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National Institutes of Health
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Re: 1 K18 DC014289-01

Dear members of the NDCD Advisory Council:

We would like to thank the reviewers for their enthusiastic support of the application and for the critique and helpful comments of the K18 application "Genetic causes as co-factors in cytomegalovirus-associated hearing loss." This letter is intended to address the weaknesses cited by the reviewers in the summary statement. Overall, all three reviewers were enthusiastic about the strengths of the application including the candidate, mentorship plan, training plan and the letters of support. Reviewers also felt that the proposed training and research plan fits in nicely with the applicant's current research on hearing loss in children with congenital CMV infection.

Critique 1Research Plan

"Small sample set (acknowledged by the investigator)."

The overarching objective of this K18 proposal is for the PI to to acquire advanced scientific knowledge and tools in the field of genetics, focusing on hearing loss in children. This application takes advantage of the availability of the patient population and specimens from the ongoing CHIMES study to conduct a pilot study to determine the role of genetic factors in CMV-associated hearing loss. The plan is to collect specimens from children participating in the CHIMES at the UAB study site. Although the number of samples to be analyzed is small, the results of the pilot study will be the basis for a more definitive larger study that includes children with congenital CMV infection identified and followed at the other CHIMES study sites.

"Genetic interpretation is not well documented and there is no clear description of how the WES data will be analyzed."

Ongoing work in the Morton lab and at the Broad Institute is focused on producing a highly accurate profile of pathogenic variation(s) in individuals with hearing loss, while producing a standardized pipeline for data generation and analysis. Analytical sophistication and bioinformatic expertise available at BWH and the Broad will be a distinct asset to this application. The Morton lab and the Broad have developed a solution-based approach to targeted sequencing, referred to as Hybrid Selection that has become the industry standard for whole exome sequencing (WES), as well as an automated pipeline optimized for high

performance and fast turnaround. The submissions pipeline automatically sends raw read data or BAM files to NCBI (or other repositories). The production pipeline aligns reads, produces BAM files, performs quality recalibration and indel realignment, marks duplicate reads, confirms sample identity by checking genetic fingerprints, checks for sample contamination, assesses GC bias, and generates data-quality metrics as feedback for process improvement. The toolkit provides further support for key data manipulation steps (sorting, indexing, merging, format conversion, validation). It includes Java implementation of SAM and BAM file formats (which we developed) and tools for these formats. It is publicly available and has had over 11,000 downloads. A high-performance visualization tool (IGV) was developed for exploration of integrated data sets which a wide variety of data types, including sequence alignments, variations, microarray data and genome annotations. IGV is publicly available with more than 10,000 registered users. Innovations in massively parallel sequencing can enable detection of SV by leveraging the information within the inserts between paired-end reads.

Critique 2

Candidate:

"It is unclear how the PI will maintain oversight of his ongoing work during his six-month stints at the Morton laboratory."

Several of the current projects (HHS-N-263-2012-00010-C, 1U01DD000922, HYKS Institute) of which the applicant is the PI are scheduled to end in December 2014. Therefore, the total effort on currently funded projects will be 3.96 calendar months beginning January 2015. During the 6-month sabbatical in the Morton laboratory, PI's responsibilities as a co-investigator on ongoing projects will be transferred to other members of the investigative team after discussions with the PIs of those projects. The two pending applications (1 U01 AI115635-01, 1 R21 HD083011-01) are multiple-PI applications allowing the transfer of those responsibilities to other PIs and co-investigators as needed.

Career Development Plan:

"Are the didactic courses unique and do they have to be undertaken at the sabbatical institution? If similar courses were available at the home institution, the PI could focus more time on laboratory work during his sabbatical stints."

As recommended, didactic courses will be undertaken at UAB whenever possible. These will include GBS 724 (Principles of Genetics) during the fall 2014, GBS 722 (GGS Bioinformatics) during spring 2015 and GBS 727 (Advanced Human Genomics) during the spring 2016. These will be in the place of GEN 202 (Human Genetics) and BIO 508 (Genomic Data Manipulation) at BWH that were included in the application.

Research Plan:

"It may be complicated for the PI to maintain his current research load at his home institution and focus on new work at the sabbatical institution during the two 6-month spans."

