

WHOLE-EXOME SEQUENCING IDENTIFIES A MISSENSE MUTATION IN THE OUTER HAIR CELLS-EXPRESSING DIAPH2 AS A LIKELY CAUSE FOR NONSYNDROMIC HEARING LOSS IN AN ITALIAN FAMILY

Chiereghin C. (1), Robusto M. (1), Lewis M. (2), Massa V. (3), Steel K.P. (2), Soldà G. (1)

(1) *Biomedical Sciences Department, Humanitas University, Pieve Emanuele, Milano (Italy)*

(2) *Wolfson Centre for Age-Related Diseases, King's College London, Guy's Campus, London (UK)*

(3) *Department of Health Sciences, Università degli Studi di Milano, Milano (Italy)*

Hearing Loss (HL) is the most common sensory disorder in humans, and more than half of cases are due to genetic factors. HL is characterised by an extreme genetic heterogeneity, with >150 loci currently associated and at least 100 genes identified, making extremely challenging to obtain a molecular diagnosis with traditional screening methods. For these reasons, whole-exome sequencing (WES) has been implemented for mutational screening and novel disease-gene identification.

WES of three siblings from an Italian family affected by recessive nonsyndromic hearing loss (NSHL) led to the identification of a missense variant in the candidate deafness-causing gene *DIAPH2*, located on the X chromosome and coding for a protein involved in actin filament elongation. The variant segregated with the phenotype in the family and was absent in an in-house cohort of about 3500 Italian exomes, as well as in 125 audiotically-tested normal-hearing controls. Despite belonging to a family of genes associated with NSHL, the question remains if also *DIAPH2* plays a role in hearing. In support of a possible function of *DIAPH2* in the inner ear, our immunohistochemical studies indicate that the mouse ortholog protein *DIAP2* is expressed during development in the cochlea, specifically in the actin-rich stereocilia of the sensory outer hair cells.

In addition, in-vitro studies showed a possible functional impairment of the mutant *DIAPH2* protein upon RhoA-dependent activation. Finally, *Diaph2* knock-out and knock-in mice were generated and auditory brainstem response measurements were performed at 4 and 8 weeks to evaluate the hearing phenotype. However, no hearing impairment was detected, at least at the time points analysed. Further studies will hopefully clarify the contribution of *DIAPH2* to HL etiology.

We thank AIBG for supporting this work through a mobility grant to perform in-vivo studies at prof. Steel's lab at King's College, London.

Milano | 4 - 5 Ottobre 2019