BIOGRAPHICAL SKETCH

NAME: **Avraham, Karen B.**

eRA COMMONS USER NAME: AKAREN

POSITION TITLE: Professor of Human Genetics, Dean of Medicine
Drs. Sarah and Felix Dumont Chair for Research of Hearing Disorders

EDUCATION/TRAINING

INSTITUTION AND LOCATION	Degree	Completion date	Field of study
Washington University, St. Louis, MO, USA	B.A.	05/1984	Biology
Weizmann Institute of Science, Rehovot, Israel	Ph.D.	06/1991	Genetics
National Cancer Institute, Frederick, MD, USA	Post-doc	12/1995	Mammalian Genetics

A. Personal Statement

I am a Professor of Human Genetics in the Department of Human Molecular Genetics and Biochemistry at the Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel and the Dean of the Faculty of Medicine, with affiliations with the Sagol School of Neuroscience and the Safra Center for Bioinformatics. I head the Laboratory for Neural and Sensory Genomics. My research focuses on the discovery and characterization of genes responsible for hereditary hearing loss and neurodevelopmental diseases. Given the complexity of the inner ear and of auditory transduction, many of us predicted that variants in any of many different genes would lead to hearing loss. This prediction has been confirmed many times over and is the basis of the genomic technologies I have integrated into our research. In the last decade, my work has covered the transcriptome and epigenome of the auditory and vestibular systems, in order to dissect the regulatory pathways of these systems. This work includes the microRNAs, long non-coding RNAs, whole genome methylation and enhancers. My team has studied the mechanisms and pathophysiology of deafness in several mouse models, which mimic human disease. We have created a number of mouse mutants using the gene editing tool CRISPR/Cas9. Moreover, we are using AAV-gene therapy to rescue hearing in mouse models for human deafness. We study the mechanisms of GRIN2D in causing developmental delay and epilepsy, which, like deafness, is a rare disease among a relatively common phenotype of epileptic encephalopathy. The research in my laboratory enables us to understand mechanisms of pathogenesis leading to human disease and the biological pathways required for development and maintenance of the inner ear and the brain.

a. Rabinski T, Sagiv S, Hausman-Kedem, Fattal-Valevski, Rubinstein M, **Avraham, KB**, Vatine GD. (2021) Reprogramming of two induced pluripotent stem cell lines from a heterozygous GRIN2D developmental and epileptic encephalopathy (DEE) patient (BGUi011-A) and from a healthy family relative (BGUi012-A). *Stem Cell Res.* 51:102178. PMID: 33482465
b. Taiber S, Cohen R, Yizhar-Barnea O, Sprinzak D, Holt JR, **Avraham KB**. (2020) AAV gene therapy rescues hearing in a mouse model of *SYNE4* deafness. *EMBO Mol Med*. 13:e13259. *Featured on cover of journal.* PMID: 33350593
c. Brownstein Z, Gulsuner S, Walsh T, Arrojo Martins FT, Taiber S, Isakov O, Lee MK, Bordeynik-Cohen M, Birkan M, Chang W, Casadei S, Danial-Farran N, Abu-Rayyan A, Carlson R, Kamal L, Örn Arnþórsson AO, Sokolov M, Gilony D, Lipschitz N, …, Pras E, Lev D, Wolf M, Steingrimsson E, Shomron N, Kelley MW, Kanaan M, Allon-Shalev S, King M-C, **Avraham KB**. (2020) Spectrum of genes for inherited hearing loss in the Israeli Jewish population, including the novel human deafness gene *ATOH1*. *Clin Genet*. 98:353–364. PMID: 33111345
d. Abu Rayyan A, Kamal L, Casadei S, Brownstein Z, Canavati C, Dweik D, Jaraysa T, Rabie G, Shahin H, Zahdeh F, Carlson R, Gulsuner S, Lee MK, **Avraham KB**, Walsh T, King M-C, Kanaan MN. (2020) Genomic analysis of inherited hearing loss in the Palestinian population. *Proc Natl Acad Sci USA*, 3:202009628. PMID: 32747562

B. Positions and Honors

Positions and Employment

1996 - 2001	Assistant Professor, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
2001 - 2007	Associate Professor, Faculty of Medicine, Tel Aviv University
2005 - 2009	Chair, Department of Human Molecular Genetics & Biochemistry, Tel Aviv University
2007 - present	Professor, Faculty of Medicine, Tel Aviv University
2010 - 2022	Vice Dean, Faculty of Medicine, Tel Aviv University
2010	Visiting Scholar, Sabbatical, Harvard Medical School, Boston, MA, USA
2011 - 2019	Visiting Professor of Medicine, Genome Sciences and Medical Genetics & Bloedel Hearing Research Center, University of Washington, Seattle, WA (3-month period each year)
2022 – present	Dean, Faculty of Medicine, Tel Aviv University

