Genetic analysis of the connexin-26 M34T variant

Andrew J Griffith

EDITOR—Existing published data cannot conclusively determine if the M34T allele of connexin-26 (*GJB2*) is a recessive allele causing hearing loss. The recent article by Houseman *et al* (*J Med Genet* 2001;38:20-5) “Genetic analysis of the connexin-26 M34T variant: identification of genotype M34T/M34T segregating with mild-moderate non-syndromic sensorineural hearing loss,” does not resolve this question. Houseman *et al* state that M34T segregates with hearing loss, although their data are inconsistent with this assertion. *GJB2* genotype data were available for five sib pairs, yet only two of the sib pairs (1 and 2) showed cosegregation of M34T with hearing loss. Sib pairs 3, 4, and 5 showed discordant inheritance of M34T with hearing loss, raising the likelihood that their hearing loss was unrelated to the *GJB2* genotype. Biallelic *GJB2* mutations and/or polymorphisms were detected only in sib pairs 1 (M34T/M34T) and 5 (M34T/35delG) and subject SP6A (M34T/35delG). It is unknown if a *trans GJB2* mutation was missed in the other subjects, or whether the observed rate of M34T heterozygosity reflects the high M34T carrier rate in the general population. Furthermore, the M34T/35delG genotype was present in SP5A but not the affected sib SP5B, raising the likelihood that their *GJB2* genotype is unrelated to the deafness phenotype.

Houseman *et al* support their hypothesis by referring to a 48 year old subject that we had previously reported with adult onset presbycusis and the compound heterozygous M34T/167delT genotype (Griffith *et al*, *Am J Hum Genet* 2000;67:745-9). However, her degree

and onset of hearing loss were not consistent with M34T being a recessive allele (in *trans* with 167delT) causing typical *GJB2* associated deafness.

M34T cannot be considered a recessive deafness allele based upon its detection in deaf probands and its reduced but detectable gap junction activity in heterologous expression systems. Its frequent detection in deaf probands and sib pairs may be coincidental to its high carrier rate in the population, which is consistent with the data of Houseman *et al*. Their reported heterozygous carrier rate of 25 in 630 subjects (3.96%), with the assumptions of random mating and no selective advantage or disadvantage, predict an expected M34T homozygosity rate of 1/635. This may be compared to their observed M34T/M34T rate of 1/173 in hearing loss index cases (where each affected sib pair is counted as a single index case), as well as their observed rate of 0/630 in normal hearing controls. A Student's *t* test cannot be applied to these data given the number of data points and the low population proportions, although the differences do not appear to be significant (1/173 *v* 1/635, 0/630 *v* 1/635). It is possible that a future meta-analysis of pooled data from multiple groups may indeed show a statistically significant association of M34T homozygosity with hearing loss.

As stated by the authors, additional research is required in order to provide genetic counseling to subjects segregating M34T. The pathogenic potential of the M34T allele of *GJB2* will remain unknown, however, unless the level of scientific rigour is significantly raised.

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Reply

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EDITOR—The authors would like to respond briefly to Andrew Griffith's letter which highlights some interesting questions arising from our manuscript. We agree that our findings do not resolve, for certain, the association of the M34T allele of *GJB2* with genetic hearing impairment owing to the observations that, in some families, M34T does not segregate with hearing impairment. However, we provided evidence that the M34T variant might act as a recessive allele with homozygosity for M34T observed in subjects with mid to high frequency sensorineural hearing loss. Other published studies have observed an association of M34T with hearing loss when it is found in *trans* with other missense *GJB2* alleles. Further supporting data for M34T acting as a recessive *GJB2* (in certain allelic combinations) is from a manuscript that has only recently come to our attention in the UK. Cucci *et al*¹ describe two other families in which homozygosity for M34T is also associated with mid to high frequency hearing loss. They also

describe M34T associated with other recessive missense *GJB2* alleles in subjects with hearing loss. In addition, it is important to emphasise further from our study and that described by Cucci *et al* (and indeed from extensive *GJB2* publications) that no homozygotes for M34T have been identified with normal hearing.

The other key observation we reported was that the majority of M34T alleles were in *cis* with a 10 bp deletion polymorphism in the 5' non-coding sequence of *GJB2*. Further studies are required to assess whether the 10 bp allele has any biological effect. In summary, we would like to reiterate that the data from our study and that of Cucci *et al*¹ suggest that further research into the role of M34T and hearing loss is required so that genetic counselling can be provided.

¹ Cucci RA, Prasad S, Kelley PM, Green GE, Storm K, Willcox S, Cohn ES, Van Camp G, Smith RJ. The M34T allele variant of connexin 26. *Genet Test* 2000;4:335-44.