Multiomics Approaches to Further the Understanding of Hearing Loss and Tinnitus: Integrating different omics data types to identify biomarkers, unravel causal pathways, and reveal treatment targets

Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Sharon Curhan

Affiliation Brigham and Women's Hospital/Harvard Medical School

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

Session Description High-throughput technologies that enable analyses of whole genomes, transcriptomes, proteomes, metabolomes and metagenomes have revolutionized investigative opportunities for research in otolaryngology. The “omics” suffix transforms a molecular term to describe a comprehensive global assessment of a set of molecules. Advances in technology enabling cost-efficient, high-throughput analysis of biologic molecules are driving exciting growth in omics research. Individually, each type of omics data can reveal differences associated with disease that are useful as biomarkers of disease processes and provide insight on biological pathways or processes that may differ among those with and without disease. Expanding on associations identified in single omics analyses, the integration of different omics data types can then be used to elucidate potential causative changes that lead to disease and identify treatment targets that can be tested in further molecular studies. Integrating multi-omics data can help us connect genotype to phenotype, lead to discovery of shared or distinct mechanisms between diseases, and can inform development of personalized treatments. Multiomics profiling enables a comprehensive landscape view of molecular changes contributing to cellular responses and normal physiology, augments biologic understanding of disease onset and progression, and facilitates drug discovery. The 2021 NIH “Multiomics in Health and Disease” strategic planning workshop prioritized research that extends genomics beyond the DNA sequence and synthesizes these multiomics data with clinical data. Ultimately, the goals in the clinical setting are to integrate these multiomics data with electronic health records and clinical decision support tools, and to extend the use of biomarker testing beyond diagnosis and treatment to include comprehensive health and wellness. This symposium will present an overview of several omics data types and approaches, provide examples of their implementation in otolaryngology research, and propose how integration of multi-omics data in large-scale studies can be a powerful and promising new approach to understand ear and hearing health and disease.

Presenter Diversity This symposium includes a diverse representation of presenters, including women and men from multiple institutions (e.g. Harvard, Yale, Stanford, Brigham and Women's Hospital), from different countries of origin (e.g. Italy, Romania, Czech Republic, US), and Junior and Senior faculty (e.g. Instructor, Lecturer, Assistant Professor, Full Professor) across a number of disciplines (e.g. Otolaryngology, Neuroscience, Hearing Science, Genetics, Epidemiology, Biostatistics, Bioinformatics, Information and Computer Engineering, Psychiatry)

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Signature Sharon Curhan

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Genomics of Hearing Loss and Tinnitus

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Submitter Renato Polimanti

Affiliation Yale University School of Medicine Department of Psychiatry

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

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system may also be involved in the pathogenesis of these disorders through transcriptomic changes in multiple brain regions. In summary, the attendees will learn about how the application of Big Data analytics to genomic information is leading our field towards novel insights into the complex pathogenesis of hearing loss and tinnitus. However, they will also learn about the challenges that investigators still need to address to make sure the translation of genomic findings will lead to reliable healthcare tools.

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First Name	Last Name	Affiliation
Renato *	Polimanti *	Yale University School of Medicine Department of Psychiatry

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Metabolomics of Hearing Loss and Tinnitus

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Submission Type Symposia

Topic Other

Status Submitted

Submitter Oana Zeleznik

Affiliation Brigham & Women's Hospital, Harvard Medical School

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

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help identify subtypes and reveal factors associated with tinnitus susceptibility, I will show how the metabolome is uniquely suited to evaluate hearing loss and tinnitus, measure the impact of environmental factors, and how metabolomic assays can be powerful tools to identify biomarkers and pathoetiologic processes.

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Oana *	Zeleznik *	Brigham & Women's Hospital, Harvard Medical School
Konstantina	Stankovic	Massachusetts Eye and Ear Infirmary
Raji	Balasubramanian	University of Massachusetts
Gary	Curhan	Brigham and Women's Hospital/Harvard Medical School
Sharon	Curhan	Brigham and Women's Hospital/Harvard Medical School

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Investigating the Microbiome to Study Hearing Loss and Tinnitus

