New Frontiers in Genetic Testing for Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Eliot Shearer

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Symposium Description In this session we will focus on the future of genetic testing for hearing loss. The common theme is the importance of accurate genetic diagnosis in the face of the extreme genetic and phenotypic heterogeneity of hearing loss. Comprehensive genetic testing for hearing loss has become integral in the evaluation of individuals with hearing loss since widespread implementation more than 10 years ago, Accumulated data have shown, in general, a diagnostic rate of about 40-60% depending on clinical characteristics of the population studied. This makes genetic testing the single most effective diagnostic test for evaluation of hearing loss but clearly indicates room for improvement. The past decade has shown the difficulty in implementing these genetic tests and interpreting the testing results. At the same time, our understanding of the clinical phenotypes associated with syndromic forms of hearing loss has expanded and we have identified key avenues for future research to improve our ability to diagnose genetic hearing loss. In this symposium we will discuss reasons and methods for early genetic diagnosis for hearing loss, including integrating genetic screening into the newborn hearing screen. We will discuss the important of considering race and ethnicity when ordering and interpreting genetic testing results. We will then focus on our expanding understanding of the contribution of syndromic hearing loss diagnoses in otherwise non-syndromic hearing loss patients. We will discuss the challenge and importance of correctly interpreting splice site variants. Finally, we will consider the advantages offered by genome sequencing for genetic evaluation of hearing loss, with particular attention to detection of structural variants that cause hearing loss. This symposium will be targeted towards auditory geneticists and clinicians who evaluate individuals with hearing loss.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The proposed panel includes investigators in the early and mid-stages of their careers. Our panel includes members and non-members of ARO to provide broad expertise in the area. The panel members include scientists from the East Coast and West Coast United States as well as Hong Kong.

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature A Eliot Shearer

New Frontiers in Genetic Testing for Hearing Loss

Genetic Testing for Hearing Loss: Early Diagnosis Critical for Best Outcomes

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Eliot Shearer

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Genetic testing for hearing loss is critical for etiologic diagnosis and has become the standard of care in evaluation of children with hearing loss. Hearing loss is the most common disorder identified on the newborn screen in the United States and earlier diagnosis leads to the best speech, language, and quality of life outcomes. Genetic newborn hearing screening is therefore the next frontier in reducing time to genetic diagnosis of hearing loss. This type of hearing screening has been developed, and is currently implemented, at some sites around the world. Early data from these genetic newborn hearing screening programs using targeted panels, exome sequencing, and genome sequencing will be presented. We will discuss progress and barriers towards widespread implementation of genetic newborn hearing screening.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Eliot *	Shearer *	Boston Children's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature A Eliot Shearer

New Frontiers in Genetic Testing for Hearing Loss

Racial and Ethnic Disparities in Genetic Testing for Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Dylan Chan

Affiliation University of California, San Francisco

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Hearing loss is the most common congenital sensory impairment, with 1:500 children born deaf or hard-of-hearing (D/HH). Hearing-loss gene-panel testing (HL-GPT) is the most impactful and effective etiologic test for childhood sensorineural hearing loss (SNHL). Genetic diagnosis for hearing loss informs prognosis, provides early identification of syndromic associations, enables family counseling, and is the foundation for impending gene therapy. Racial/ethnic disparities in hearing-loss genetic testing access and outcomes are enormous: Latino and Black individuals with SNHL are 5 times less likely to receive a genetic diagnosis upon standard clinical HL-GPT compared with Whites and Asians. This difference is connected with a tremendous disparity among the populations that have been included in published hearing-loss genetic studies, with individuals of African or indigenous American genetic ancestry vastly underrepresented compared with their European and Asian counterparts. In this presentation, we will review the impact and extent of racial and ethnic disparities in hearing-loss genetics and genetic testing, and discuss the importance of greater inclusion of underrepresented minority groups in both clinical and research efforts going forward.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Dylan *	Chan *	University of California, San Francisco

Michelle	Florentine	University of California, San Francisco
Jacqueline	Harris	University of California, San Francisco
Stephanie	Rouse	Boston Children's Hospital
Sonia	Scaria	University of California, San Francisco

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Dylan Chan

New Frontiers in Genetic Testing for Hearing Loss

Non-Syndromic Hearing Loss mimics: Beyond Usher and Pendred Syndrome

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Shelby Redfield

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Syndromic hearing loss (SHL) accounts for approximately 30% of genetic diagnoses for pediatric hearing loss (HL) and has important implications for patients and families. Current clinical algorithms for genetic testing do not include all HL phenotypes, such as unilateral and asymmetric HL. Some recent studies suggest that a larger number of SHL genes than was previously appreciated can mimic a nonsyndromic HL phenotype, especially in early childhood. This raises the possibility of underdiagnosis of SHL. We identified cases of nonsyndromic HL mimics with genetic diagnoses of SHL in our pediatric patient population via retrospective chart review. While many SHL patients who presented with apparently isolated HL had Usher or Pendred syndrome, 12 patients with isolated HL received SHL diagnoses for conditions typically associated with additional features in early childhood. Pathogenic variants were identified in 8 genes (MITF, PAX3, SOX10, FGFR3, EYA1, LARS2, KMT2C, and TFAP2A). In some cases, subtle syndromic features were appreciated after genetic diagnosis. A majority of these 12 patients had unilateral or asymmetric HL. Of the 12 diagnoses, 6 had Waardenburg syndrome, 2 subjects had Muenke syndrome, and 1 subject had Kleefstra syndrome type 2, Perrault syndrome type 4, or branchiootorenal syndrome. One patient had isolated unilateral HL and a dual diagnosis of branchiooculofacial syndrome and mosaic chromosome 5p15.33p13.3 gain. Pediatric otolaryngologists are often the first specialist to see a child with subtle SHL after a newborn hearing screen referral. Increased access to comprehensive genetic testing for patients with any hearing loss phenotype within an otolaryngology pracitce will improve SHL diagnosis and facilitate early referral to appropriate specialists, tailored intervention, and improved prognostic and recurrence information for families.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Shelby *	Redfield *	Boston Children's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Shelby Redfield

New Frontiers in Genetic Testing for Hearing Loss

In or Out: The Role of RNA-Splicing in Hereditary Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Kevin Booth

Affiliation Harvard Medical School Dept. Neurobiology

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract RNA-splicing is a highly complex and tightly regulated process. RNA-binding proteins (spliceosome proteins) recognize key nucleotide motifs, which allows for an orchestrated removal of intronic sequences and the formation of messenger RNA (mRNA). DNA variants which alter the highly conserved nucleotide motifs where the spliceosome protein members bind can result in mis-regulation of RNA-splicing and consequently the formation of mutant mRNA. Historically, only variants impacting the highly conserved donor or acceptor splice-sites (+/- 2 base pairs into the intron) have been considered as splice-altering variants. More recently, exonic coding variants and intronic variants (outside the canonical splice-sites), have been implicated in impacting RNA-splicing. Additionally, growing evidence suggests a large number exonic disease-causing variants attenuate wildtype RNA-splicing. Interestingly, not all coding variants that result in mis-splicing, have the same effect and often there are many mutant mRNA transcripts created. Outside the analysis of patient RNA, mini-gene in vitro splicing assays have become the cornerstone of understanding a variants impact on RNA splicing. Understanding a variants effect, is critical to providing an accurate genetic diagnosis. Furthermore, understanding a variants impact on RNA-splicing has important therapeutic implications as defects in RNA-splicing can be corrected using Antisense Oligonucleotides. In this podium session, I highlight the in silco and in vitro workflows of analyzing a variants impact on RNA-splicing and highlight the importance of investigating coding variants impact on RNA-splicing using case studies.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation

Kevin *	Booth *	Harvard Medical School Dept. Neurobiology

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Kevin T Booth

New Frontiers in Genetic Testing for Hearing Loss

Implications of Structural Variations for Hearing Loss Detected in Newborn Genome Sequencing Data.

