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Genetic Hearing Impairment
Its Clinical Presentations

Volume Editors

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Contents

IX Foreword
   Stephens, D. (Cardiff)

XI Foreword
   Battey, J. (Bethesda, Md.)

XIII Preface
   Cremers, C.W.R.J. (Nijmegen); Smith, R.J.H. (Iowa City, Iowa)

Introduction

1 Understanding Inner Ear Physiology at the Molecular Level
   Hone, S.W.; Smith, R.J.H. (Iowa City, Iowa)

11 Molecular Diagnosis of Hereditary Hearing Impairment
   Kremer, H.; Hoefsloot, L.H. (Nijmegen)

28 Developments in Cochlear Gene Therapy
   Lalwani, A.K. (San Francisco, Calif.); Jero, J. (San Francisco, Calif./Helsinki); Mhatre, A.N. (San Francisco, Calif.)

DFNA

34 Auditory Phenotype of DFNA1
   Leon, P.E. (San Jose, Costa Rica); Lalwani, A.K. (San Francisco, Calif.)

41 DFNA2/KCNQ4 and Its Manifestations
   De Leenheer, E.M.R.; Ensink, R.J.H.; Kunst, H.P.M.; Marres, H.A.M. (Nijmegen); Talebizadeh, Z. (Kansas City, Mo.); Declau, F. (Antwerp); Smith, S.D. (Omaha, Nebr.); Usami, S.-i. (Matsumoto); Van de Heyning, P.H.; Van Camp, G. (Antwerp); Huygen, P.L.M.; Cremers, C.W.R.J. (Nijmegen)

47 DFNA3
   Denoyelle, F.; Lina-Granade, G.; Petit, C. (Paris)
Clinical Features of DFNA5
De Leenheer, E.M.R. (Nijmegen); van Zuijlen, D.A. (Utrecht); Van Laer, L.; Van Camp, G. (Antwerp); Huygen, P.L.M. (Nijmegen); Huizing, E.H. (Utrecht); Cremers, C.W.R.J. (Nijmegen)

Clinical Presentation of DFNA8–DFNA12
Govaerts, P.J.; De Ceulaer, G.; Daemers, K.; Verhoeven, K.; Van Camp, G.; Schatteman, I.; Verstreken, M. (Antwerp); Willems, P.J. (Rotterdam); Somers, T.; Offeciers, F.E. (Antwerp)

DFNA9/COCH and Its Phenotype

DFNA10/EYA4 – The Clinical Picture
De Leenheer, E.M.R.; Huygen, P.L.M. (Nijmegen); Wayne, S. (Iowa City, Iowa); Verstreken, M.; Declau, F.; Van Camp, G.; Van de Heyning, P.H. (Antwerp); Smith, R.J.H. (Iowa City, Iowa); Cremers, C.W.R.J. (Nijmegen)

Clinical Presentation of DFNA11 (MYO7A)

The Phenotype of DFNA13/COL11A2
De Leenheer, E.M.R. (Nijmegen); McGuirt, W.T. (Iowa City, Iowa); Kunst, H.P.M.; Huygen, P.L.M. (Nijmegen); Smith, R.J.H. (Iowa City, Iowa); Cremers, C.W.R.J. (Nijmegen)

The Clinical Presentation of DFNA15/POU4F3
Gottfried, I. (Tel Aviv); Huygen, P.L.M. (Nijmegen); Avraham, K.B. (Tel Aviv)

Clinical Presentation of the DFNA Loci Where Causative Genes Have Not Yet Been Cloned: DFNA4, DFNA6/14, DFNA7, DFNA16, DFNA20 and DFNA21
Huygen, P.L.M.; Bom, S.J.H. (Nijmegen); Van Camp, G. (Antwerp); Cremers, C.W.R.J. (Nijmegen)

Auditory Phenotype of DFNA17
Lalwani, A.K.; Goldstein, J.A.; Mhatre, A.N. (San Francisco, Calif.)

DFNB

Clinical Presentation of DFNB1

The Clinical Presentation of DFNB2
Liu, X.Z. (Miami, Fla.)

DFNB3, Spectrum of MYO15A Recessive Mutant Alleles and an Emerging Genotype-Phenotype Correlation
131 **Pendred Syndrome Redefined:** Report of a New Family with Fluctuating and Progressive Hearing Loss  
Stinckens, C. (Leuven); Huygen, P.L.M. (Nijmegen); Van Camp, G. (Antwerp); Cremers, C.W.R.J. (Nijmegen)

142 **DFNB9**  
Denoyelle, F.; Petit, C. (Paris)

145 **Clinical Presentation of DFNB12 and Usher Syndrome Type 1D**  
Bork, J.M.; Morell, R.J. (Rockville, Md.); Khan, S.; Riazuddin, S. (Lahore); Wilcox, E.R.; Friedman, T.B.; Griffith, A.J. (Rockville, Md.)