Please see the response above to the first comment by reviewer #2.

Critique 3:

Research Plan:

"The specific features to be extracted from the whole genome and whole exome analyses are not well elaborated. In particular, there is limited discussion of the computational strategies used to associate genomic and exomi polymorphisms with hearing deficits."

Please see the above response to the comment by reviewer #1.

Budget and Period of Support:

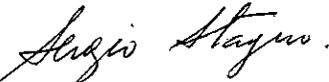
"There is some concern whether sufficient time is allocated. The PI's total commitment of 6 calendar months corresponds to 6 months in the Morton lab. Will there be sufficient research time during the two 6-month stints at home institution to continue these analyses as described?"

UAB has pledged institutional support to the PI in pursuing the proposed career enhancement activities described in the application. Dr. Stagno, Chair, Department of Pediatrics at UAB has agreed to provide the applicant with the needed support to continue training and research activities as part of the K18 mechanism during the 6-month blocks at UAB.

Thank you for this opportunity to respond to the reviewers comments of this K18 application.

Sincerely,


Suresh Boppana, MD
Professor of Pediatrics and Microbiology
UAB Pediatric Infectious Diseases


Sergio Stagno, MD
Katharine Reynolds Ireland
Distinguished Professor and Chair
UAB Department of Pediatrics

Candidate's Background

The candidate, Dr. Boppana, is a pediatric infectious disease clinician and investigator who has been committed to an academic career studying congenital CMV infections (cCMV) and CMV-associated sensorineural hearing loss (SNHL) over the past two decades. His research activities have been focused on understanding the natural history and pathogenesis of maternal and congenital CMV infections and SNHL as a consequence of cCMV. His current focus is to define the contribution of cCMV to overall SNHL in children, identify predictors, and to understand better the pathogenesis of CMV-associated SNHL, which is poorly understood. He is interested in understanding whether genetics play a role in SNHL in children with congenital CMV infection and therefore, motivated in acquiring advanced training and skills necessary to address questions related to genetic basis of hearing loss. Through the K18 award, he seeks to complement this training by acquiring advanced skills in molecular genetics by undertaking a sabbatical in Dr. Cynthia Morton's laboratory at Brigham and Women's Hospital and participating in various didactic and other learning opportunities outlined below. This formal didactic training as well as hands-on experience in Dr. Morton's laboratory will provide him with the necessary tools to expand and enhance his research capabilities.

Dr. Boppana completed his medical education at the Guntur Medical College and pediatric training at the Andhra Medical College, Visakhapatnam, India. He came to the United States for specialty training and undertook a 2nd residency in Pediatrics at the University of Medicine and Dentistry of New Jersey Robert Wood Johnson Medical School where he also served as the chief resident. Dr. Boppana was always interested in infectious diseases and immunology and this interest led him to seek fellowship training in Allergy and Immunology at the University of California, San Francisco. The desire to combine his immunology training with infectious diseases brought him to UAB for additional training in pediatric infectious diseases. During this 2nd fellowship, he elected to work with Dr. Bill Britt, a leading herpesvirologist and an authority in CMV biology, for advanced virology training and began his work in the area of maternal and congenital CMV infections. He received support from the "Dixon Foundation" during his infectious disease training. He has devoted his scientific career to define the disease burden from cCMV infection especially, CMV-associated SNHL in children, identifying early predictors and to prevent or reduce the burden of this disability. Dr. Boppana has made significant contributions to the field over the past two decades, and continues to actively investigate this area.

Dr. Boppana is a successful academic investigator in clinical and translational research with a proven track record of extramural funding and scholarly contributions. Beginning with his K08 award from NIDCD during his postdoctoral training in pediatric infectious disease, Dr. Boppana has been successful in maintaining extramural funding from the NIH over the past 20 years. In addition, he serves as a co-investigator for several NIH-funded projects. He is currently the PI of a large, multicenter NIDCD-sponsored study to define the natural history of CMV-associated SNHL, determine the contribution of CMV-associated hearing loss to overall hearing loss in infants and children, and to develop methodologies that can be adapted for large-scale newborn CMV screening (CMV and Hearing Multicenter Screening Study or CHIMES study, HHS-N-260-2005-00008-C). For this project, he has assembled a large team of investigators at UAB and six other U.S. academic medical centers. Further demonstration of his ability to develop productive collaborative relationships with investigators from a variety of institutions is provided by his studies in India, Brazil, Finland and South Africa. Dr. Boppana has also mentored postdoctoral fellows in pediatrics as well as high school, undergraduate and medical student-level trainees, providing guidance in translational and clinical research projects. He served as a member of the Communication Disorders Review Committee, the NIDCD institutional review committee, for a four-year term and served as an ad-hoc reviewer for a number of NIH study sections. The following are some of Dr. Boppana's contributions and accomplishments in the area of cCMV and CMV-associated hearing loss:

- Defined the characteristics of newborn disease in a large cohort of infants with symptomatic cCMV (Boppana et al. *Pediatr Infect Dis J*, 1992).
- Described the modified rapid culture assay that can be used to test a large number of newborn urine specimens (Boppana et al. *J Clin Microbiol*, 1992).
- Demonstrated that tegument proteins of CMV, pp65 and pp150, are the major immunodominant cytotoxic T-cell targets in seropositive individuals. This study was the first to describe important targets for CMV-specific CD8 T-cell responses (Boppana and Britt, *Virology*, 1996).

- Demonstrated that congenitally infected children born to women with non-primary maternal CMV infections can also experience symptomatic infection and newborn disease (Boppana et al. Pediatrics, 1999) and hearing loss (Ross et al. J Pediatr, 2006). These findings have challenged the long-held dogma that prevention of primary maternal infections alone can significantly reduce the burden of cCMV and led a reexamination of vaccine development strategies to prevent or reduce the number of children with neurologic sequelae due to cCMV.
- Documented that CMV reinfections occur frequently in seropositive women and such reinfections can lead to intrauterine transmission of CMV, newborn disease, and hearing loss, challenging the long-standing belief that CMV reinfections are inconsequential and do not lead to intrauterine transmission and newborn disease (Boppana et al. N Engl J Med, 2001). Although controversial at that time, the concept of CMV reinfections and the importance of non-primary maternal infections are now accepted by the wider scientific community.
- Provided evidence from a large prospective multicenter newborn screening study that real-time PCR of dried blood spots from neonates is insufficiently sensitive to detect the majority of CMV-infected newborns (Boppana et al. JAMA 2010).
- Developed a high throughput real-time PCR assay to test newborn saliva specimens for CMV that is adaptable for screening large numbers of newborns for CMV (Boppana, N Engl J Med, 2011).
- Demonstrated extensive genetic diversity among CMV strains in individuals infected with CMV including congenitally infected infants (Novak et al. J Clin Microbiol, 2008; Ross et al. J Infect Dis, 2011; Pati et al. Pediatr Infect Dis, 2013).
- Interim findings from the CHIMES study: The ongoing CHIMES study is expected to provide reliable estimates of the prevalence of congenital CMV infection and CMV-associated hearing loss in different racial and ethnic groups. Results from the CHIMES study on prevalence and natural history of CMV-associated hearing loss and the contribution of congenital CMV infection to overall hearing loss in children are expected to have a major clinical impact by demonstrating the importance of congenital CMV infection in childhood hearing loss and determining whether universal newborn CMV screening is warranted as a public health policy.
 - Significantly higher prevalence of cCMV in non-Hispanic black infants (0.99%) compared to non-Hispanic white (0.28%), Hispanic white (0.30%) and Asian infants (0.14%).
 - Significantly more CMV-infected infants (7.1%) did not pass their newborn hearing screen (NHS) compared with only 0.9% of CMV-negative babies. Among cCMV infants, 64% of those who did not pass NHS had SNHL and 3.3% of those who passed their hearing screening.
 - Overall, 7.6% (35/462) of CMV-infected cohort in the CHIMES had SNHL at birth.

Dr. Boppana has secured commitment from the leaders of the Division of Infectious Diseases and the Department of Pediatrics at UAB and the Department of Obstetrics and Gynecology at BWH to support his proposed training plan that includes a sabbatical in Dr. Cynthia Morton's laboratory at BWH and participating in various didactic and other learning opportunities. His experiences and accomplishments outlined above demonstrate Dr. Boppana' level of commitment and dedication to continued pursuit in enhancing his academic career.