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Matthew Hoi Kin Chau

Affiliation The Chinese University of Hong Kong

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Genetic screening in congenitally deaf and hard-of-hearing (DHH) newborns at birth allows for early intervention and diagnosis which leads to improved speech and language outcomes, depending on the DHH etiology. Recently, compelling evidence has shown that genetic testing in newborn hearing screening (NBHS) positively impacted clinical outcomes. SEQaBOO (SEQuencing a Baby for an Optimal Outcome) is a program at Harvard Medical School evaluating genome sequencing and parental attitudes towards genomic medicine in DHH newborns following a positive NBHS or confirmatory diagnostic audiometry (1 month). SEQaBOO also incorporated optional reporting of ACMG secondary findings v3.0 for parents. While single nucleotide variants and small insertions and deletions (indels) in genes associated with nonsyndromic and syndromic DHH have been reported previously, a collaboration with the Chinese University of Hong Kong then investigated additional chromosomal abnormalities in the genome sequence data. Genome-wide copy number variations were detected from genome sequencing data of SEQaBOO participants using a read-depth-based approach. Structural rearrangements were detected by discordant read pairs. Absence of heterozygosity (AOH) was assessed by the rates of heterozygous genotypes. The additional value and clinical significance of structural variants (SVs) detected were investigated. Among SEQaBOO babies ultimately diagnosed as DHH (n=31), a causative genetic etiology (SNV & indels) was reported previously in 6 babies. The SV detection protocol in 81 families revealed incidental findings in 9 babies. These included one case of XYY syndrome and four cases of inherited heterozygous deletions of STRC and CATSPER2. Biallelic pathogenic variants or contiguous gene deletions across this region are associated with deafness-infertility syndrome. In one family, both parents carried heterozygous deletions of STRC and CATSPER2 and are at risk (1/4) of having affected offspring. Balanced chromosomal translocations were detected in two families who had conceived by IVF following multiple miscarriages. GS results fine mapped the breakpoints of these translocations to the nucleotide level, of which they disrupted three genes including CDK19, DYM, and PHF21B. These findings have implications for subsequent pregnancy management. Extended

regions of absence of heterozygosity (AOH) on two chromosomes were detected in two probands, suggestive of uniparental disomy or remnants of identity by descent, warranting further follow up. SV detection in the genome sequencing data of the SEQaBOO study revealed additional clinically relevant findings. These data and others show the effectiveness of genome sequencing for SV detection in newborns with hearing loss.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Matthew Hoi Kin *	Chau *	The Chinese University of Hong Kong
Calli	Mitchell	Harvard Medical School
Zirui	Dong	The Chinese University of Hong Kong
Ye	Cao	The Chinese University of Hong Kong
Kwong Wai	Choy	The Chinese University of Hong Kong
Jun	Shen	Brigham and Women's Hospital
Sami	Amr	Harvard Medical School
Anne	Giersch	Brigham and Women's Hospital
Cynthia	Morton	Brigham and Women's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Matthew Chau

New Frontiers in Genetic Testing for Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Eliot Shearer

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Symposium Description In this session we will focus on the future of genetic testing for hearing loss. The common theme is the importance of accurate genetic diagnosis in the face of the extreme genetic and phenotypic heterogeneity of hearing loss. Comprehensive genetic testing for hearing loss has become integral in the evaluation of individuals with hearing loss since widespread implementation more than 10 years ago, Accumulated data have shown, in general, a diagnostic rate of about 40-60% depending on clinical characteristics of the population studied. This makes genetic testing the single most effective diagnostic test for evaluation of hearing loss but clearly indicates room for improvement. The past decade has shown the difficulty in implementing these genetic tests and interpreting the testing results. At the same time, our understanding of the clinical phenotypes associated with syndromic forms of hearing loss has expanded and we have identified key avenues for future research to improve our ability to diagnose genetic hearing loss. In this symposium we will discuss reasons and methods for early genetic diagnosis for hearing loss, including integrating genetic screening into the newborn hearing screen. We will discuss the important of considering race and ethnicity when ordering and interpreting genetic testing results. We will then focus on our expanding understanding of the contribution of syndromic hearing loss diagnoses in otherwise non-syndromic hearing loss patients. We will discuss the challenge and importance of correctly interpreting splice site variants. Finally, we will consider the advantages offered by genome sequencing for genetic evaluation of hearing loss, with particular attention to detection of structural variants that cause hearing loss. This symposium will be targeted towards auditory geneticists and clinicians who evaluate individuals with hearing loss.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The proposed panel includes investigators in the early and mid-stages of their careers. Our panel includes members and non-members of ARO to provide broad expertise in the area. The panel members include scientists from the East Coast and West Coast United States as well as Hong Kong.

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature A Eliot Shearer

New Frontiers in Genetic Testing for Hearing Loss

Genetic Testing for Hearing Loss: Early Diagnosis Critical for Best Outcomes

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Eliot Shearer

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Genetic testing for hearing loss is critical for etiologic diagnosis and has become the standard of care in evaluation of children with hearing loss. Hearing loss is the most common disorder identified on the newborn screen in the United States and earlier diagnosis leads to the best speech, language, and quality of life outcomes. Genetic newborn hearing screening is therefore the next frontier in reducing time to genetic diagnosis of hearing loss. This type of hearing screening has been developed, and is currently implemented, at some sites around the world. Early data from these genetic newborn hearing screening programs using targeted panels, exome sequencing, and genome sequencing will be presented. We will discuss progress and barriers towards widespread implementation of genetic newborn hearing screening.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Eliot *	Shearer *	Boston Children's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature A Eliot Shearer

New Frontiers in Genetic Testing for Hearing Loss

Racial and Ethnic Disparities in Genetic Testing for Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Dylan Chan

Affiliation University of California, San Francisco

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Hearing loss is the most common congenital sensory impairment, with 1:500 children born deaf or hard-of-hearing (D/HH). Hearing-loss gene-panel testing (HL-GPT) is the most impactful and effective etiologic test for childhood sensorineural hearing loss (SNHL). Genetic diagnosis for hearing loss informs prognosis, provides early identification of syndromic associations, enables family counseling, and is the foundation for impending gene therapy. Racial/ethnic disparities in hearing-loss genetic testing access and outcomes are enormous: Latino and Black individuals with SNHL are 5 times less likely to receive a genetic diagnosis upon standard clinical HL-GPT compared with Whites and Asians. This difference is connected with a tremendous disparity among the populations that have been included in published hearing-loss genetic studies, with individuals of African or indigenous American genetic ancestry vastly underrepresented compared with their European and Asian counterparts. In this presentation, we will review the impact and extent of racial and ethnic disparities in hearing-loss genetics and genetic testing, and discuss the importance of greater inclusion of underrepresented minority groups in both clinical and research efforts going forward.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Dylan *	Chan *	University of California, San Francisco

Michelle	Florentine	University of California, San Francisco
Jacqueline	Harris	University of California, San Francisco
Stephanie	Rouse	Boston Children's Hospital
Sonia	Scaria	University of California, San Francisco

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Dylan Chan

New Frontiers in Genetic Testing for Hearing Loss

Non-Syndromic Hearing Loss mimics: Beyond Usher and Pendred Syndrome

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Shelby Redfield

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Syndromic hearing loss (SHL) accounts for approximately 30% of genetic diagnoses for pediatric hearing loss (HL) and has important implications for patients and families. Current clinical algorithms for genetic testing do not include all HL phenotypes, such as unilateral and asymmetric HL. Some recent studies suggest that a larger number of SHL genes than was previously appreciated can mimic a nonsyndromic HL phenotype, especially in early childhood. This raises the possibility of underdiagnosis of SHL. We identified cases of nonsyndromic HL mimics with genetic diagnoses of SHL in our pediatric patient population via retrospective chart review. While many SHL patients who presented with apparently isolated HL had Usher or Pendred syndrome, 12 patients with isolated HL received SHL diagnoses for conditions typically associated with additional features in early childhood. Pathogenic variants were identified in 8 genes (MITF, PAX3, SOX10, FGFR3, EYA1, LARS2, KMT2C, and TFAP2A). In some cases, subtle syndromic features were appreciated after genetic diagnosis. A majority of these 12 patients had unilateral or asymmetric HL. Of the 12 diagnoses, 6 had Waardenburg syndrome, 2 subjects had Muenke syndrome, and 1 subject had Kleefstra syndrome type 2, Perrault syndrome type 4, or branchiootorenal syndrome. One patient had isolated unilateral HL and a dual diagnosis of branchiooculofacial syndrome and mosaic chromosome 5p15.33p13.3 gain. Pediatric otolaryngologists are often the first specialist to see a child with subtle SHL after a newborn hearing screen referral. Increased access to comprehensive genetic testing for patients with any hearing loss phenotype within an otolaryngology pracitce will improve SHL diagnosis and facilitate early referral to appropriate specialists, tailored intervention, and improved prognostic and recurrence information for families.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Shelby *	Redfield *	Boston Children's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Shelby Redfield