Submission ID 3003158

Submission Type Symposia

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Status Submitted

Submitter Jacqueline Starr

Affiliation Brigham & Women's Hospital, Harvard Medical School

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

Individual Abstract In the human-microbe superorganism, the number of genes in a person's microbiome has been estimated at 200 times the number of genes in the human genome. Humans depend on bacterial activity for the normal development of immunity and digestion. In all resident body sites—the gut, oral cavity, skin, nares, and ear—microbes mediate our responses to diet, medications, and other exogenous exposures. Emerging evidence supports a gut microbial contribution to neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Molecules derived from the gut microbiome, such as amyloid-like peptides and short-chain fatty acids, influence neuroinflammation and blood-brain barrier permeability modulation in animal models, and these molecules may act as neurotransmitters. Rigorously proven examples are accumulating of microbial mediation of pharmacologic efficacy or toxicity. It is highly plausible that microbial activity could mediate the otoxicity of medications or other chemical exposures. Yet almost nothing is known about microbial effects on hearing health or auditory dysfunction. Such information could point to novel approaches to design targeted interventions for prevention and/or treatment of hearing loss and tinnitus. We will provide an overview of methods for studying the human microbiome as an etiologic agent. We will describe established techniques and some current challenges. We will illustrate with examples relevant to the study of hearing loss and tinnitus.

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Jacqueline *	Starr *	Brigham & Women's Hospital, Harvard Medical School
Sharon	Curhan	Brigham and Women's Hospital/Harvard Medical School

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Signature Jacqueline R. Starr

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Using Omics to Uncover Mechanisms at the Bench: A Comparative Transcriptomic Analysis of Human Vestibular Schwannomas from Archival Ffpe Tissue Reveals Inflammatory Pathways Involved in Tinnitus

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Topic Other

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Submitter Konstantina Stankovic

Affiliation Department of Otolaryngology Head and Neck Surgery, Stanford School of Medicine

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

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differentially expressed. Our study demonstrates the feasibility of next-generation sequencing from archival FFPE VS tissue and identifies novel molecular players in VS-associated tinnitus. Further, future studies that integrate transcriptomics with other omic strategies could provide a more comprehensive understanding of alterations related to tinnitus and ultimately inform clinical testing and the development of tailored therapeutics.

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First Name	Last Name	Affiliation
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Krishna	Bommakanti	Department of Otolaryngology Head and Neck Surgery, UCLA
Richard	Seist	Department of Otolaryngology Head and Neck Surgery, Stanford School of Medicine
Phanidhar	Kukutla	Harvard University
Murat	Cetinbas	Massachusetts General Hospital
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Submitter Sharon Curhan

Affiliation Brigham and Women's Hospital/Harvard Medical School

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

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Submitter Renato Polimanti

Affiliation Yale University School of Medicine Department of Psychiatry

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

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Renato *	Polimanti *	Yale University School of Medicine Department of Psychiatry

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Signature Renato Polimanti

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Metabolomics of Hearing Loss and Tinnitus

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Submitter Oana Zeleznik

Affiliation Brigham & Women's Hospital, Harvard Medical School

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

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Raji	Balasubramanian	University of Massachusetts
Gary	Curhan	Brigham and Women's Hospital/Harvard Medical School
Sharon	Curhan	Brigham and Women's Hospital/Harvard Medical School

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Investigating the Microbiome to Study Hearing Loss and Tinnitus

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Submitter Jacqueline Starr

Affiliation Brigham & Women's Hospital, Harvard Medical School

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

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Jacqueline *	Starr *	Brigham & Women's Hospital, Harvard Medical School
Sharon	Curhan	Brigham and Women's Hospital/Harvard Medical School

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Submitter Konstantina Stankovic

Affiliation Department of Otolaryngology Head and Neck Surgery, Stanford School of Medicine

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

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differentially expressed. Our study demonstrates the feasibility of next-generation sequencing from archival FFPE VS tissue and identifies novel molecular players in VS-associated tinnitus. Further, future studies that integrate transcriptomics with other omic strategies could provide a more comprehensive understanding of alterations related to tinnitus and ultimately inform clinical testing and the development of tailored therapeutics.