153 **DFNB21**  
Denoyelle, F.; Mustapha, M.; Petit, C. (Paris)

156 **Clinical Manifestations of DFNB29 Deafness**  
Ahmed, Z.M. (Rockville, Md./Lahore); Riazuddin, Sa.; Friedman, T.B. (Rockville, Md.); Riazuddin, Sh. (Lahore); Wilcox, E.R.; Griffith, A.J. (Rockville, Md.)

**DFN**

161 **X-Linked Mixed Deafness Syndrome with Congenital Fixation of the Stapedial Footplate and Perilymphatic Gusher (DFN3)**  
Cremers, C.W.R.J.; Snik, A.F.M.; Huygen, P.L.M.; Joosten, F.B.M.; Cremers, F.P.M. (Nijmegen)

168 **Clinical Phenotype of DFN2, DFN4 and DFN6**  
Pfister, M.H.F. (Tübingen); Lalwani, A.K. (San Francisco, Calif.)

**Mitochondrial Deafness**

172 **The Clinical Spectrum of Maternally Transmitted Hearing Loss**  
Ensink, R.J.H.; Huygen, P.L.M.; Cremers, C.W.R.J. (Nijmegen)

**Audiometric Patterns in Types of Common Syndromic Deafness**

184 **Hearing Impairment in Usher’s Syndrome**  
Penning, R.J.E.; Wagenaar, M.; van Aarem, A.; Huygen, P.L.M. (Nijmegen); Kimberling, W.J. (Omaha, Nebr.); Cremers, C.W.R.J. (Nijmegen)

192 **The Branchio-Oto-Renal Syndrome**  
Kemperman, M.H. (Nijmegen); Stinckens, C. (Leuven); Kumar, S. (Omaha, Nebr.); Joosten, F.B.M.; Huygen, P.L.M.; Cremers, C.W.R.J. (Nijmegen)

201 **Clinical Features of the Waardenburg Syndromes**  
Newton, V.E. (Manchester)

209 **Hearing Loss in the Treacher-Collins Syndrome**  
Marres, H.A.M. (Nijmegen)

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Contents VII
216 Hearing Impairment in Stickler Syndrome
Admiraal, R.J.C. (Nijmegen); Szymko, Y.M.; Griffith, A.J. (Rockville, Md.);
Brunner, H.G.; Huygen, P.L.M. (Nijmegen)

Implications for the Future

224 Genetic Modifiers of Hereditary Hearing Loss
Riazuddin, Sa. (Rockville, Md.); Ahmed, Z.M. (Rockville, Md./Lahore);
Friedman, T.B.; Griffith, A.J. (Rockville, Md.); Riazuddin, Sh. (Lahore);
Wilcox, E.R. (Rockville, Md.)

230 Genetic Evaluation and Counseling for Congenital Deafness
Green, G.E.; Cunniff, C. (Tucson, Ariz.)

241 Author Index

243 Subject Index
The past ten years have witnessed a major revolution in our way of thinking about genetic hearing impairment. The range of genes with mutations responsible for causing this hearing impairment are gradually being identified and the number of different types of nonsyndromal disorders appears to be converging on a figure which was previously based on no more than statistical concepts. Over 20 genes have now been identified and over 70 gene locations specified for nonsyndromal hearing impairment.

Our previous concepts that a mutation on one gene would result in a specific audiological abnormality have been discredited. Out goes the simplistic genotype-phenotype match! Even the idea of one gene causing a nonsyndromal impairment but never resulting in a syndromal condition is increasingly being shown to be a gross oversimplification, with genes for Pendred syndrome and Usher syndrome also being associated with nonsyndromal hearing impairment, as discussed in this book. In those, however, the audiometric configurations are broadly similar in the syndromal and nonsyndromal conditions. Most recently, however, the gene responsible for Wolfram (DIDMOAD) syndrome which usually has a high-frequency hearing impairment, has interestingly also been shown to result, with different mutations, in a nonsyndromal low-frequency hearing impairment associated with DFNA6, 14 and 38.

In addition, other genes, such as the Connexin 26 gene (GJB2), may result in a dominant as well as recessively inherited disorder and a moderate as well as a profound hearing impairment. Furthermore, modifier genes, both mitochondrial and nuclear, have been shown to play an important role in some types of genetic hearing impairments, and undoubtedly others will emerge.