New Frontiers in Genetic Testing for Hearing Loss

In or Out: The Role of RNA-Splicing in Hereditary Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Kevin Booth

Affiliation Harvard Medical School Dept. Neurobiology

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract RNA-splicing is a highly complex and tightly regulated process. RNA-binding proteins (spliceosome proteins) recognize key nucleotide motifs, which allows for an orchestrated removal of intronic sequences and the formation of messenger RNA (mRNA). DNA variants which alter the highly conserved nucleotide motifs where the spliceosome protein members bind can result in mis-regulation of RNA-splicing and consequently the formation of mutant mRNA. Historically, only variants impacting the highly conserved donor or acceptor splice-sites (+/- 2 base pairs into the intron) have been considered as splice-altering variants. More recently, exonic coding variants and intronic variants (outside the canonical splice-sites), have been implicated in impacting RNA-splicing. Additionally, growing evidence suggests a large number exonic disease-causing variants attenuate wildtype RNA-splicing. Interestingly, not all coding variants that result in mis-splicing, have the same effect and often there are many mutant mRNA transcripts created. Outside the analysis of patient RNA, mini-gene in vitro splicing assays have become the cornerstone of understanding a variants impact on RNA splicing. Understanding a variants effect, is critical to providing an accurate genetic diagnosis. Furthermore, understanding a variants impact on RNA-splicing has important therapeutic implications as defects in RNA-splicing can be corrected using Antisense Oligonucleotides. In this podium session, I highlight the in silco and in vitro workflows of analyzing a variants impact on RNA-splicing and highlight the importance of investigating coding variants impact on RNA-splicing using case studies.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation

Kevin *	Booth *	Harvard Medical School Dept. Neurobiology

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Kevin T Booth

New Frontiers in Genetic Testing for Hearing Loss

Implications of Structural Variations for Hearing Loss Detected in Newborn Genome Sequencing Data.

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Matthew Hoi Kin Chau

Affiliation The Chinese University of Hong Kong

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Genetic screening in congenitally deaf and hard-of-hearing (DHH) newborns at birth allows for early intervention and diagnosis which leads to improved speech and language outcomes, depending on the DHH etiology. Recently, compelling evidence has shown that genetic testing in newborn hearing screening (NBHS) positively impacted clinical outcomes. SEQaBOO (SEQuencing a Baby for an Optimal Outcome) is a program at Harvard Medical School evaluating genome sequencing and parental attitudes towards genomic medicine in DHH newborns following a positive NBHS or confirmatory diagnostic audiometry (1 month). SEQaBOO also incorporated optional reporting of ACMG secondary findings v3.0 for parents. While single nucleotide variants and small insertions and deletions (indels) in genes associated with nonsyndromic and syndromic DHH have been reported previously, a collaboration with the Chinese University of Hong Kong then investigated additional chromosomal abnormalities in the genome sequence data. Genome-wide copy number variations were detected from genome sequencing data of SEQaBOO participants using a read-depth-based approach. Structural rearrangements were detected by discordant read pairs. Absence of heterozygosity (AOH) was assessed by the rates of heterozygous genotypes. The additional value and clinical significance of structural variants (SVs) detected were investigated. Among SEQaBOO babies ultimately diagnosed as DHH (n=31), a causative genetic etiology (SNV & indels) was reported previously in 6 babies. The SV detection protocol in 81 families revealed incidental findings in 9 babies. These included one case of XYY syndrome and four cases of inherited heterozygous deletions of STRC and CATSPER2. Biallelic pathogenic variants or contiguous gene deletions across this region are associated with deafness-infertility syndrome. In one family, both parents carried heterozygous deletions of STRC and CATSPER2 and are at risk (1/4) of having affected offspring. Balanced chromosomal translocations were detected in two families who had conceived by IVF following multiple miscarriages. GS results fine mapped the breakpoints of these translocations to the nucleotide level, of which they disrupted three genes including CDK19, DYM, and PHF21B. These findings have implications for subsequent pregnancy management. Extended

regions of absence of heterozygosity (AOH) on two chromosomes were detected in two probands, suggestive of uniparental disomy or remnants of identity by descent, warranting further follow up. SV detection in the genome sequencing data of the SEQaBOO study revealed additional clinically relevant findings. These data and others show the effectiveness of genome sequencing for SV detection in newborns with hearing loss.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Matthew Hoi Kin *	Chau *	The Chinese University of Hong Kong
Calli	Mitchell	Harvard Medical School
Zirui	Dong	The Chinese University of Hong Kong
Ye	Cao	The Chinese University of Hong Kong
Kwong Wai	Choy	The Chinese University of Hong Kong
Jun	Shen	Brigham and Women's Hospital
Sami	Amr	Harvard Medical School
Anne	Giersch	Brigham and Women's Hospital
Cynthia	Morton	Brigham and Women's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Matthew Chau

New Frontiers in Genetic Testing for Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Eliot Shearer

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Symposium Description In this session we will focus on the future of genetic testing for hearing loss. The common theme is the importance of accurate genetic diagnosis in the face of the extreme genetic and phenotypic heterogeneity of hearing loss. Comprehensive genetic testing for hearing loss has become integral in the evaluation of individuals with hearing loss since widespread implementation more than 10 years ago, Accumulated data have shown, in general, a diagnostic rate of about 40-60% depending on clinical characteristics of the population studied. This makes genetic testing the single most effective diagnostic test for evaluation of hearing loss but clearly indicates room for improvement. The past decade has shown the difficulty in implementing these genetic tests and interpreting the testing results. At the same time, our understanding of the clinical phenotypes associated with syndromic forms of hearing loss has expanded and we have identified key avenues for future research to improve our ability to diagnose genetic hearing loss. In this symposium we will discuss reasons and methods for early genetic diagnosis for hearing loss, including integrating genetic screening into the newborn hearing screen. We will discuss the important of considering race and ethnicity when ordering and interpreting genetic testing results. We will then focus on our expanding understanding of the contribution of syndromic hearing loss diagnoses in otherwise non-syndromic hearing loss patients. We will discuss the challenge and importance of correctly interpreting splice site variants. Finally, we will consider the advantages offered by genome sequencing for genetic evaluation of hearing loss, with particular attention to detection of structural variants that cause hearing loss. This symposium will be targeted towards auditory geneticists and clinicians who evaluate individuals with hearing loss.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The proposed panel includes investigators in the early and mid-stages of their careers. Our panel includes members and non-members of ARO to provide broad expertise in the area. The panel members include scientists from the East Coast and West Coast United States as well as Hong Kong.

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature A Eliot Shearer

New Frontiers in Genetic Testing for Hearing Loss

Genetic Testing for Hearing Loss: Early Diagnosis Critical for Best Outcomes

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Eliot Shearer

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Genetic testing for hearing loss is critical for etiologic diagnosis and has become the standard of care in evaluation of children with hearing loss. Hearing loss is the most common disorder identified on the newborn screen in the United States and earlier diagnosis leads to the best speech, language, and quality of life outcomes. Genetic newborn hearing screening is therefore the next frontier in reducing time to genetic diagnosis of hearing loss. This type of hearing screening has been developed, and is currently implemented, at some sites around the world. Early data from these genetic newborn hearing screening programs using targeted panels, exome sequencing, and genome sequencing will be presented. We will discuss progress and barriers towards widespread implementation of genetic newborn hearing screening.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Eliot *	Shearer *	Boston Children's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature A Eliot Shearer

New Frontiers in Genetic Testing for Hearing Loss

Racial and Ethnic Disparities in Genetic Testing for Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Dylan Chan

