



“Inner ear manifestations in CHARGE: Abnormalities, treatments, animal models, and progress toward treatments in auditory and vestibular structures”

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AUTHORS AND THEIR CONNECTION TO THE CHARGE SYNDROME FOUNDATION:



Daniel Choo, MD, is Professor and Director of Otolaryngology - Head and Neck Surgery at Cincinnati Children's Hospital Medical Center (CCHMC). He specializes in the management of ear and hearing disorders and serves as co-director of the Charge Center at CCHMC, where he follows dozens of children with CHARGE syndrome (CS).

Dan is actively involved with clinical CHARGE research and has presented at the international CS conferences and at the Cincinnati CS conferences.



Kareem Tawfik, MD, is an Otolaryngology Fellow at the Department of Otolaryngology - Head and Neck Surgery, CCHMC, with Dr. Choo. His research interest and publications include inner ear diseases and cochlear implants in children and adults. Kareem was a Sandra Davenport CHARGE Syndrome Fellow at the 2017 CS conference. See his reflections on his Fellowship experience in the [Winter 2018 CHARGE Accounts](#) newsletter.



Donna Martin, MD, PhD, is Professor of Pediatrics and Human Genetics at the University of Michigan, where she evaluates and cares for individuals with CHARGE syndrome. Her research areas of expertise are human genetics, mouse genetics, and developmental disorders of the nervous system. Donna serves as a mentor to medical, genetic counseling, and PhD students studying CHARGE-related disciplines. Donna has been an active member of the CHARGE Syndrome Foundation for years and serves as the head of the Foundation's Scientific Advisory Board.



Yehoash Raphael, PhD, is a Professor of Otolaryngology - Head and Neck Surgery at the University of Michigan. In his lab at Kresge Hearing Research Institute, he investigates inner ear biology with emphasis on prevention and cure of hearing loss and balance disorders.

Much of his research has been in collaboration with Donna Martin on inner ear aspects of CHARGE syndrome.

SUMMARY OF THE PAPER:

Abstract: The inner ear contains the sensory organs for hearing and balance. Both hearing and balance are commonly affected in individuals with CHARGE syndrome (CS). Absence or abnormality of the semicircular canals in individuals with CS contributes to delayed gross motor skills and walking. Great progress has been made in understanding the role of *CHD7* in the development and function of the inner ear, as well as in related organs such as the middle ear and auditory and vestibular neural pathways. The goals of current research on *CHD7* and CS are to (a) improve our understanding of the changes caused by *CHD7* pathogenic variants (mutations) and (b) to provide better tools for prognosis, treatment and management. The mouse is an excellent model for exploring mechanisms of *Chd7* function in the ear because of the evolutionary conservation of ear structure and similarity of features seen in *Chd7* mice and *CHD7* humans. Newly recognized developmental functions for mouse *Chd7* are shedding light on how abnormalities in *CHD7* might lead to CS symptoms in humans. Here we review known human inner ear changes associated with CS, summarize progress toward diagnosis and treatment of inner ear-related pathologies, and explore new avenues for treatment based on basic science discoveries.

Additional summary: Birth to age 3 is a critical window when the brain is most ready for language acquisition. Because of the other medical complexities of CS, identification and management of hearing issues may be delayed. The vast majority of children with CS have hearing loss, most often a mixed (conductive and sensorineural) loss. Rigorous protocols beyond newborn hearing screening (hearing loss diagnostic battery) are necessary to determine the type and extent of loss. When possible, such testing should be done during sleep or in conjunction with other procedures requiring anesthesia. Imaging (CT and MRI) is described, along with specifics for what views need to be obtained and examples of normal and CS images of the inner ear. Specific knowledge of inner ear anatomy and specific vestibular functional testing may be helpful in guiding physiotherapy in children with CS. Hearing aids, auditory implants (cochlear and bone conduction) and other potential surgical interventions are presented in a discussion of under which circumstances each might be considered. The authors review the literature on procedures, outcomes of various interventions, including potential complications and special considerations for children with CS. Many of the delays in both language and motor development in CS can be traced directly to the hearing and balance issues common in CS.

There is a discussion of the *CHD7* gene and the high degree of homology between human *CHD7* and *Chd7* of many models (mouse, zebrafish, fly and even yeast). In all models (well, except yeast), the gene is highly expressed in many tissues, including neurons and auditory and vestibular tissues. *CHD7* likely has effects on many, many “downstream” targets, indirectly affecting additional tissues. Mouse models are described in detail, shedding light on mechanisms that are likely happening in people as well. Identification of cells that express *Chd7* or are affected by the lack of *Chd7* may eventually help guide potential therapies. From here, the authors go on to talk about the current status of treating hereditary deafness. Here, information on hearing loss caused by other genes may end up being helpful to individuals with CS. They conclude by describing what the future might hold for treatments in CS – including potential therapies and caveats regarding cutting edge genetic and other treatments.

WHAT DOES THIS MEAN TO FAMILY/PERSON WITH CHARGE?

This paper is a combination of really solid practical information (what imaging and other testing should be done, what treatments might be considered), descriptions of where this information comes from (human, animal and cell studies) and what to watch for in the future. The mouse studies may help you understand how the CS gene is affecting hearing, balance and so many other systems in the body. Sections 1-4 of the paper lay out explicit information about what to look for in CS and what to take into account when considering surgeries, auditory augmentation and physiotherapies (OT, PT, O&M).

SHOULD I READ IT? SHOULD ONE OF MY DOCTORS READ IT?

Yes and Yes. There likely will be sections that are over your head or that contain jargon that only physicians or lab researchers will immediately understand. But there are many jewels here. Your ENT/Otolaryngologist, Audiologist and perhaps Neurologist should have copies of this paper. It is an expert compilation of the state of the art knowledge on hearing and vestibular information (and more) in CS.

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