Honors and Awards

1998	Stacher Memorial Award, School of Medicine, Tel Aviv University
1999	Burt Evans Young Investigator Award, U.S. National Organization for Hearing Research
2000	Hestrin Young Investigator Award for Excellence, Israel Society Biochem. Molec. Biology
2002	Sir Bernard Katz Lecture Prize, Humboldt Foundation, Germany
2008	Bruno Memorial Prize, Rothschild Foundation, Israel
2011	Groundbreaking Research in Diseases Prize, Teva Pharmaceuticals, Israel
2013	Teva Founders Prize on Breakthroughs, Teva Pharmaceuticals, Israel
2014	Dean's Award for Excellence in Teaching, Graduate School, Tel Aviv University
2014	Distinguished Mentor Award, Sagol School of Neuroscience, Tel Aviv University
2016	Israeli Discoveries; Exhibit of Ministry of Science & Technology, Ben Gurion Airport, Israel
2016	Drs. Sarah and Felix Dumont Chair for Research of Hearing Disorders, Tel Aviv University
2017	Dean's Award for Excellence in Teaching, School of Medicine Graduate School, Tel Aviv U
2019	Ernest and Bonnie Beutler Research Program of Excellence in Genomic Medicine Award
2021	Special Recognition for Long-Term Contribution to Graduate School, Tel Aviv University
2022	Faculty of Scholars of the Human Genome Organization, Inaugural member
2023	FISEB STAR-Award for Scientific Excellence and Leadership

Other Experience and Professional Memberships

2001 - present	Elected Member, European Molecular Biology Organization (EMBO)
2002 - present	Elected Member, Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum (CORLAS)
2006 - 2011	Board Member, European Society of Human Genetics (ESHG)
2009 - present	*European Journal of Human Genetics (EJHG)*, Clinical Genetics Associate Editor
2010 - 2011	President, Association for Research in Otolaryngology (ARO)
2011 - 2013	President, Genetic Society of Israel (GSI)
2011 - 2019	President, Israel Society for Auditory Research (ISAR)
2014 - 2017	President, Federation of Israel Societies of Experimental Biology (FISEB)
2013 - present	Member, Israel National Center for Personalized Medicine (INCPM) Steering Committee
2013 - 2020	Member, Helmholtz-Israel Cooperation in Personalized Medicine Steering Committee
2014 - 2021	Elected Member, HUGO (Human Genome Organization) Council
2014 - present	President, Scientific Committee, Foundation Pour L'Audition – Acting for Hearing (Paris)
2016 - 2021	Elected Member, EMBO Council
2016 - present	Member, ClinGen Hearing Loss Expert Panel
2016 - present	Genetics Society of Israel, Comptroller
2016 - present	ScienceAbroad, Advisory Board
2017 - present	Biobank Steering Committee, Maccabi Health Data Science Institute, Member
2017 - present	Director, M.Sc. Program in Medical Sciences with a Specialty in Genetic Counseling
2018 - present	Wolfson Advisory Committee, The Wolfson Family Charitable Trust, Member
2018 - 2021	*Human Genomics*, Associate Editor
2018 - present	Rappaport Prize for Established/Young Israeli Scientist, Rappaport Foundation, Panel judge
2018 - present	Minerva Centers Committee, Germany, member
2018 - 2019	*Gene*, Co-Editor, Special Issue, Genetic Epidemiology of Deafness (S Usami & R Smith)
2019 - 2022	Co-Director, Aufzien Family Center for Prevention & Treatment of Parkinson's Disease
2019 - present	Lancet Commission on Hearing Loss, member

2019 - present	International Society for Inner Ear Therapeutics (ISIET), Founding member
2019 - 2022	Israeli BioInnovators Fellowships, Teva, Evaluation committee, Tel Aviv U
2019 - present	CureGRIN Scientific Advisory Board, member
2020 - 2022	Director, Healthy Longevity Research Center, Tel Aviv U
2020 - present	Co-Director, Taube-Koret Global Collaboration in Neurodegenerative Diseases, Tel Aviv U

C. Contributions to Science

My contributions to science have focused on the discovery and functional characterization of genes responsible for human disease and the control of gene expression. A major goal in auditory science is to understand how the cells of the inner ear develop to provide the exquisite precision of hearing. At a molecular level, the interactions of proteins of the auditory system orchestrate a remarkable feat that is revealed by our ability to hear. The challenge in auditory science is to determine how a pathogenic variant in a gene or regulatory element can cause this system to fail. We have been asking what genes are responsible for hearing loss and how does regulation of gene expression govern pathways controlling inner ear function. Our studies on epileptic encephalopathies involve neuronal and synaptic changes caused by a *GRIN2D* pathogenic variant, as well as examining the therapeutic potential of drug treatments.

