workshop a3: friday, march 10

Genetics of Deafness

Genetics and hearing loss. R.J.H. Smith. Univ. of Iowa, IA.

Hearing loss is a common sensory impairment, with nearly one in two persons developing a significant auditory deficit (>25 dB) during their lifetime. The etiology is multifactorial and can include numerous environmental and genetic factors. For prelingual hearing loss, epidemiological data show that 1 neonate in 1,000 is born with severe-to-profound or profound hearing impairment and in half that number, the loss is inherited. Similar data are not available for post-lingual hearing impairment, however it has been demonstrated that even for age-related hearing impairment, hereditary factors are prominent.

Interestingly, and unexpectedly, mutations in one gene, *GJB2*, are responsible for half of severe-to-profound autosomal recessive non-syndromic hearing loss in multiplex families from France, Britain, Tunisia, New Zealand, and the United States. This finding makes *GJB2*-related deafness the most common type of hereditary congenital hearing loss in these countries. In approximately two-thirds of persons with *GJB2*-related deafness, a single mutation is found, the deletion of one of six contiguous deoxyguanosines, referred to as the 35delG mutation. The carrier frequency for this allele in the general population in the Midwestern United States is 2.5% (+/- 0.66%). The total carrier rate for all *GJB2* deafness-causing mutations is 3.01% (range, 2.54%-3.56%). The corresponding predicted prevalence of *GJB2*-related congenital deafness is 22.7 (range, 15.1-31.9) per 100,000 births. More than two-thirds of these individuals have profound or severe-to-profound hearing loss, although there can be phenotypic variability in the degree of loss even within the same family.

These data can be used to provide information for genetic counseling and estimates of recurrence risks for hearing couples with a deaf child. The chance for a normal-hearing couple to have a second deaf child can be calculated to be 17.5% (range, 15.0%-20.4%). If the first deaf child undergoes genetic testing and *GJB2* deafness-causing mutations are identified, the recurrence risk climbs to 25%. In the absence of these mutations, it drops to 14%. As genetic testing becomes more prevalent, it is likely that this information will facilitate earlier habilitation in a substantial percentage of deaf infants and ultimately may provide parents with valuable prognostic and therapeutic information.

Mitochondrial Deafness. N. Fischel-Ghodsian. Department of Pediatrics and Medical Genetics, Cedars-Sinai Medical Center and UCLA, Los Angeles, CA

Several mitochondrial mutations have been implicated in predisposing to non-syndromic and ototoxic hearing impairment. In addition acquired mitochondrial mutations may be involved in presbycusis, the hearing loss associated with aging. While the elucidation of these mutations allows genetic counseling and prevention of a significant proportion of aminoglycoside induced ototoxicity, the intracellular pathophysiological events leading from the mutations to the deafness phenotype have remained poorly understood. In addition, despite the fact that most inherited mitochondrial mutations associated with hearing impairment are homoplasmic, the clinical phenotype can generally not be predicted.

Using a genetic approach we have demonstrated that even in the simplest case of a homoplasmic mitochondrial mutation, with minimal or no variability in mitochondrial haplotype, and minimal variability in environmental exposures, the clinical phenotype depends on several nuclear factors. To elucidate these modulating nuclear genes, and in order to understand the pathophysiology of the mitochondrial deafness mutations, we use a combined genetic and candidate gene approach. The genetic approach involves systematic genome screens in families with the mitochondrial mutation and hearing impaired family members. Candidate genes are mainly sought among genes that affect mitochondrial RNA processing and/or translation. We have thus started to identify and characterize the nuclear encoded genes and proteins involved in these processes, and screen them for cochlea specific isoforms or splice variants.

Our approach can serve as a general model on how to dissect pathophysiological pathways between genetic mutations and phenotype. This will be necessary both for polygenic and simple Mendelian genetic diseases. The analysis of these intracellular pathways represents the challenge of genetics in the next few decades, may require new models of thinking about intracellular interactions, and will be an important step in the development of therapeutic interventions and a detailed understanding of cochlea specific processes. Mitochondrial mutations with their puzzling features of incomplete penetrance and tissue specificity represent an excellent paradigm to attack these questions.

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