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Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

Session Description High-throughput technologies that enable analyses of whole genomes, transcriptomes, proteomes, metabolomes and metagenomes have revolutionized investigative opportunities for research in otolaryngology. The “omics” suffix transforms a molecular term to describe a comprehensive global assessment of a set of molecules. Advances in technology enabling cost-efficient, high-throughput analysis of biologic molecules are driving exciting growth in omics research. Individually, each type of omics data can reveal differences associated with disease that are useful as biomarkers of disease processes and provide insight on biological pathways or processes that may differ among those with and without disease. Expanding on associations identified in single omics analyses, the integration of different omics data types can then be used to elucidate potential causative changes that lead to disease and identify treatment targets that can be tested in further molecular studies. Integrating multi-omics data can help us connect genotype to phenotype, lead to discovery of shared or distinct mechanisms between diseases, and can inform development of personalized treatments. Multiomics profiling enables a comprehensive landscape view of molecular changes contributing to cellular responses and normal physiology, augments biologic understanding of disease onset and progression, and facilitates drug discovery. The 2021 NIH “Multiomics in Health and Disease” strategic planning workshop prioritized research that extends genomics beyond the DNA sequence and synthesizes these multiomics data with clinical data. Ultimately, the goals in the clinical setting are to integrate these multiomics data with electronic health records and clinical decision support tools, and to extend the use of biomarker testing beyond diagnosis and treatment to include comprehensive health and wellness. This symposium will present an overview of several omics data types and approaches, provide examples of their implementation in otolaryngology research, and propose how integration of multi-omics data in large-scale studies can be a powerful and promising new approach to understand ear and hearing health and disease.

Presenter Diversity This symposium includes a diverse representation of presenters, including women and men from multiple institutions (e.g. Harvard, Yale, Stanford, Brigham and Women's Hospital), from different countries of origin (e.g. Italy, Romania, Czech Republic, US), and Junior and Senior faculty (e.g. Instructor, Lecturer, Assistant Professor, Full Professor) across a number of disciplines (e.g. Otolaryngology, Neuroscience, Hearing Science, Genetics, Epidemiology, Biostatistics, Bioinformatics, Information and Computer Engineering, Psychiatry)

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Signature Sharon Curhan

Multiomics Approaches to Further the Understanding of Hearing Loss and Tinnitus: Integrating different omics data types to identify biomarkers, unravel causal pathways, and reveal treatment targets

Genomics of Hearing Loss and Tinnitus

Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Renato Polimanti

Affiliation Yale University School of Medicine Department of Psychiatry

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

Individual Abstract Hearing loss and tinnitus are complex disorders due to the interplay of multiple genetic and environmental factors. Indeed, although rare monogenic forms of hearing loss (i.e., caused by mutations in a single gene) are present, most hearing loss cases are linked to the cumulative effect of many common genetic variants with small individual effects (i.e., polygenic risk) that act together with several environmental risk factors (such as noise exposure, tobacco smoking, drugs). Large-scale genomic studies based on hundreds of thousands of participants recruited by many biobanks around the world are permitting investigators to study the molecular basis of human diseases and traits at an unprecedented depth. In recent years, genome-wide association studies of hearing loss and tinnitus identified dozens of risk loci involved in the pathogenesis of these disorders, also showing that there is a large correlation between their genetic risk. This strongly supports that the pathogenesis of these disorders is partially shared. The present talk will provide an overview of the most recent advancement in our understanding of the genomics of hearing loss. This will include the discovery of risk loci mapped in genes involved in biological pathways that could be targeted for the development of novel drugs or repurposing of existing molecular compounds. Another important aspect is related to the characterization of the polygenic risk of hearing loss and tinnitus across diverse ancestral backgrounds to stratify disease risk and prioritize possible interventions for individuals at high risk. The effect of genetic variants on hearing loss and tinnitus has also been used to conduct genetically-informative causal inference analyses to distinguish possible causes and consequences among comorbid traits and diseases (e.g., depression, immunological conditions, and neurologic disorders). Beyond genetic associations, analyses of the transcriptomic regulation of specific tissues and cells in the context of their effect on hearing loss and tinnitus showed that several genes previously implicated in HL pathogenesis because of their potential involvement in the peripheral structures of the auditory

system may also be involved in the pathogenesis of these disorders through transcriptomic changes in multiple brain regions. In summary, the attendees will learn about how the application of Big Data analytics to genomic information is leading our field towards novel insights into the complex pathogenesis of hearing loss and tinnitus. However, they will also learn about the challenges that investigators still need to address to make sure the translation of genomic findings will lead to reliable healthcare tools.