1. Discovery and characterization of genes and gene therapy for hearing loss in human families. Both in my own lab and with my partners, I have discovered genes leading to hearing loss in Israeli and Palestinian populations. We have characterized each of these genes in cell culture and animal models, leading to an understanding of the mechanisms associated with deafness in humans, as well as rescued hearing in mouse models.

a. Vahava O, Morell R, Lynch ED, Weiss S, Kagan ME, Ahituv N, Morrow JE, Lee MK, Skvorak AB, Morton CC, Blumenfeld A, Frydman M, Friedman TB, King M-C, **Avraham KB** (1998) Mutation in transcription factor *POU4F3* associated with inherited progressive hearing loss in humans. *Science* 279: 1950-1954. PMID: 9506947

b. Horn HF, Brownstein Z, Lenz DR, Shivatzki S, Dror AA, Dagan-Rosenfeld O, Friedman LM, Roux KJ, Kozlov S, Jeang K-T, Frydman M, Burke B, Stewart CL, **Avraham KB** (2013) The LINC complex is essential for hearing. *J Clin Invest*. 123: 740-750. PMCID: PMC3561815

c. Taiber S, Cohen R, Yizhar-Barnea O, Sprinzak D, Holt JR, **Avraham KB**. (2021) AAV gene therapy rescues hearing in a mouse model of *SYNE4* deafness. *EMBO Mol Med*, 13:e13259. *Featured on cover of journal.* PMID: 33350593

d. Taiber S, Gozlan O, Cohen R, Andrade LR, Gregory EF, Starr DA, Moran Y, Hipp R, Kelley MW, Manor U, Sprinzak D, Avraham KB (2022) A nesprin-4/kinesin-1 cargo model for nuclear positioning in cochlear outer hair cells. *Front Cell Dev Biol*. 10:974168. PMID: 36211453

2. Discovery and characterization of genes for hearing loss in mouse models. My group identified the genes responsible for deafness in mouse mutants *Myo6*^{sv}, *Myo6*^{Tlc}, *Myo7a*^{Hdb}, *Jag1*^{Htu}, *Slc26a4* ^{loop}, and *Tmc1*^{Bth}, and carried out extensive characterization of the mice. Some of these mutants were directly associated with discoveries of human mutations in our population. Others led to increased understanding of mechanisms for hearing loss; for example, the role of Nesprin-4 in outer hair cell function and Gpsm2/Lgn in planar cell polarity.

a. Hertzano R, Shalit E, Rzadzinska AK, Dror AA, Song L, Ron U, Tan JT, Starovolsky Shitrit A, Fuchs H, Hasson T, Ben-Tal N, Sweeney HL, Hrabé de Angelis M, Steel KP, **Avraham KB** (2008) A *Myo6* mutation destroys coordination between the myosin heads, revealing new functions of myosin VI in the stereocilia of mammalian inner ear hair cells. *PLoS Genet*. 4: e1000207. PMCID: PMC2543112

b. Dror AA, Politi Y, Shahin H, Lenz DR, Dossena S, Nofziger C, Fuchs H, Hrabé de Angelis M, Markus P, Weiner S, **Avraham KB** (2010). Calcium oxalate stone formation in the inner ear as a result of an *Slc26a4* mutation. *J Biol Chem*. 285: 21724-21735. PMCID: PMC2898392

c. Bhonker Y, Abu-Rayyan A, Ushakov K, Amir-Zilberstein A, Shivatzki S, Yizhar-Barnea O, Elkan-Miller T, Tayeb-Fligelman E, Kim SM, Landau M, Kanaan K, Chen P, Matsuzaki F, Sprinzak D, **Avraham KB** (2015) The GPSM2/LGN GoLoco motifs are essential for hearing. *Mamm Genome* 27:29-46. PMID 26662512

d. Nadar-Ponniah PT, Taiber S, Caspi M, Koffler-Brill T, Dror AA, Siman-Tov R, Rubinstein M, Padmanabhan K, Luxenburg C, Lang RA, **Avraham KB***, Rosin-Arbesfeld R*. (2020) Striatin is required for hearing and affects inner hair cells and ribbon synapses. *Front Cell Dev Biol*. 8:615. PMID: 3276624

