



Uncovering
Genetic Links
to Ear Disease

Most human diseases have a genetic basis. The potential for many hearing disorders is embedded in our genes before birth. But little is known at the molecular level about them.

The prevalence and impact of genetic ear diseases that cause hearing and balance problems and the lack of knowledge about them are what drive Rick A. Friedman, M.D., Ph.D., to search for answers.

Some of the more common ear diseases are believed to contain genetic components. For example, age-related hearing loss (presbycusis) accounts for more than 30% of all hearing loss cases. Meniere's disease afflicts more than half a million people in the U.S. alone. Even noise-induced hearing loss

(NIHL), which is largely preventable, is being looked at for a possible genetic component that makes some people more susceptible to it than others.

Using today's sophisticated technologies that help scientists extract and examine DNA, House Ear Institute's genetic research lab, led by Dr. Friedman, has the capabilities to uncover genetic sequences that are associated with predispositions to ear diseases. "What we are interested in today are not single gene abnormalities that are transmitted through families, but the genetic traits in complex diseases," said Friedman. "In other words, we are focused on the things that may represent subtle changes in a multitude of genes that, when combined, lead to susceptibility to disease."

Dr. Friedman, an accomplished scientist, brings a medical perspective to his genetic research studies at the House Ear Institute. In addition to significant breakthroughs in the field of genetic research, he is also a neurotologist with a full-time practice at the House Clinic and is chief of skull base surgery at Cedars-Sinai Medical Center. In his practice he routinely sees several patients daily who are suffering from the effects of hearing loss and other ear disorders due in part to genetic predispositions.

"Throughout my career, I have loved the study of medicine, but wanted to do more than just treat patients," said Friedman. "I always had a big interest in science. When I was getting my start in medicine at the University of California, San Diego, my mentor encouraged me to look into the field of molecular biology and genetics. I went into the field in the late 80s, at a time when gene discovery was becoming an exciting area. There was very little

known about genes involved in hearing and development of the inner ear. That's what sparked my interest."



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In 1998, when the House Ear Institute first opened its lab for Dr. Friedman's work, one of the first studies involved identification and characterization of genes associated with branchial-oto-renal (BOR) syndrome. BOR is inherited as an autosomal dominant genetic trait. This means that you only need to get the abnormal gene from one parent in order to inherit the disease. It is characterized by pits or ear tags in front of the outer ear, abnormal passages from the throat to the outside surface of the neck (branchial fistulas), branchial cysts, hearing loss and/or kidney (renal) abnormalities. While much progress has

been made, a complex investigation is still underway.

"It is going very well, bringing us closer to a dream come true," says Friedman. "We've defined the gene responsible for BOR syndrome. Based on our lab models, we've also identified two genes that modify the deafness that results from the BOR syndrome, which in our view is a major breakthrough."

According to Dr. Friedman, he and his staff are also close to discovering two new genes involved in what appears to be the coiling of the inner ear's cochlea (hearing organ) and development of the cochlea's sensory cells. Most recently, the lab completed what is reported to be "the first ever and largest genome-wide association study for age-related hearing loss." The study, which led to major discoveries of several genes, was conducted in collaboration with colleagues at the Translational Genomics Research Institute (TGen),

Affymetrix, and the University of Antwerp, Belgium, and made possible in part through a \$1 million grant from the Seaver Foundation. One gene in particular, which is believed to put people at risk for hearing loss in old age, is now being explored in Friedman's lab as an excellent potential candidate for pharmaceutical manipulation, and ultimately future drug therapy.

"Our approach involves genome-wide association," said Friedman. "You need to recruit hundreds, if not thousands, of individuals across a spectrum to conduct this type of study. All of the study participants need to be very well characterized populations for the disorder." Friedman and his colleagues then utilize current technology to score markers across the entire genome of these large populations. They use the marker results to identify associations



Rick A. Friedman, M.D., Ph.D.

Principal Investigator, Hereditary Ear Disorders

Rick Friedman received his medical degree in 1988 and completed his doctoral degree in 1994 at the University of California, San Diego. While earning his Ph.D., Friedman served as a resident in the Division of Otolaryngology at the UCSD Medical Center. In 1995, Dr. Friedman came to the House Clinic as a clinical fellow and then joined the group as an associate. Under the direction of EVP Research, David Meyer, Ph.D., Dr. Friedman now leads the hereditary ear disorders research in the House Ear Institute's Division of Cell Biology and Genetics.

He also serves as associate professor at the USC Keck School of Medicine. Dr. Friedman's surgical interests include microsurgery for acoustic neuromas, gamma knife radiosurgery and surgery for treatment of otosclerosis, cholesteatoma and Meniere's disease.

Dr. Friedman belongs to the American Academy of Otolaryngology – Head and Neck Surgery, the American Otological Society, the Acoustic Neuroma Association, the American Neurotology Society, the North American Skull Base Society, the Triological Society and the NIH/

National Institute of Deafness and Other Communication Disorders (NIDCD) where he serves as an ad hoc reviewer.

In addition to presenting his work at more than 30 medical conferences and congresses around the world, Dr. Friedman has published nearly 50 articles and chapters in publications and books such as the *Annual Review of Medicine*, *Clinical Otology*, *Journal of Biological Chemistry*, *Surgery of the Skull Base* and *Otolaryngology – Head and Neck Surgery*.

with a particular disease. Often they find that the markers lie within or very close to specific genes. It also gives some indication of the multitude of genes that may be involved in a given disorder.

The lab's latest genome-wide study, which is just beginning, looks at the inherent genetic traits of Meniere's disease in an effort to better understand its pathogenesis. While symptoms of Meniere's can be debilitating, current diagnosis and treatment is difficult because the disease is not well understood and can prove to be highly variable between individuals.

"At this point, nothing is known about the molecular basis for Meniere's and many other ear diseases," Friedman commented. "Therefore, we often can only treat them empirically rather than scientifically. The ultimate goal of our Meniere's studies is to identify the molecules and proteins that can be manipulated in patients to provide a direct therapy to end their terrible symptoms."

The lab is also preparing to embark on a study to identify and characterize

the heritable aberrant forms of genes that may predispose people to noise-induced hearing loss (NIHL). The Institute is recruiting research subjects for this study through the U.S. Marine Corps at Camp Pendleton. The study will be in partnership with physicians at the U.S. Naval Hospital, San Diego.

Currently, the biggest challenges are recruiting enough subjects and garnering the necessary financial support to conduct the studies. Recognizing the need and huge potential impact of ongoing genetic research at House Ear Institute, Los Angeles entrepreneur and philanthropist Rick Caruso and his wife Tina have established The Rick and Tina Caruso Fund for Genetic Hearing Loss. Their generous commitment has created an exceptional opportunity for other donors to join them in support of Dr. Friedman's groundbreaking work at the Institute.

A portion of House Ear Institute's newly constructed research wing will help accommodate the future growth and space requirements projected for Dr. Friedman's genetic research laboratories. ♦

For information on ways to support this research at the House Ear Institute, contact our Office of Development at (213) 483-4431, ext. 7027.

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