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* Presenting Author

First Name	Last Name	Affiliation
Renato *	Polimanti *	Yale University School of Medicine Department of Psychiatry

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Multiomics Approaches to Further the Understanding of Hearing Loss and Tinnitus: Integrating different omics data types to identify biomarkers, unravel causal pathways, and reveal treatment targets

Metabolomics of Hearing Loss and Tinnitus

Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Oana Zeleznik

Affiliation Brigham & Women's Hospital, Harvard Medical School

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

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help identify subtypes and reveal factors associated with tinnitus susceptibility, I will show how the metabolome is uniquely suited to evaluate hearing loss and tinnitus, measure the impact of environmental factors, and how metabolomic assays can be powerful tools to identify biomarkers and pathoetiologic processes.

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Oana *	Zeleznik *	Brigham & Women's Hospital, Harvard Medical School
Konstantina	Stankovic	Massachusetts Eye and Ear Infirmary
Raji	Balasubramanian	University of Massachusetts
Gary	Curhan	Brigham and Women's Hospital/Harvard Medical School
Sharon	Curhan	Brigham and Women's Hospital/Harvard Medical School

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Signature Oana Zeleznik

Multiomics Approaches to Further the Understanding of Hearing Loss and Tinnitus: Integrating different omics data types to identify biomarkers, unravel causal pathways, and reveal treatment targets

Investigating the Microbiome to Study Hearing Loss and Tinnitus

Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Jacqueline Starr

Affiliation Brigham & Women's Hospital, Harvard Medical School

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

Individual Abstract In the human-microbe superorganism, the number of genes in a person's microbiome has been estimated at 200 times the number of genes in the human genome. Humans depend on bacterial activity for the normal development of immunity and digestion. In all resident body sites—the gut, oral cavity, skin, nares, and ear—microbes mediate our responses to diet, medications, and other exogenous exposures. Emerging evidence supports a gut microbial contribution to neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Molecules derived from the gut microbiome, such as amyloid-like peptides and short-chain fatty acids, influence neuroinflammation and blood-brain barrier permeability modulation in animal models, and these molecules may act as neurotransmitters. Rigorously proven examples are accumulating of microbial mediation of pharmacologic efficacy or toxicity. It is highly plausible that microbial activity could mediate the otoxicity of medications or other chemical exposures. Yet almost nothing is known about microbial effects on hearing health or auditory dysfunction. Such information could point to novel approaches to design targeted interventions for prevention and/or treatment of hearing loss and tinnitus. We will provide an overview of methods for studying the human microbiome as an etiologic agent. We will describe established techniques and some current challenges. We will illustrate with examples relevant to the study of hearing loss and tinnitus.

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Jacqueline *	Starr *	Brigham & Women's Hospital, Harvard Medical School
Sharon	Curhan	Brigham and Women's Hospital/Harvard Medical School

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Signature Jacqueline R. Starr

Multiomics Approaches to Further the Understanding of Hearing Loss and Tinnitus: Integrating different omics data types to identify biomarkers, unravel causal pathways, and reveal treatment targets

Using Omics to Uncover Mechanisms at the Bench: A Comparative Transcriptomic Analysis of Human Vestibular Schwannomas from Archival Ffpe Tissue Reveals Inflammatory Pathways Involved in Tinnitus

Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Konstantina Stankovic

Affiliation Department of Otolaryngology Head and Neck Surgery, Stanford School of Medicine

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

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differentially expressed. Our study demonstrates the feasibility of next-generation sequencing from archival FFPE VS tissue and identifies novel molecular players in VS-associated tinnitus. Further, future studies that integrate transcriptomics with other omic strategies could provide a more comprehensive understanding of alterations related to tinnitus and ultimately inform clinical testing and the development of tailored therapeutics.

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First Name	Last Name	Affiliation
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Krishna	Bommakanti	Department of Otolaryngology Head and Neck Surgery, UCLA
Richard	Seist	Department of Otolaryngology Head and Neck Surgery, Stanford School of Medicine
Phanidhar	Kukutla	Harvard University
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Signature Konstantina Stankovic

Multiomics Approaches to Further the Understanding of Hearing Loss and Tinnitus: Integrating different omics data types to identify biomarkers, unravel causal pathways, and reveal treatment targets

Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Sharon Curhan

Affiliation Brigham and Women's Hospital/Harvard Medical School

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

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Genomics of Hearing Loss and Tinnitus

Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Renato Polimanti

Affiliation Yale University School of Medicine Department of Psychiatry

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

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* Presenting Author

First Name	Last Name	Affiliation
Renato *	Polimanti *	Yale University School of Medicine Department of Psychiatry