3. Genomic technology for mutation discovery in hearing research. I have been instrumental in developing a targeted gene capture and massively parallel sequencing approach to facilitate identification of mutations responsible for hearing loss. In our system, the coding regions of more than 300 genes associated with hearing are sequenced on a high-throughput platform, HEar-Seq, followed by interpretation driven by our knowledge of the genes. Candidate pathogenic variants are examined for co-segregation with hearing loss in families and with functional assays.

a. Brownstein Z, Friedman LM, Shahin H, Oron-Karni V, Kol N, Abu Rayyan A, Parzefall T, Lev D, Shalev S, Frydman M, Davidov B, Shohat M, Rahile M, Lieberman S, Levy-Lahad E, Lee M, Shomron N, King M-C, Walsh T, Kanaan M, **Avraham KB** (2011) Targeted genomic capture and massively parallel sequencing to identify genes for hereditary hearing loss in Middle Eastern families. *Genome Biol*. 12: R89. PMCID: PMC3308052

b. Brownstein Z, Abu-Rayyan A, Karfunkel-Doron D, Sirigu S, Davidov B, Shohat M, Frydman M, Houdusse A, Kanaan M, **Avraham KB** (2013) Novel myosin mutations for hereditary hearing loss revealed by targeted genomic capture and massively parallel sequencing. *Eur J Hum Genet*. 22:768-75. PMID: 24105371

c. Parzefall T, Shivatzki S, Lenz DR, Rathkolb B, Ushakov K, Karfunkel D, Shapira Y, Wolf M, Mohr M, Wolf E, Sabrautzki S, Hrabé de Angelis M, Frydman M, Brownstein Z, **Avraham KB** (2013) Cytoplasmic mislocalization of POU3F4 due to novel mutations leads to deafness in humans and mice. *Hum Mut.* 34:1102-1110. PMID: 23606368

d. Danial-Farran N, Brownstein Z, Gulsuner S, Tammer L, Khayat M, Aleme O, Chervinsky E, Aboleile Zoubi O, Walsh T, Ast G, King M-C, **Avraham KB***, Shalev SA* (2018) Genetics of hearing loss in the Arab population of northern Israel. *Eur J Hum Genet*. 26:1840-1847. (*shared authorship). PMID: 30139988.

4. Non-coding RNAs and methylation. I studied microRNAs in the inner ear by creating mice lacking *Dicer*, an essential enzyme for microRNA formation whose absence leads to reduction of microRNAs and subsequently deafness in the inner ear. I was the first to use RNA-seq to identify the most prominent microRNAs and lncRNAs in the inner ear and to define microRNA-target pairs that participate in pathways crucial for inner ear function. Our group was first to characterize methylation in the sensory epithelium and identify putative enhancers for deafness genes.

a. Friedman LM, Dror AA, Mor E, Tenne T, Toren G, Satoh T, Biesemeier DJ, Shomron N, Fekete DM, Hornstein E, **Avraham KB** (2009) MicroRNAs are essential for development and function of inner ear hair cells in vertebrates. *Proc Natl Acad Sci USA* 106: 7915-7920. PMCID: PMC2683084

b. Rudnicki A, Shivatzki S, Beyer LA, Takada Y, Raphael Y, **Avraham KB** (2014) microRNA-224 regulates Pentraxin-3, a component of the humoral arm of innate immunity, in inner ear inflammation. *Hum Molec Genet.* 23:3138-46. PMID: 24470395

c. Rudnicki A, Isakov O, Ushakov K, Shivatzki S, Weiss I, Friedman LM, Shomron N, **Avraham KB** (2014) Next-generation sequencing of small RNAs from inner ear sensory epithelium identifies microRNAs and defines regulatory pathways. *BMC Genomics*. 15:484. PMCID: PMC4073505

d. Ushakov K, Koffler-Brill T, Rom A, Perl K, Ulitsky I, **Avraham KB**. (2017) Genome-wide identification and expression profiling of long non-coding RNAs in auditory and vestibular systems. *Sci Rep*. 7:8637. PMCID: PMC5561060.

e. Yizhar-Barnea O, Valensisi C, Doni- Jayavelu N, Kishore K, Andrus C, Koffler-Brill T, Ushakov K, Perl K, Noy Y, Bhonker Y, Pelizzola M, Hawkins RD, **Avraham KB**. (2018) DNA methylation dynamics during embryonic development and postnatal maturation of the mouse auditory sensory epithelium. *Sci Rep*. 8:17348. PMCID: PMC6255903.

f. Koffler-Brill T, Taiber S, Anaya A, Bordeynik-Cohen M, Rosen E, Kolla L, Messika-Gold N, Elkon R, Kelley MW, Ulitsky I, **Avraham KB**. (2020) Identification and characterization of key long non-coding RNAs in the mouse cochlea. *RNA Biol*. 1-10. PMID: 33131415.