Affiliation University of California, San Francisco

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Hearing loss is the most common congenital sensory impairment, with 1:500 children born deaf or hard-of-hearing (D/HH). Hearing-loss gene-panel testing (HL-GPT) is the most impactful and effective etiologic test for childhood sensorineural hearing loss (SNHL). Genetic diagnosis for hearing loss informs prognosis, provides early identification of syndromic associations, enables family counseling, and is the foundation for impending gene therapy. Racial/ethnic disparities in hearing-loss genetic testing access and outcomes are enormous: Latino and Black individuals with SNHL are 5 times less likely to receive a genetic diagnosis upon standard clinical HL-GPT compared with Whites and Asians. This difference is connected with a tremendous disparity among the populations that have been included in published hearing-loss genetic studies, with individuals of African or indigenous American genetic ancestry vastly underrepresented compared with their European and Asian counterparts. In this presentation, we will review the impact and extent of racial and ethnic disparities in hearing-loss genetics and genetic testing, and discuss the importance of greater inclusion of underrepresented minority groups in both clinical and research efforts going forward.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Dylan *	Chan *	University of California, San Francisco

Michelle	Florentine	University of California, San Francisco
Jacqueline	Harris	University of California, San Francisco
Stephanie	Rouse	Boston Children's Hospital
Sonia	Scaria	University of California, San Francisco

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Dylan Chan

New Frontiers in Genetic Testing for Hearing Loss

Non-Syndromic Hearing Loss mimics: Beyond Usher and Pendred Syndrome

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Shelby Redfield

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Syndromic hearing loss (SHL) accounts for approximately 30% of genetic diagnoses for pediatric hearing loss (HL) and has important implications for patients and families. Current clinical algorithms for genetic testing do not include all HL phenotypes, such as unilateral and asymmetric HL. Some recent studies suggest that a larger number of SHL genes than was previously appreciated can mimic a nonsyndromic HL phenotype, especially in early childhood. This raises the possibility of underdiagnosis of SHL. We identified cases of nonsyndromic HL mimics with genetic diagnoses of SHL in our pediatric patient population via retrospective chart review. While many SHL patients who presented with apparently isolated HL had Usher or Pendred syndrome, 12 patients with isolated HL received SHL diagnoses for conditions typically associated with additional features in early childhood. Pathogenic variants were identified in 8 genes (MITF, PAX3, SOX10, FGFR3, EYA1, LARS2, KMT2C, and TFAP2A). In some cases, subtle syndromic features were appreciated after genetic diagnosis. A majority of these 12 patients had unilateral or asymmetric HL. Of the 12 diagnoses, 6 had Waardenburg syndrome, 2 subjects had Muenke syndrome, and 1 subject had Kleefstra syndrome type 2, Perrault syndrome type 4, or branchiootorenal syndrome. One patient had isolated unilateral HL and a dual diagnosis of branchiooculofacial syndrome and mosaic chromosome 5p15.33p13.3 gain. Pediatric otolaryngologists are often the first specialist to see a child with subtle SHL after a newborn hearing screen referral. Increased access to comprehensive genetic testing for patients with any hearing loss phenotype within an otolaryngology pracitce will improve SHL diagnosis and facilitate early referral to appropriate specialists, tailored intervention, and improved prognostic and recurrence information for families.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Shelby *	Redfield *	Boston Children's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Shelby Redfield

New Frontiers in Genetic Testing for Hearing Loss

In or Out: The Role of RNA-Splicing in Hereditary Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Kevin Booth

Affiliation Harvard Medical School Dept. Neurobiology

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract RNA-splicing is a highly complex and tightly regulated process. RNA-binding proteins (spliceosome proteins) recognize key nucleotide motifs, which allows for an orchestrated removal of intronic sequences and the formation of messenger RNA (mRNA). DNA variants which alter the highly conserved nucleotide motifs where the spliceosome protein members bind can result in mis-regulation of RNA-splicing and consequently the formation of mutant mRNA. Historically, only variants impacting the highly conserved donor or acceptor splice-sites (+/- 2 base pairs into the intron) have been considered as splice-altering variants. More recently, exonic coding variants and intronic variants (outside the canonical splice-sites), have been implicated in impacting RNA-splicing. Additionally, growing evidence suggests a large number exonic disease-causing variants attenuate wildtype RNA-splicing. Interestingly, not all coding variants that result in mis-splicing, have the same effect and often there are many mutant mRNA transcripts created. Outside the analysis of patient RNA, mini-gene in vitro splicing assays have become the cornerstone of understanding a variants impact on RNA splicing. Understanding a variants effect, is critical to providing an accurate genetic diagnosis. Furthermore, understanding a variants impact on RNA-splicing has important therapeutic implications as defects in RNA-splicing can be corrected using Antisense Oligonucleotides. In this podium session, I highlight the in silco and in vitro workflows of analyzing a variants impact on RNA-splicing and highlight the importance of investigating coding variants impact on RNA-splicing using case studies.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation

Kevin *	Booth *	Harvard Medical School Dept. Neurobiology

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Kevin T Booth

New Frontiers in Genetic Testing for Hearing Loss

Implications of Structural Variations for Hearing Loss Detected in Newborn Genome Sequencing Data.

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Matthew Hoi Kin Chau

Affiliation The Chinese University of Hong Kong

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Genetic screening in congenitally deaf and hard-of-hearing (DHH) newborns at birth allows for early intervention and diagnosis which leads to improved speech and language outcomes, depending on the DHH etiology. Recently, compelling evidence has shown that genetic testing in newborn hearing screening (NBHS) positively impacted clinical outcomes. SEQaBOO (SEQuencing a Baby for an Optimal Outcome) is a program at Harvard Medical School evaluating genome sequencing and parental attitudes towards genomic medicine in DHH newborns following a positive NBHS or confirmatory diagnostic audiometry (1 month). SEQaBOO also incorporated optional reporting of ACMG secondary findings v3.0 for parents. While single nucleotide variants and small insertions and deletions (indels) in genes associated with nonsyndromic and syndromic DHH have been reported previously, a collaboration with the Chinese University of Hong Kong then investigated additional chromosomal abnormalities in the genome sequence data. Genome-wide copy number variations were detected from genome sequencing data of SEQaBOO participants using a read-depth-based approach. Structural rearrangements were detected by discordant read pairs. Absence of heterozygosity (AOH) was assessed by the rates of heterozygous genotypes. The additional value and clinical significance of structural variants (SVs) detected were investigated. Among SEQaBOO babies ultimately diagnosed as DHH (n=31), a causative genetic etiology (SNV & indels) was reported previously in 6 babies. The SV detection protocol in 81 families revealed incidental findings in 9 babies. These included one case of XYY syndrome and four cases of inherited heterozygous deletions of STRC and CATSPER2. Biallelic pathogenic variants or contiguous gene deletions across this region are associated with deafness-infertility syndrome. In one family, both parents carried heterozygous deletions of STRC and CATSPER2 and are at risk (1/4) of having affected offspring. Balanced chromosomal translocations were detected in two families who had conceived by IVF following multiple miscarriages. GS results fine mapped the breakpoints of these translocations to the nucleotide level, of which they disrupted three genes including CDK19, DYM, and PHF21B. These findings have implications for subsequent pregnancy management. Extended

regions of absence of heterozygosity (AOH) on two chromosomes were detected in two probands, suggestive of uniparental disomy or remnants of identity by descent, warranting further follow up. SV detection in the genome sequencing data of the SEQaBOO study revealed additional clinically relevant findings. These data and others show the effectiveness of genome sequencing for SV detection in newborns with hearing loss.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Matthew Hoi Kin *	Chau *	The Chinese University of Hong Kong
Calli	Mitchell	Harvard Medical School
Zirui	Dong	The Chinese University of Hong Kong
Ye	Cao	The Chinese University of Hong Kong
Kwong Wai	Choy	The Chinese University of Hong Kong
Jun	Shen	Brigham and Women's Hospital
Sami	Amr	Harvard Medical School
Anne	Giersch	Brigham and Women's Hospital
Cynthia	Morton	Brigham and Women's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Matthew Chau

New Frontiers in Genetic Testing for Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Eliot Shearer

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Symposium Description In this session we will focus on the future of genetic testing for hearing loss. The common theme is the importance of accurate genetic diagnosis in the face of the extreme genetic and phenotypic heterogeneity of hearing loss. Comprehensive genetic testing for hearing loss has become integral in the evaluation of individuals with hearing loss since widespread implementation more than 10 years ago, Accumulated data have shown, in general, a diagnostic rate of about 40-60% depending on clinical characteristics of the population studied. This makes genetic testing the single most effective diagnostic test for evaluation of hearing loss but clearly indicates room for improvement. The past decade has shown the difficulty in implementing these genetic tests and interpreting the testing results. At the same time, our understanding of the clinical phenotypes associated with syndromic forms of hearing loss has expanded and we have identified key avenues for future research to improve our ability to diagnose genetic hearing loss. In this symposium we will discuss reasons and methods for early genetic diagnosis for hearing loss, including integrating genetic screening into the newborn hearing screen. We will discuss the important of considering race and ethnicity when ordering and interpreting genetic testing results. We will then focus on our expanding understanding of the contribution of syndromic hearing loss diagnoses in otherwise non-syndromic hearing loss patients. We will discuss the challenge and importance of correctly interpreting splice site variants. Finally, we will consider the advantages offered by genome sequencing for genetic evaluation of hearing loss, with particular attention to detection of structural variants that cause hearing loss. This symposium will be targeted towards auditory geneticists and clinicians who evaluate individuals with hearing loss.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The proposed panel includes investigators in the early and mid-stages of their careers. Our panel includes members and non-members of ARO to provide broad expertise in the area. The panel members include scientists from the East Coast and West Coast United States as well as Hong Kong.