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Signature Renato Polimanti

Multiomics Approaches to Further the Understanding of Hearing Loss and Tinnitus: Integrating different omics data types to identify biomarkers, unravel causal pathways, and reveal treatment targets

Metabolomics of Hearing Loss and Tinnitus

Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Oana Zeleznik

Affiliation Brigham & Women's Hospital, Harvard Medical School

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

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Raji	Balasubramanian	University of Massachusetts
Gary	Curhan	Brigham and Women's Hospital/Harvard Medical School
Sharon	Curhan	Brigham and Women's Hospital/Harvard Medical School

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Signature Oana Zeleznik

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Investigating the Microbiome to Study Hearing Loss and Tinnitus

Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Jacqueline Starr

Affiliation Brigham & Women's Hospital, Harvard Medical School

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

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Jacqueline *	Starr *	Brigham & Women's Hospital, Harvard Medical School
Sharon	Curhan	Brigham and Women's Hospital/Harvard Medical School

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Multiomics Approaches to Further the Understanding of Hearing Loss and Tinnitus: Integrating different omics data types to identify biomarkers, unravel causal pathways, and reveal treatment targets

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Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Konstantina Stankovic

Affiliation Department of Otolaryngology Head and Neck Surgery, Stanford School of Medicine

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

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differentially expressed. Our study demonstrates the feasibility of next-generation sequencing from archival FFPE VS tissue and identifies novel molecular players in VS-associated tinnitus. Further, future studies that integrate transcriptomics with other omic strategies could provide a more comprehensive understanding of alterations related to tinnitus and ultimately inform clinical testing and the development of tailored therapeutics.

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Richard	Seist	Department of Otolaryngology Head and Neck Surgery, Stanford School of Medicine
Phanidhar	Kukutla	Harvard University
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Signature Konstantina Stankovic

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Submission ID 3003158

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Topic Other

Status Submitted

Submitter Sharon Curhan

Affiliation Brigham and Women's Hospital/Harvard Medical School

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

Session Description High-throughput technologies that enable analyses of whole genomes, transcriptomes, proteomes, metabolomes and metagenomes have revolutionized investigative opportunities for research in otolaryngology. The “omics” suffix transforms a molecular term to describe a comprehensive global assessment of a set of molecules. Advances in technology enabling cost-efficient, high-throughput analysis of biologic molecules are driving exciting growth in omics research. Individually, each type of omics data can reveal differences associated with disease that are useful as biomarkers of disease processes and provide insight on biological pathways or processes that may differ among those with and without disease. Expanding on associations identified in single omics analyses, the integration of different omics data types can then be used to elucidate potential causative changes that lead to disease and identify treatment targets that can be tested in further molecular studies. Integrating multi-omics data can help us connect genotype to phenotype, lead to discovery of shared or distinct mechanisms between diseases, and can inform development of personalized treatments. Multiomics profiling enables a comprehensive landscape view of molecular changes contributing to cellular responses and normal physiology, augments biologic understanding of disease onset and progression, and facilitates drug discovery. The 2021 NIH “Multiomics in Health and Disease” strategic planning workshop prioritized research that extends genomics beyond the DNA sequence and synthesizes these multiomics data with clinical data. Ultimately, the goals in the clinical setting are to integrate these multiomics data with electronic health records and clinical decision support tools, and to extend the use of biomarker testing beyond diagnosis and treatment to include comprehensive health and wellness. This symposium will present an overview of several omics data types and approaches, provide examples of their implementation in otolaryngology research, and propose how integration of multi-omics data in large-scale studies can be a powerful and promising new approach to understand ear and hearing health and disease.

Presenter Diversity This symposium includes a diverse representation of presenters, including women and men from multiple institutions (e.g. Harvard, Yale, Stanford, Brigham and Women's Hospital), from different countries of origin (e.g. Italy, Romania, Czech Republic, US), and Junior and Senior faculty (e.g. Instructor, Lecturer, Assistant Professor, Full Professor) across a number of disciplines (e.g. Otolaryngology, Neuroscience, Hearing Science, Genetics, Epidemiology, Biostatistics, Bioinformatics, Information and Computer Engineering, Psychiatry)

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Signature Sharon Curhan

Multiomics Approaches to Further the Understanding of Hearing Loss and Tinnitus: Integrating different omics data types to identify biomarkers, unravel causal pathways, and reveal treatment targets