5. Leadership and mentoring. I have created programs to promote scientific excellence and to encourage

development of junior faculty at Tel Aviv University. I have recruited 70 new faculty members to the Faculty of Medicine. I created Biomed@TAU Research Hubs to bring together scientists in common fields from different parts of campus. I founded the Summer Research Program in the Sciences for international students and the Women Graduate Scientist's Mentoring Program. I have trained 25 PhD, 37 MSc, 5 MD-PhD students in my laboratory; 6 former students have faculty positions.

List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/42071644/?sort=date&direction=ascending
Total manuscripts: 125; total reviews and chapters: 58, H-Index: 62 (Google Scholar), Citation: 15,556

D. Research Support

Ongoing Research Support

Breakthrough Research Grant - Israeli Science Foundation 10/2022 - 09/2027
Avraham (PI)
Title: Regulatory Elements for Therapy in Deafness
Abstract: The goal of this project is to identify enhancer regulatory elements to be used for gene therapy, combining epigenomic profiling, characterization of candidate enhancer sequences, whole-genome sequencing, and genome editing experiments to define the role of enhancers in auditory development and function and in human deafness.

Israeli Science Foundation 10/2020 - 09/2024
Avraham (PI)
Title: The Emergence of Long Non-Coding RNAs in Inner Ear Biology
Abstract: Our focus is how lncRNAs regulate gene expression programs in specialized sensory cells of the inner ear, the hair cells. We will identify lncRNAs that are expressed in the hair cells of the inner ear, using fluorescence-activated single-cell sorting of dissected mouse inner ears. To evaluate the chosen candidate lncRNAs directly in the auditory system, CRISPR-Cas9 lncRNA knock-out mice will be created for three to five lncRNAs. This study will be the first of its kind to explore lncRNA mechanisms in hair cells of the auditory system.

US-Israel Binational Science Foundation 10/2020 - 09/2024
Avraham, Geleoc, Holt (Co-PIs)
Title: Gene Therapy for Deafness in Middle Eastern Populations
Abstract: We seek to rescue hearing in three different mouse models for forms of human deafness genes. We will use a combination of innovative methods employing CRISPR/Cas9 mouse mutant production, adeno-associated viruses (AAV) and a dual AAV strategy for restoring the function of large genes. These studies will pave the road for the development of gene replacement therapies for inherited forms of deafness.

Ernest and Bonnie Beutler Research Program of Excellence in Genomic Medicine 10/2019 - 09/2024
Avraham (PI)
Title: Non-coding RNAs & Methylation of Neurosensory Hair Cell: Implications for Hereditary Hearing Loss
Abstract: Our goal is to create an epigenomic profile of non-coding RNA and methylation of hair cells and identify critical regulatory elements for pathways such as cell patterning, planar cell polarity, synaptogenesis, and mechanotransduction. This project will employ high-throughput sequencing and CRISPR-genome editing. By discovering epigenetic mechanisms of hearing loss, this project will help improve early detection and identify new targets for therapy.

Israel Precision Medicine Partnership Program (IPMP) 10/2019 - 09/2023
Avraham (PI)
Title: Big Data to Therapy: Personalized Medicine for the Deaf in the Diverse Jewish Population
Abstract: We propose a big data research on a large-scale deaf population taken from the Maccabi Tipa Biobank Whole exome sequencing (WES) will be conducted, followed by thorough bioinformatics analysis, variant validation, and investigation of genotype-phenotype-ancestry correlations. Audiology and genetics clinics will be informed of any new variants, establishing a guideline for precision medicine for HL in Israel. Novel variants will be investigated functionally, using mouse models and gene therapy. This project will expand the scope of personalized medicine for deafness in the Israeli Jewish population.

NIH/NIDCD, 2R01DC011835-06A1 06/2018 - 05/2023
Avraham, King, Kanaan (MPIs)
Title: Genomic Approaches to Discovery and Characterization of Genes for Inherited Hearing Loss
Abstract: The goal of this project is to discover and characterize new genes for inherited hearing loss by studying

highly informative families from the Middle East. We propose to use modern tools of genetics and genomics to reveal and characterize genes essential for development and maintenance of hearing. Our discoveries will aid in the development of biological strategies for treatment or cures for deafness.