Where does this leave us as clinical audiologists? One outcome of the first European Union Concerted Action Programme (HEAR) was an attempt to tabulate the relationship between genotypes and phenotypes of nonsyndromal
hearing impairment [Martini et al. (eds): Definitions and Protocols in Genetic Hearing Impairment. Whurr, London 2001]. Many of the data used in that presentation were from the three leading groups in this field – from Antwerp, Iowa City and Nijmegen. It is therefore particularly appropriate that these groups have come together in the present publication to focus on the difficulties and complexities in this field and to extend our knowledge and understanding in what is a significant step forward.

Dafydd Stephens, Cardiff
Foreword

Over the last decade, remarkable progress has been made towards determining the sequence and structure of the human genome. Thousands of useful markers have been identified, providing the tools needed to map the location of genes that cause all forms of hereditary diseases and disorders. About half of the sequence of the human genome has been determined at very high accuracy, and nearly all of the sequence is known in draft form.

This infrastructure resource freely available to the entire research community in public databases has enabled auditory scientists to map the location of over 70 genes whose mutation results in nonsyndromic hereditary hearing impairment. Over 20 of these genes have been identified using positional cloning technology since 1997. These genes encode proteins with varied functions, including unconventional myosins (intracellular motor molecules), transcription factors (gene regulatory proteins), cadherins, claudins, and gap junction proteins (forming specialized junctions between cells), as well as intra- and intercellular signaling molecules. These breakthroughs are the starting point for precise determination of the etiology of hereditary hearing impairment, leading to early intervention that will optimize development of language skills, as well as intervention strategies in cases where the hearing impairment is progressive. Allelic variants of these genes may predispose individuals to more common forms of hearing impairment, such as presbycusis and noise-induced hearing loss. Beyond any question, understanding the genes whose mutation results in hereditary hearing impairment will provide a fundamental new understanding of the molecular and cellular functions that are essential for normal auditory function.

In this volume, the authors and editors have carefully examined the similarities and differences in audiometric profile associated with hereditary hearing impairment caused by different genetic alterations. With the recent discovery of so many different genes whose mutations result in hearing impairment, this
analysis is both timely and important. This collection of papers shows clearly that not all forms of hereditary hearing impairment present with the same audiometric profile. Some forms of hereditary hearing impairment are selective for either high or low frequencies. Hereditary hearing impairment can be either early onset, progressive, mild to moderate, or profound, depending both on the gene involved, the nature of the mutation, and the genetic background of the affected individual.

The number of genes whose mutation results in hereditary hearing impairment is large and still growing at a rapid rate. With so many different genes to consider, a comprehensive search to find the genetic change associated with hearing impairment in a patient can be a daunting challenge. In the future, careful audiometric analysis may be helpful in focusing efforts to identify the underlying genetic basis for hereditary hearing impairment, resulting in more precise diagnosis and hopefully better intervention strategies for our patients.

James Battey, Jr., Bethesda, MD
New ways of seeing can disclose new things…
Do new things make for new ways of seeing?
*William Least Heat-Moon* – Blue Highways, 1982

During the past decade, tremendous progress has been made in the genetics of hearing impairment. Over 70 nonsyndromic deafness loci have been identified and for many of these loci, causative genes have been cloned. Though less prevalent, syndromic deafness has been shown to be equally complex. While only a handful of the over 400 types account for most syndromic deafness, these select few are themselves complicated. For example, the most common recessive and dominant forms of syndromic deafness, Usher syndrome and Waardenburg syndrome, are heterogeneous.

The identification of deafness-causing genes has provided scientists with a heretofore unavailable insight into inner ear physiology at the protein level, but it is also providing clinicians with new methods to diagnose and evaluate the deaf patient. It is with the latter thought in mind that this book is being published. While we acknowledge that ‘The Clinical Presentation of Genetic Hearing Impairment’ represents only the first step in recognizing the various types of genetic deafness by their clinical phenotype, we believe it represents an important step.

Many observations about genetic deafness are beginning to emerge. For example, the most common type of autosomal recessive nonsyndromic deafness is caused by mutations in *GJB2* and the deafness is typically moderate-to-profound and always symmetric between ears. Of all types of Usher syndrome, the most common, USH2A and USH1B, can be distinguished by a simple audiogram. In persons with Waardenburg syndrome, it is a clinical difference, lateral displacement of the inner canthi that distinguishes WS1 and WS3 from WS2 and WS4. Recognizing a unique aspect of a given hearing-loss phenotype when at first there appears to be none is the clinical challenge we will continue
to face. In meeting this challenge, we will be able to provide our patients with better care, offer them better genetic counseling, and spend healthcare resources wisely.

Cor W.R.J. Cremers
Richard J.H. Smith

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