Genomics of Hearing Loss and Tinnitus

Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Renato Polimanti

Affiliation Yale University School of Medicine Department of Psychiatry

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

Individual Abstract Hearing loss and tinnitus are complex disorders due to the interplay of multiple genetic and environmental factors. Indeed, although rare monogenic forms of hearing loss (i.e., caused by mutations in a single gene) are present, most hearing loss cases are linked to the cumulative effect of many common genetic variants with small individual effects (i.e., polygenic risk) that act together with several environmental risk factors (such as noise exposure, tobacco smoking, drugs). Large-scale genomic studies based on hundreds of thousands of participants recruited by many biobanks around the world are permitting investigators to study the molecular basis of human diseases and traits at an unprecedented depth. In recent years, genome-wide association studies of hearing loss and tinnitus identified dozens of risk loci involved in the pathogenesis of these disorders, also showing that there is a large correlation between their genetic risk. This strongly supports that the pathogenesis of these disorders is partially shared. The present talk will provide an overview of the most recent advancement in our understanding of the genomics of hearing loss. This will include the discovery of risk loci mapped in genes involved in biological pathways that could be targeted for the development of novel drugs or repurposing of existing molecular compounds. Another important aspect is related to the characterization of the polygenic risk of hearing loss and tinnitus across diverse ancestral backgrounds to stratify disease risk and prioritize possible interventions for individuals at high risk. The effect of genetic variants on hearing loss and tinnitus has also been used to conduct genetically-informative causal inference analyses to distinguish possible causes and consequences among comorbid traits and diseases (e.g., depression, immunological conditions, and neurologic disorders). Beyond genetic associations, analyses of the transcriptomic regulation of specific tissues and cells in the context of their effect on hearing loss and tinnitus showed that several genes previously implicated in HL pathogenesis because of their potential involvement in the peripheral structures of the auditory

system may also be involved in the pathogenesis of these disorders through transcriptomic changes in multiple brain regions. In summary, the attendees will learn about how the application of Big Data analytics to genomic information is leading our field towards novel insights into the complex pathogenesis of hearing loss and tinnitus. However, they will also learn about the challenges that investigators still need to address to make sure the translation of genomic findings will lead to reliable healthcare tools.

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Signature Renato Polimanti

Multiomics Approaches to Further the Understanding of Hearing Loss and Tinnitus: Integrating different omics data types to identify biomarkers, unravel causal pathways, and reveal treatment targets

Metabolomics of Hearing Loss and Tinnitus

Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Oana Zeleznik

Affiliation Brigham & Women's Hospital, Harvard Medical School

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

Individual Abstract The development of omics tools has shifted metabolic research from a reductionist approach focused on specific metabolic pathways to a discovery-based approach that provides an unbiased and comprehensive view of an individual’s metabolic status. The metabolome is defined as the collection of all small molecule metabolites (e.g., organic acids, amino acids, nucleotides, sugars, acylcarnitines and lipids) in a biological sample (e.g., plasma, urine, saliva and tissues). Currently, multiple metabolomics approaches and technologies are used to measure the metabolome. Targeted approaches measure a distinct set of previously characterized metabolites while untargeted approaches measure all metabolites in a sample, including known and unknown metabolites. Nuclear magnetic resonance-based technologies are suitable for detection of a smaller number of metabolites with M-µM concentrations while mass-spectrometry-based technologies are superior for the detection of a large number of known and unknown metabolites with lower concentrations (up to fM). Metabolomic profiles can be used to characterize healthy tissue, to study tissue metabolism and disease pathology, and to identify biomarkers and risk factors for disease. Metabolomics also offers a valuable approach for drug discovery and evaluation of treatment efficacy, side effects and toxicity. Metabolite levels are ‘downstream’ of transcriptional and translational processes and reflect direct input from the genotype, diet, environment and microbiome. Thus, the systematic analysis of metabolites can uncover valuable insights into complex otolaryngologic conditions, including hearing loss, tinnitus, vestibular disorders, sinusitis, and head and neck cancers. In this presentation, we will provide an overview of methods for investigating the human metabolome and illustrate their implementation in recent metabolomics investigations of hearing loss and of tinnitus. For example, using examples from recent investigations of plasma metabolomic profiles among individuals with persistent tinnitus, I will describe the use of metabolomics to better understand the diverse etiologies that underlie tinnitus,

help identify subtypes and reveal factors associated with tinnitus susceptibility, I will show how the metabolome is uniquely suited to evaluate hearing loss and tinnitus, measure the impact of environmental factors, and how metabolomic assays can be powerful tools to identify biomarkers and pathoetiologic processes.

