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Identification of modifier genes for connexin 26-related hearing impairment

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Background: GJB2 encodes the connexin 26 protein and is the most frequently mutated gene in patients with non syndromic autosomal recessive hearing loss. More than 80 mutations have been identified, causing a variable hearing loss ranging from mild to profound, with 35delG as the most common mutation in Caucasians. For most genotypes, a specific genotype-phenotype correlations was established by analysing the audiometric profile of 1351 patients with biallelic GJB2 mutations (Snoexkx et al, 2005). Despite this correlation, a variability within the genotypes remains for all mutations and is most clear for patients with a homozygous 35delG genotype. We believe that modifier genes are partly responsible for this variability.

Methods: We aimed to detect modifier genes by collecting 35delG homozygous patients together with their general and audiometric data. The idenfication of these genes will be done by performing an association study using a case-control paradigm.

Results: The association study was first performed on a selection of 9 candidate genes functionally related to connexin 26. Secondly, the first phase of a genome-wide association study (WGA) was performed using an established pooling strategy (Pearson et al, 2007). The pools were analysed by two high-density SNP chips. The results of these analyses will allow to make a selection of the 250 most significant SNP's which will afterwards be genotyped individually on the same sample set. Confirmation of these results should be done by genoyping of the significant SNP's in an independent replication population.

Conclusions: In order to identify modifier genes for connexin 26 related hearing loss, we performed an association study. In a first phase, we used a candidate gene approach and we subsequently performed a WGA on the same sample set. To replicate the results of this study, we will need to collect additional samples to set up a replication population.

Literatur:

Snoeckx et al, Am. J. Hum. Genet. 2005 Dec;77(6):945-57
Pearson et al, Am. J. Hum. Genet. 2007 Jan;80(1):126-39