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature A Eliot Shearer

New Frontiers in Genetic Testing for Hearing Loss

Genetic Testing for Hearing Loss: Early Diagnosis Critical for Best Outcomes

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Eliot Shearer

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Genetic testing for hearing loss is critical for etiologic diagnosis and has become the standard of care in evaluation of children with hearing loss. Hearing loss is the most common disorder identified on the newborn screen in the United States and earlier diagnosis leads to the best speech, language, and quality of life outcomes. Genetic newborn hearing screening is therefore the next frontier in reducing time to genetic diagnosis of hearing loss. This type of hearing screening has been developed, and is currently implemented, at some sites around the world. Early data from these genetic newborn hearing screening programs using targeted panels, exome sequencing, and genome sequencing will be presented. We will discuss progress and barriers towards widespread implementation of genetic newborn hearing screening.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Eliot *	Shearer *	Boston Children's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature A Eliot Shearer

New Frontiers in Genetic Testing for Hearing Loss

Racial and Ethnic Disparities in Genetic Testing for Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Dylan Chan

Affiliation University of California, San Francisco

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Hearing loss is the most common congenital sensory impairment, with 1:500 children born deaf or hard-of-hearing (D/HH). Hearing-loss gene-panel testing (HL-GPT) is the most impactful and effective etiologic test for childhood sensorineural hearing loss (SNHL). Genetic diagnosis for hearing loss informs prognosis, provides early identification of syndromic associations, enables family counseling, and is the foundation for impending gene therapy. Racial/ethnic disparities in hearing-loss genetic testing access and outcomes are enormous: Latino and Black individuals with SNHL are 5 times less likely to receive a genetic diagnosis upon standard clinical HL-GPT compared with Whites and Asians. This difference is connected with a tremendous disparity among the populations that have been included in published hearing-loss genetic studies, with individuals of African or indigenous American genetic ancestry vastly underrepresented compared with their European and Asian counterparts. In this presentation, we will review the impact and extent of racial and ethnic disparities in hearing-loss genetics and genetic testing, and discuss the importance of greater inclusion of underrepresented minority groups in both clinical and research efforts going forward.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Dylan *	Chan *	University of California, San Francisco

Michelle	Florentine	University of California, San Francisco
Jacqueline	Harris	University of California, San Francisco
Stephanie	Rouse	Boston Children's Hospital
Sonia	Scaria	University of California, San Francisco

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Dylan Chan

New Frontiers in Genetic Testing for Hearing Loss

Non-Syndromic Hearing Loss mimics: Beyond Usher and Pendred Syndrome

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Shelby Redfield

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Syndromic hearing loss (SHL) accounts for approximately 30% of genetic diagnoses for pediatric hearing loss (HL) and has important implications for patients and families. Current clinical algorithms for genetic testing do not include all HL phenotypes, such as unilateral and asymmetric HL. Some recent studies suggest that a larger number of SHL genes than was previously appreciated can mimic a nonsyndromic HL phenotype, especially in early childhood. This raises the possibility of underdiagnosis of SHL. We identified cases of nonsyndromic HL mimics with genetic diagnoses of SHL in our pediatric patient population via retrospective chart review. While many SHL patients who presented with apparently isolated HL had Usher or Pendred syndrome, 12 patients with isolated HL received SHL diagnoses for conditions typically associated with additional features in early childhood. Pathogenic variants were identified in 8 genes (MITF, PAX3, SOX10, FGFR3, EYA1, LARS2, KMT2C, and TFAP2A). In some cases, subtle syndromic features were appreciated after genetic diagnosis. A majority of these 12 patients had unilateral or asymmetric HL. Of the 12 diagnoses, 6 had Waardenburg syndrome, 2 subjects had Muenke syndrome, and 1 subject had Kleefstra syndrome type 2, Perrault syndrome type 4, or branchiootorenal syndrome. One patient had isolated unilateral HL and a dual diagnosis of branchiooculofacial syndrome and mosaic chromosome 5p15.33p13.3 gain. Pediatric otolaryngologists are often the first specialist to see a child with subtle SHL after a newborn hearing screen referral. Increased access to comprehensive genetic testing for patients with any hearing loss phenotype within an otolaryngology pracitce will improve SHL diagnosis and facilitate early referral to appropriate specialists, tailored intervention, and improved prognostic and recurrence information for families.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Shelby *	Redfield *	Boston Children's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Shelby Redfield

New Frontiers in Genetic Testing for Hearing Loss

In or Out: The Role of RNA-Splicing in Hereditary Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Kevin Booth

Affiliation Harvard Medical School Dept. Neurobiology

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract RNA-splicing is a highly complex and tightly regulated process. RNA-binding proteins (spliceosome proteins) recognize key nucleotide motifs, which allows for an orchestrated removal of intronic sequences and the formation of messenger RNA (mRNA). DNA variants which alter the highly conserved nucleotide motifs where the spliceosome protein members bind can result in mis-regulation of RNA-splicing and consequently the formation of mutant mRNA. Historically, only variants impacting the highly conserved donor or acceptor splice-sites (+/- 2 base pairs into the intron) have been considered as splice-altering variants. More recently, exonic coding variants and intronic variants (outside the canonical splice-sites), have been implicated in impacting RNA-splicing. Additionally, growing evidence suggests a large number exonic disease-causing variants attenuate wildtype RNA-splicing. Interestingly, not all coding variants that result in mis-splicing, have the same effect and often there are many mutant mRNA transcripts created. Outside the analysis of patient RNA, mini-gene in vitro splicing assays have become the cornerstone of understanding a variants impact on RNA splicing. Understanding a variants effect, is critical to providing an accurate genetic diagnosis. Furthermore, understanding a variants impact on RNA-splicing has important therapeutic implications as defects in RNA-splicing can be corrected using Antisense Oligonucleotides. In this podium session, I highlight the in silco and in vitro workflows of analyzing a variants impact on RNA-splicing and highlight the importance of investigating coding variants impact on RNA-splicing using case studies.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation

Kevin *	Booth *	Harvard Medical School Dept. Neurobiology

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Kevin T Booth

New Frontiers in Genetic Testing for Hearing Loss

Implications of Structural Variations for Hearing Loss Detected in Newborn Genome Sequencing Data.

