNA^{Gln} gene, since it had been described in the only pedigree previously reported with the 7510T>C mutation.¹⁵ No patient in family S258 carried the 4336A>G mutation.

RESULTS

Auditory impairment was confirmed in 21 out of 26 carriers of the mutation. Four carriers were asymptomatic. No audiological data could be obtained from III.12. No syndromic features were observed in affected subjects. Two subjects (IV.18 and V.2) had been treated with streptomycin in early childhood. Patient IV.1 suffered from measles at 9 months of age, resulting in prelingual profound hearing impairment (fig 2). Four females (III.4, III.15, IV.9, and IV.11) reported that their auditory impairment worsened coincidentally with pregnancy. Environmental factors were excluded as causes of hearing loss in the remaining subjects. Conductive hearing loss was ruled out by otoscopic examination, tympanometry with acoustic reflex testing, and the use of tuning fork tests. Pure tone audiometry, testing for air and bone conduction, confirmed that the hearing impairment was sensorineural in all cases. However, a remarkable intrafamilial phenotypic variation was observed (fig 2). Onset occurred in the first two decades of life. Hearing loss was postlingual and progressive, ranging from moderate to profound. In a majority of cases it was symmetrical, with flat or gently sloping audiogram shapes. In other cases (for example, IV.3, IV.7, IV.9), it was moderately asymmetrical. Ascending (for example, III.17, IV.11) or U shaped (for example, IV.3, IV.19) audiograms were also observed. Most of the affected subjects complained of tinnitus. There were no symptoms of vestibular dysfunction.

DISCUSSION

The finding of the 7510T>C mutation in a second family with maternally inherited hearing impairment lends further support to its pathogenic role. The comparison of the clinical data of affected subjects from the two families so far reported shows wide phenotypic variation, both intrafamilial and interfamilial, concerning age of onset, progression, symmetry, severity, and shape of the audiogram. This suggests that other factors, environmental and/or genetic, contribute to modulate the phenotype of hearing loss. It is intriguing that several females in the Spanish family associated pregnancy with an increase in their hearing loss, which suggests that the complex hormonal changes that take place during this period may play a role in accelerating the progression of the auditory impairment. On the other hand, the hypothesis of the existence of nuclear genes acting as modifiers of mitochondrial hearing impairment has recently received strong support from different experimental approaches.²⁵⁻²⁹ These studies have been focused mainly on the 1555A>G mutation because of its higher prevalence. The identification of additional large families carrying the other mitochondrial mutations responsible for non-syndromic hearing loss, like the one described in this report, should help to find their hypothetical modifier genes.

It has also been proposed that the mitochondrial DNA background may be responsible for intrafamilial variation of the phenotype associated with these mutations. In fact, it has been shown that some carriers of the 1555A>G mutation also bear mutations in the tRNA^{Ser(UCN)} gene.³⁰ In family S258, we have ruled out the presence of 1555A>G or other mutations in the tRNA^{Ser(UCN)} gene, as well as of 4336A>G (found to be associated with 7510T>C in the first report of this mutation).¹⁵ This last finding also indicates that the 7510T>C mutation

found in the two families so far reported had different origins. Similar results have been obtained when investigating the origins of the 1555A>G and 7472insC mutations.^{31, 32}

According to our study, the prevalence of the 1095T>C and 7510T>C mutations is low in Spanish patients with non-syndromic hearing loss. Nevertheless, given that hearing loss resulting from mitochondrial mutations usually exhibits incomplete penetrance and phenotypic variability, which frequently mask the maternal inheritance, and given the simplicity of the detection tests, screening for these mutations should be recommended in all cases of non-syndromic hearing impairment in which maternal inheritance cannot be clearly excluded.

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