A mutation in the gamma actin 1 (*ACTG1*) gene causes autosomal dominant hearing loss (DFNA20/26)

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Linkage analysis in a multigenerational family with autosomal dominant hearing loss yielded a chromosomal localization of the underlying genetic defect in the DFNA20/26 locus at 17q25-qter. The 6-cM critical region harbored the gamma-1 actin (*ACTG1*) gene which was considered an attractive candidate gene because actins constitute important structural elements of the inner ear hair cells. We identified a Thr278Ile mutation in helix 9 of the modeled protein structure. The alteration of residue Thr278 is predicted to have a small but significant effect on the gamma 1 actin structure due to its close proximity to a methionine residue at position 313 in helix 11. Met313 has no space in the structure to move away. Moreover, the Thr278 residue is highly conserved throughout eukaryotic evolution. Using a known actin structure the mutation could be predicted to impair actin polymerization. These findings strongly suggest that the Thr278Ile mutation in *ACTG1* represents the first disease causing germline mutation in a cytoplasmic actin isoform.

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