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Matthew Hoi Kin Chau

Affiliation The Chinese University of Hong Kong

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Genetic screening in congenitally deaf and hard-of-hearing (DHH) newborns at birth allows for early intervention and diagnosis which leads to improved speech and language outcomes, depending on the DHH etiology. Recently, compelling evidence has shown that genetic testing in newborn hearing screening (NBHS) positively impacted clinical outcomes. SEQaBOO (SEQuencing a Baby for an Optimal Outcome) is a program at Harvard Medical School evaluating genome sequencing and parental attitudes towards genomic medicine in DHH newborns following a positive NBHS or confirmatory diagnostic audiometry (1 month). SEQaBOO also incorporated optional reporting of ACMG secondary findings v3.0 for parents. While single nucleotide variants and small insertions and deletions (indels) in genes associated with nonsyndromic and syndromic DHH have been reported previously, a collaboration with the Chinese University of Hong Kong then investigated additional chromosomal abnormalities in the genome sequence data. Genome-wide copy number variations were detected from genome sequencing data of SEQaBOO participants using a read-depth-based approach. Structural rearrangements were detected by discordant read pairs. Absence of heterozygosity (AOH) was assessed by the rates of heterozygous genotypes. The additional value and clinical significance of structural variants (SVs) detected were investigated. Among SEQaBOO babies ultimately diagnosed as DHH (n=31), a causative genetic etiology (SNV & indels) was reported previously in 6 babies. The SV detection protocol in 81 families revealed incidental findings in 9 babies. These included one case of XYY syndrome and four cases of inherited heterozygous deletions of STRC and CATSPER2. Biallelic pathogenic variants or contiguous gene deletions across this region are associated with deafness-infertility syndrome. In one family, both parents carried heterozygous deletions of STRC and CATSPER2 and are at risk (1/4) of having affected offspring. Balanced chromosomal translocations were detected in two families who had conceived by IVF following multiple miscarriages. GS results fine mapped the breakpoints of these translocations to the nucleotide level, of which they disrupted three genes including CDK19, DYM, and PHF21B. These findings have implications for subsequent pregnancy management. Extended

regions of absence of heterozygosity (AOH) on two chromosomes were detected in two probands, suggestive of uniparental disomy or remnants of identity by descent, warranting further follow up. SV detection in the genome sequencing data of the SEQaBOO study revealed additional clinically relevant findings. These data and others show the effectiveness of genome sequencing for SV detection in newborns with hearing loss.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Matthew Hoi Kin *	Chau *	The Chinese University of Hong Kong
Calli	Mitchell	Harvard Medical School
Zirui	Dong	The Chinese University of Hong Kong
Ye	Cao	The Chinese University of Hong Kong
Kwong Wai	Choy	The Chinese University of Hong Kong
Jun	Shen	Brigham and Women's Hospital
Sami	Amr	Harvard Medical School
Anne	Giersch	Brigham and Women's Hospital
Cynthia	Morton	Brigham and Women's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Matthew Chau

New Frontiers in Genetic Testing for Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Eliot Shearer

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Symposium Description In this session we will focus on the future of genetic testing for hearing loss. The common theme is the importance of accurate genetic diagnosis in the face of the extreme genetic and phenotypic heterogeneity of hearing loss. Comprehensive genetic testing for hearing loss has become integral in the evaluation of individuals with hearing loss since widespread implementation more than 10 years ago, Accumulated data have shown, in general, a diagnostic rate of about 40-60% depending on clinical characteristics of the population studied. This makes genetic testing the single most effective diagnostic test for evaluation of hearing loss but clearly indicates room for improvement. The past decade has shown the difficulty in implementing these genetic tests and interpreting the testing results. At the same time, our understanding of the clinical phenotypes associated with syndromic forms of hearing loss has expanded and we have identified key avenues for future research to improve our ability to diagnose genetic hearing loss. In this symposium we will discuss reasons and methods for early genetic diagnosis for hearing loss, including integrating genetic screening into the newborn hearing screen. We will discuss the important of considering race and ethnicity when ordering and interpreting genetic testing results. We will then focus on our expanding understanding of the contribution of syndromic hearing loss diagnoses in otherwise non-syndromic hearing loss patients. We will discuss the challenge and importance of correctly interpreting splice site variants. Finally, we will consider the advantages offered by genome sequencing for genetic evaluation of hearing loss, with particular attention to detection of structural variants that cause hearing loss. This symposium will be targeted towards auditory geneticists and clinicians who evaluate individuals with hearing loss.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The proposed panel includes investigators in the early and mid-stages of their careers. Our panel includes members and non-members of ARO to provide broad expertise in the area. The panel members include scientists from the East Coast and West Coast United States as well as Hong Kong.

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature A Eliot Shearer

New Frontiers in Genetic Testing for Hearing Loss

Genetic Testing for Hearing Loss: Early Diagnosis Critical for Best Outcomes

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Eliot Shearer

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Genetic testing for hearing loss is critical for etiologic diagnosis and has become the standard of care in evaluation of children with hearing loss. Hearing loss is the most common disorder identified on the newborn screen in the United States and earlier diagnosis leads to the best speech, language, and quality of life outcomes. Genetic newborn hearing screening is therefore the next frontier in reducing time to genetic diagnosis of hearing loss. This type of hearing screening has been developed, and is currently implemented, at some sites around the world. Early data from these genetic newborn hearing screening programs using targeted panels, exome sequencing, and genome sequencing will be presented. We will discuss progress and barriers towards widespread implementation of genetic newborn hearing screening.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Eliot *	Shearer *	Boston Children's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature A Eliot Shearer

New Frontiers in Genetic Testing for Hearing Loss

Racial and Ethnic Disparities in Genetic Testing for Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Dylan Chan

Affiliation University of California, San Francisco

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Hearing loss is the most common congenital sensory impairment, with 1:500 children born deaf or hard-of-hearing (D/HH). Hearing-loss gene-panel testing (HL-GPT) is the most impactful and effective etiologic test for childhood sensorineural hearing loss (SNHL). Genetic diagnosis for hearing loss informs prognosis, provides early identification of syndromic associations, enables family counseling, and is the foundation for impending gene therapy. Racial/ethnic disparities in hearing-loss genetic testing access and outcomes are enormous: Latino and Black individuals with SNHL are 5 times less likely to receive a genetic diagnosis upon standard clinical HL-GPT compared with Whites and Asians. This difference is connected with a tremendous disparity among the populations that have been included in published hearing-loss genetic studies, with individuals of African or indigenous American genetic ancestry vastly underrepresented compared with their European and Asian counterparts. In this presentation, we will review the impact and extent of racial and ethnic disparities in hearing-loss genetics and genetic testing, and discuss the importance of greater inclusion of underrepresented minority groups in both clinical and research efforts going forward.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Dylan *	Chan *	University of California, San Francisco

Michelle	Florentine	University of California, San Francisco
Jacqueline	Harris	University of California, San Francisco
Stephanie	Rouse	Boston Children's Hospital
Sonia	Scaria	University of California, San Francisco

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Dylan Chan

New Frontiers in Genetic Testing for Hearing Loss

Non-Syndromic Hearing Loss mimics: Beyond Usher and Pendred Syndrome

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Shelby Redfield

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Syndromic hearing loss (SHL) accounts for approximately 30% of genetic diagnoses for pediatric hearing loss (HL) and has important implications for patients and families. Current clinical algorithms for genetic testing do not include all HL phenotypes, such as unilateral and asymmetric HL. Some recent studies suggest that a larger number of SHL genes than was previously appreciated can mimic a nonsyndromic HL phenotype, especially in early childhood. This raises the possibility of underdiagnosis of SHL. We identified cases of nonsyndromic HL mimics with genetic diagnoses of SHL in our pediatric patient population via retrospective chart review. While many SHL patients who presented with apparently isolated HL had Usher or Pendred syndrome, 12 patients with isolated HL received SHL diagnoses for conditions typically associated with additional features in early childhood. Pathogenic variants were identified in 8 genes (MITF, PAX3, SOX10, FGFR3, EYA1, LARS2, KMT2C, and TFAP2A). In some cases, subtle syndromic features were appreciated after genetic diagnosis. A majority of these 12 patients had unilateral or asymmetric HL. Of the 12 diagnoses, 6 had Waardenburg syndrome, 2 subjects had Muenke syndrome, and 1 subject had Kleefstra syndrome type 2, Perrault syndrome type 4, or branchiootorenal syndrome. One patient had isolated unilateral HL and a dual diagnosis of branchiooculofacial syndrome and mosaic chromosome 5p15.33p13.3 gain. Pediatric otolaryngologists are often the first specialist to see a child with subtle SHL after a newborn hearing screen referral. Increased access to comprehensive genetic testing for patients with any hearing loss phenotype within an otolaryngology pracitce will improve SHL diagnosis and facilitate early referral to appropriate specialists, tailored intervention, and improved prognostic and recurrence information for families.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Shelby *	Redfield *	Boston Children's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Shelby Redfield

New Frontiers in Genetic Testing for Hearing Loss

In or Out: The Role of RNA-Splicing in Hereditary Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Kevin Booth

