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 presbyscusis 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.
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 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 suggest that further research into the role of M34T and hearing loss is required so that genetic counselling can be provided.