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Raji	Balasubramanian	University of Massachusetts
Gary	Curhan	Brigham and Women's Hospital/Harvard Medical School
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Signature Oana Zeleznik

Multiomics Approaches to Further the Understanding of Hearing Loss and Tinnitus: Integrating different omics data types to identify biomarkers, unravel causal pathways, and reveal treatment targets

Investigating the Microbiome to Study Hearing Loss and Tinnitus

Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Jacqueline Starr

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Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

Individual Abstract In the human-microbe superorganism, the number of genes in a person's microbiome has been estimated at 200 times the number of genes in the human genome. Humans depend on bacterial activity for the normal development of immunity and digestion. In all resident body sites—the gut, oral cavity, skin, nares, and ear—microbes mediate our responses to diet, medications, and other exogenous exposures. Emerging evidence supports a gut microbial contribution to neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Molecules derived from the gut microbiome, such as amyloid-like peptides and short-chain fatty acids, influence neuroinflammation and blood-brain barrier permeability modulation in animal models, and these molecules may act as neurotransmitters. Rigorously proven examples are accumulating of microbial mediation of pharmacologic efficacy or toxicity. It is highly plausible that microbial activity could mediate the otoxicity of medications or other chemical exposures. Yet almost nothing is known about microbial effects on hearing health or auditory dysfunction. Such information could point to novel approaches to design targeted interventions for prevention and/or treatment of hearing loss and tinnitus. We will provide an overview of methods for studying the human microbiome as an etiologic agent. We will describe established techniques and some current challenges. We will illustrate with examples relevant to the study of hearing loss and tinnitus.

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Signature Jacqueline R. Starr

Multiomics Approaches to Further the Understanding of Hearing Loss and Tinnitus: Integrating different omics data types to identify biomarkers, unravel causal pathways, and reveal treatment targets

Using Omics to Uncover Mechanisms at the Bench: A Comparative Transcriptomic Analysis of Human Vestibular Schwannomas from Archival Ffpe Tissue Reveals Inflammatory Pathways Involved in Tinnitus

Submission ID 3003158

Submission Type Symposia

Topic Other

Status Submitted

Submitter Konstantina Stankovic

Affiliation Department of Otolaryngology Head and Neck Surgery, Stanford School of Medicine

Participant(s) Sharon Curhan (Chair), Renato Polimanti (Presenter), Oana Zeleznik (Presenter), Jacqueline Starr (Presenter), Konstantina Stankovic (Presenter)

SUBMISSION DETAILS

Individual Abstract Similar to the way genomics expanded the focus of genetics from individual variants and genes to encompass large-scale interrogations of the entire genome, other omics approaches have rapidly been developed to investigate entire pools of transcripts, proteins, metabolites, microbiota, and exposures. These multiple omics data types afford a powerful discovery opportunity to better understand disease pathogenesis, uncover new treatment targets and inform molecular studies. For example, transcriptome profiling is an increasingly used approach to investigate human diseases at the molecular level. Transcriptomics examines RNA levels across the genome, identifies the presence of specific transcripts, novel splice sites and RNA editing sites, and quantifies the expression of transcripts. Numerous expression studies have identified molecular biomarkers and therapeutic targets for a variety of pathologies. In this presentation, I will discuss how evaluating transcriptome profiles can be a powerful approach to gain insights into the molecular mechanisms underlying complex auditory disorders and illustrate with a specific example of an investigation of tinnitus. Although the etiology of tinnitus is heterogenous, tinnitus is present in over 70% of patients with a vestibular schwannoma (VS). VSs are histologically benign intracranial tumors that arise from Schwann cells of the vestibular nerve, and typically lead to hearing loss, tinnitus and dizziness. To gain molecular insight into VS-associated tinnitus, we performed next generation sequencing on RNA extracted from archival formalin-fixed paraffin-embedded (FFPE) VS tissue from patients with and without tinnitus. A comprehensive bioinformatic analysis revealed inflammatory pathways, such as the allograft rejection pathway, as

differentially expressed. Our study demonstrates the feasibility of next-generation sequencing from archival FFPE VS tissue and identifies novel molecular players in VS-associated tinnitus. Further, future studies that integrate transcriptomics with other omic strategies could provide a more comprehensive understanding of alterations related to tinnitus and ultimately inform clinical testing and the development of tailored therapeutics.

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