Affiliation Harvard Medical School Dept. Neurobiology

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract RNA-splicing is a highly complex and tightly regulated process. RNA-binding proteins (spliceosome proteins) recognize key nucleotide motifs, which allows for an orchestrated removal of intronic sequences and the formation of messenger RNA (mRNA). DNA variants which alter the highly conserved nucleotide motifs where the spliceosome protein members bind can result in mis-regulation of RNA-splicing and consequently the formation of mutant mRNA. Historically, only variants impacting the highly conserved donor or acceptor splice-sites (+/- 2 base pairs into the intron) have been considered as splice-altering variants. More recently, exonic coding variants and intronic variants (outside the canonical splice-sites), have been implicated in impacting RNA-splicing. Additionally, growing evidence suggests a large number exonic disease-causing variants attenuate wildtype RNA-splicing. Interestingly, not all coding variants that result in mis-splicing, have the same effect and often there are many mutant mRNA transcripts created. Outside the analysis of patient RNA, mini-gene in vitro splicing assays have become the cornerstone of understanding a variants impact on RNA splicing. Understanding a variants effect, is critical to providing an accurate genetic diagnosis. Furthermore, understanding a variants impact on RNA-splicing has important therapeutic implications as defects in RNA-splicing can be corrected using Antisense Oligonucleotides. In this podium session, I highlight the in silco and in vitro workflows of analyzing a variants impact on RNA-splicing and highlight the importance of investigating coding variants impact on RNA-splicing using case studies.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation

Kevin *	Booth *	Harvard Medical School Dept. Neurobiology

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Kevin T Booth

New Frontiers in Genetic Testing for Hearing Loss

Implications of Structural Variations for Hearing Loss Detected in Newborn Genome Sequencing Data.

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Matthew Hoi Kin Chau

Affiliation The Chinese University of Hong Kong

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Genetic screening in congenitally deaf and hard-of-hearing (DHH) newborns at birth allows for early intervention and diagnosis which leads to improved speech and language outcomes, depending on the DHH etiology. Recently, compelling evidence has shown that genetic testing in newborn hearing screening (NBHS) positively impacted clinical outcomes. SEQaBOO (SEQuencing a Baby for an Optimal Outcome) is a program at Harvard Medical School evaluating genome sequencing and parental attitudes towards genomic medicine in DHH newborns following a positive NBHS or confirmatory diagnostic audiometry (1 month). SEQaBOO also incorporated optional reporting of ACMG secondary findings v3.0 for parents. While single nucleotide variants and small insertions and deletions (indels) in genes associated with nonsyndromic and syndromic DHH have been reported previously, a collaboration with the Chinese University of Hong Kong then investigated additional chromosomal abnormalities in the genome sequence data. Genome-wide copy number variations were detected from genome sequencing data of SEQaBOO participants using a read-depth-based approach. Structural rearrangements were detected by discordant read pairs. Absence of heterozygosity (AOH) was assessed by the rates of heterozygous genotypes. The additional value and clinical significance of structural variants (SVs) detected were investigated. Among SEQaBOO babies ultimately diagnosed as DHH (n=31), a causative genetic etiology (SNV & indels) was reported previously in 6 babies. The SV detection protocol in 81 families revealed incidental findings in 9 babies. These included one case of XYY syndrome and four cases of inherited heterozygous deletions of STRC and CATSPER2. Biallelic pathogenic variants or contiguous gene deletions across this region are associated with deafness-infertility syndrome. In one family, both parents carried heterozygous deletions of STRC and CATSPER2 and are at risk (1/4) of having affected offspring. Balanced chromosomal translocations were detected in two families who had conceived by IVF following multiple miscarriages. GS results fine mapped the breakpoints of these translocations to the nucleotide level, of which they disrupted three genes including CDK19, DYM, and PHF21B. These findings have implications for subsequent pregnancy management. Extended

regions of absence of heterozygosity (AOH) on two chromosomes were detected in two probands, suggestive of uniparental disomy or remnants of identity by descent, warranting further follow up. SV detection in the genome sequencing data of the SEQaBOO study revealed additional clinically relevant findings. These data and others show the effectiveness of genome sequencing for SV detection in newborns with hearing loss.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Matthew Hoi Kin *	Chau *	The Chinese University of Hong Kong
Calli	Mitchell	Harvard Medical School
Zirui	Dong	The Chinese University of Hong Kong
Ye	Cao	The Chinese University of Hong Kong
Kwong Wai	Choy	The Chinese University of Hong Kong
Jun	Shen	Brigham and Women's Hospital
Sami	Amr	Harvard Medical School
Anne	Giersch	Brigham and Women's Hospital
Cynthia	Morton	Brigham and Women's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Matthew Chau

New Frontiers in Genetic Testing for Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Eliot Shearer

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Symposium Description In this session we will focus on the future of genetic testing for hearing loss. The common theme is the importance of accurate genetic diagnosis in the face of the extreme genetic and phenotypic heterogeneity of hearing loss. Comprehensive genetic testing for hearing loss has become integral in the evaluation of individuals with hearing loss since widespread implementation more than 10 years ago, Accumulated data have shown, in general, a diagnostic rate of about 40-60% depending on clinical characteristics of the population studied. This makes genetic testing the single most effective diagnostic test for evaluation of hearing loss but clearly indicates room for improvement. The past decade has shown the difficulty in implementing these genetic tests and interpreting the testing results. At the same time, our understanding of the clinical phenotypes associated with syndromic forms of hearing loss has expanded and we have identified key avenues for future research to improve our ability to diagnose genetic hearing loss. In this symposium we will discuss reasons and methods for early genetic diagnosis for hearing loss, including integrating genetic screening into the newborn hearing screen. We will discuss the important of considering race and ethnicity when ordering and interpreting genetic testing results. We will then focus on our expanding understanding of the contribution of syndromic hearing loss diagnoses in otherwise non-syndromic hearing loss patients. We will discuss the challenge and importance of correctly interpreting splice site variants. Finally, we will consider the advantages offered by genome sequencing for genetic evaluation of hearing loss, with particular attention to detection of structural variants that cause hearing loss. This symposium will be targeted towards auditory geneticists and clinicians who evaluate individuals with hearing loss.

Young Investigator Attestation I and the majority of my participants are within 10 years of receiving a PhD.

Presenter Diversity The proposed panel includes investigators in the early and mid-stages of their careers. Our panel includes members and non-members of ARO to provide broad expertise in the area. The panel members include scientists from the East Coast and West Coast United States as well as Hong Kong.

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature A Eliot Shearer

New Frontiers in Genetic Testing for Hearing Loss

Genetic Testing for Hearing Loss: Early Diagnosis Critical for Best Outcomes

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Eliot Shearer

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Genetic testing for hearing loss is critical for etiologic diagnosis and has become the standard of care in evaluation of children with hearing loss. Hearing loss is the most common disorder identified on the newborn screen in the United States and earlier diagnosis leads to the best speech, language, and quality of life outcomes. Genetic newborn hearing screening is therefore the next frontier in reducing time to genetic diagnosis of hearing loss. This type of hearing screening has been developed, and is currently implemented, at some sites around the world. Early data from these genetic newborn hearing screening programs using targeted panels, exome sequencing, and genome sequencing will be presented. We will discuss progress and barriers towards widespread implementation of genetic newborn hearing screening.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Eliot *	Shearer *	Boston Children's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature A Eliot Shearer

New Frontiers in Genetic Testing for Hearing Loss

Racial and Ethnic Disparities in Genetic Testing for Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Dylan Chan

Affiliation University of California, San Francisco

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Hearing loss is the most common congenital sensory impairment, with 1:500 children born deaf or hard-of-hearing (D/HH). Hearing-loss gene-panel testing (HL-GPT) is the most impactful and effective etiologic test for childhood sensorineural hearing loss (SNHL). Genetic diagnosis for hearing loss informs prognosis, provides early identification of syndromic associations, enables family counseling, and is the foundation for impending gene therapy. Racial/ethnic disparities in hearing-loss genetic testing access and outcomes are enormous: Latino and Black individuals with SNHL are 5 times less likely to receive a genetic diagnosis upon standard clinical HL-GPT compared with Whites and Asians. This difference is connected with a tremendous disparity among the populations that have been included in published hearing-loss genetic studies, with individuals of African or indigenous American genetic ancestry vastly underrepresented compared with their European and Asian counterparts. In this presentation, we will review the impact and extent of racial and ethnic disparities in hearing-loss genetics and genetic testing, and discuss the importance of greater inclusion of underrepresented minority groups in both clinical and research efforts going forward.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Dylan *	Chan *	University of California, San Francisco

Michelle	Florentine	University of California, San Francisco
Jacqueline	Harris	University of California, San Francisco
Stephanie	Rouse	Boston Children's Hospital
Sonia	Scaria	University of California, San Francisco

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Dylan Chan

New Frontiers in Genetic Testing for Hearing Loss

Non-Syndromic Hearing Loss mimics: Beyond Usher and Pendred Syndrome

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Shelby Redfield

Affiliation Boston Children's Hospital

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Syndromic hearing loss (SHL) accounts for approximately 30% of genetic diagnoses for pediatric hearing loss (HL) and has important implications for patients and families. Current clinical algorithms for genetic testing do not include all HL phenotypes, such as unilateral and asymmetric HL. Some recent studies suggest that a larger number of SHL genes than was previously appreciated can mimic a nonsyndromic HL phenotype, especially in early childhood. This raises the possibility of underdiagnosis of SHL. We identified cases of nonsyndromic HL mimics with genetic diagnoses of SHL in our pediatric patient population via retrospective chart review. While many SHL patients who presented with apparently isolated HL had Usher or Pendred syndrome, 12 patients with isolated HL received SHL diagnoses for conditions typically associated with additional features in early childhood. Pathogenic variants were identified in 8 genes (MITF, PAX3, SOX10, FGFR3, EYA1, LARS2, KMT2C, and TFAP2A). In some cases, subtle syndromic features were appreciated after genetic diagnosis. A majority of these 12 patients had unilateral or asymmetric HL. Of the 12 diagnoses, 6 had Waardenburg syndrome, 2 subjects had Muenke syndrome, and 1 subject had Kleefstra syndrome type 2, Perrault syndrome type 4, or branchiootorenal syndrome. One patient had isolated unilateral HL and a dual diagnosis of branchiooculofacial syndrome and mosaic chromosome 5p15.33p13.3 gain. Pediatric otolaryngologists are often the first specialist to see a child with subtle SHL after a newborn hearing screen referral. Increased access to comprehensive genetic testing for patients with any hearing loss phenotype within an otolaryngology pracitce will improve SHL diagnosis and facilitate early referral to appropriate specialists, tailored intervention, and improved prognostic and recurrence information for families.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Shelby *	Redfield *	Boston Children's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Shelby Redfield

New Frontiers in Genetic Testing for Hearing Loss

In or Out: The Role of RNA-Splicing in Hereditary Hearing Loss

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Kevin Booth

Affiliation Harvard Medical School Dept. Neurobiology

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract RNA-splicing is a highly complex and tightly regulated process. RNA-binding proteins (spliceosome proteins) recognize key nucleotide motifs, which allows for an orchestrated removal of intronic sequences and the formation of messenger RNA (mRNA). DNA variants which alter the highly conserved nucleotide motifs where the spliceosome protein members bind can result in mis-regulation of RNA-splicing and consequently the formation of mutant mRNA. Historically, only variants impacting the highly conserved donor or acceptor splice-sites (+/- 2 base pairs into the intron) have been considered as splice-altering variants. More recently, exonic coding variants and intronic variants (outside the canonical splice-sites), have been implicated in impacting RNA-splicing. Additionally, growing evidence suggests a large number exonic disease-causing variants attenuate wildtype RNA-splicing. Interestingly, not all coding variants that result in mis-splicing, have the same effect and often there are many mutant mRNA transcripts created. Outside the analysis of patient RNA, mini-gene in vitro splicing assays have become the cornerstone of understanding a variants impact on RNA splicing. Understanding a variants effect, is critical to providing an accurate genetic diagnosis. Furthermore, understanding a variants impact on RNA-splicing has important therapeutic implications as defects in RNA-splicing can be corrected using Antisense Oligonucleotides. In this podium session, I highlight the in silco and in vitro workflows of analyzing a variants impact on RNA-splicing and highlight the importance of investigating coding variants impact on RNA-splicing using case studies.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation

Kevin *	Booth *	Harvard Medical School Dept. Neurobiology

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Kevin T Booth

New Frontiers in Genetic Testing for Hearing Loss

Implications of Structural Variations for Hearing Loss Detected in Newborn Genome Sequencing Data.

Submission ID 3003157

Submission Type Young Investigator Symposia

Topic Genetics A: Genomics and Gene Regulation

Status Submitted

Submitter Matthew Hoi Kin Chau

Affiliation The Chinese University of Hong Kong

Participant(s) Eliot Shearer (Chair), Dylan Chan (Presenter), Shelby Redfield (Presenter), Kevin Booth (Presenter), Matthew Hoi Kin Chau (Presenter), Eliot Shearer (Presenter)

SUBMISSION DETAILS

Individual Abstract Genetic screening in congenitally deaf and hard-of-hearing (DHH) newborns at birth allows for early intervention and diagnosis which leads to improved speech and language outcomes, depending on the DHH etiology. Recently, compelling evidence has shown that genetic testing in newborn hearing screening (NBHS) positively impacted clinical outcomes. SEQaBOO (SEQuencing a Baby for an Optimal Outcome) is a program at Harvard Medical School evaluating genome sequencing and parental attitudes towards genomic medicine in DHH newborns following a positive NBHS or confirmatory diagnostic audiometry (1 month). SEQaBOO also incorporated optional reporting of ACMG secondary findings v3.0 for parents. While single nucleotide variants and small insertions and deletions (indels) in genes associated with nonsyndromic and syndromic DHH have been reported previously, a collaboration with the Chinese University of Hong Kong then investigated additional chromosomal abnormalities in the genome sequence data. Genome-wide copy number variations were detected from genome sequencing data of SEQaBOO participants using a read-depth-based approach. Structural rearrangements were detected by discordant read pairs. Absence of heterozygosity (AOH) was assessed by the rates of heterozygous genotypes. The additional value and clinical significance of structural variants (SVs) detected were investigated. Among SEQaBOO babies ultimately diagnosed as DHH (n=31), a causative genetic etiology (SNV & indels) was reported previously in 6 babies. The SV detection protocol in 81 families revealed incidental findings in 9 babies. These included one case of XYY syndrome and four cases of inherited heterozygous deletions of STRC and CATSPER2. Biallelic pathogenic variants or contiguous gene deletions across this region are associated with deafness-infertility syndrome. In one family, both parents carried heterozygous deletions of STRC and CATSPER2 and are at risk (1/4) of having affected offspring. Balanced chromosomal translocations were detected in two families who had conceived by IVF following multiple miscarriages. GS results fine mapped the breakpoints of these translocations to the nucleotide level, of which they disrupted three genes including CDK19, DYM, and PHF21B. These findings have implications for subsequent pregnancy management. Extended

regions of absence of heterozygosity (AOH) on two chromosomes were detected in two probands, suggestive of uniparental disomy or remnants of identity by descent, warranting further follow up. SV detection in the genome sequencing data of the SEQaBOO study revealed additional clinically relevant findings. These data and others show the effectiveness of genome sequencing for SV detection in newborns with hearing loss.

Enter all co-authors. You may search for any co-authors by using the search box. If you cannot find a co-author in this database, you may type them into the grid below. Please use the arrows to move authorship into the correct order. This is the order that will be printed in any program materials.

* Presenting Author

First Name	Last Name	Affiliation
Matthew Hoi Kin *	Chau *	The Chinese University of Hong Kong
Calli	Mitchell	Harvard Medical School
Zirui	Dong	The Chinese University of Hong Kong
Ye	Cao	The Chinese University of Hong Kong
Kwong Wai	Choy	The Chinese University of Hong Kong
Jun	Shen	Brigham and Women's Hospital
Sami	Amr	Harvard Medical School
Anne	Giersch	Brigham and Women's Hospital
Cynthia	Morton	Brigham and Women's Hospital

In-Person Participation I intend to participate in the MidWinter Meeting in-person for the entirety of the scheduled meeting.

Video Consent & Release of Rights I have read and agree to the above terms and conditions. My presentation can be recorded and available post the conclusion of the 2023 MidWinter Meeting for 2 weeks or 14 days.

Signature Matthew Chau