Career Goals and objectives

The **long-term career goal** of Dr. Boppana is to refocus his investigative career to the study of genetic basis of hearing loss in children with cCMV and children with non-syndromic deafness. Support through the K18 mechanism will be instrumental to accomplish this goal by providing protected time for a sabbatical in Dr. Morton's laboratory at BWH and obtain advanced training in molecular genetics to supplement his existing research skills.

Specific **objectives** of this proposal include:

1. Strengthen the candidate's knowledge and skills in molecular genetics and the genetic basis of hearing loss.
2. Obtain advanced didactic training in molecular genetics and bioinformatics.
3. Conduct a study to determine whether genetic co-factors are present in CMV-associated hearing loss by analyzing a subset of samples (peripheral blood and dried blood spots) from the cohort participating in the ongoing CHIMES study.
4. Continue to make scholarly contributions in the area of CMV-associated deafness.
5. Develop collaborations and seek extramural funding to carry out studies to elucidate mechanisms of CMV-associated hearing loss.

The completion of these objectives will equip Dr. Boppana with the skills necessary to compete and obtain independent funding in the study of the genetics of hearing loss and to make significant contributions to the field. Equally important is his longer-term objective of organizing and developing a comprehensive hearing research program at UAB.

Career Development Activities during Award Period

In order to achieve Dr. Boppana's short- and long-term objectives, he constructed a career development plan with the help of the mentoring team to address the following needs:

- The need for advanced hands-on training and experience in molecular genetics.
- The need for didactic training in cutting-edge molecular genetic concepts and technologies.
- The need for additional training in bioinformatics required to analyze the large amounts of data generated from whole genome sequencing and other high-throughput molecular genetic protocols.
- The need to develop collaborations with established investigators and experts in the field.

The objectives and plans to achieve the above needs include hands-on laboratory experience and focused didactic component in both years 1 and 2. As summarized in **Table 1**, the candidate will participate in focused educational activities (seminars and workshops at BWH and the Broad Institute, lab meetings and selected lectures) during the sabbatical. The plans to achieve the objectives are outlined below and are designed to address the corresponding needs listed.

The candidate plans to devote two six-month blocks over a period of two years in the laboratory of Dr. Morton at the Brigham and Women's Hospital (BWH). The BWH/Partners HealthCare System and other Harvard-affiliated institutions provide a rich scientific environment full of opportunities that help enhance the training and develop interdisciplinary collaborations. Coupled with international scientific meetings in genetics and hearing, these programs help the candidate to interact and share research ideas and findings. Activities listed below are planned as part of the training associated with this award:

Didactic and Other Structured Learning Activities:

GEN 202. Human Genetics (Appendix #1): This weekly three-hour course provides a comprehensive examination of human inheritance and the principles of human genetics applied to disease gene identification. The course is divided between lectures and class discussion, allowing students to learn and discuss the most recent advances in human genetics.

BIO 508. Genomic Data Manipulation (Appendix #2): This twice-weekly 90-minute course introduces the candidate to genomic data, computational methods for interpreting these data and current functional genomics research. The course covers biologic data processing, programming for large datasets, and high-throughput data allowing students to become familiar with basic concepts of genomic data manipulation.

BMI 714. Introduction to Next-Generation Sequencing: Methods, Analysis, and Applications (Appendix #3): This course focuses on technical, computational, algorithmic and biomedical knowledge databases, genetic variant information systems, and ontology and related resources and tools to conduct practical genome-wide analysis, annotation and interpretation of next-generation sequencing (NGS) data.

Primer on Medical and Population Genetics (MPG, Appendix #4): This semester-long seminar series at the Broad Institute includes informal discussions by leading experts in the field and offers an in-depth introduction to many genetic concepts, current and cutting edge methods, and analysis.

The Broad Institute's Medical and Population Genetics Seminar (weekly): This seminar series brings together researchers from multiple Boston area institutions, as well as guest lecturers from around the world, to present the most recent work in small and large scale medical genetics research. This series will offer a forum to discuss clinical aspects of research, methods, techniques, and results.

Harvard Medical School's Department of Genetics Seminar (weekly): This departmental seminar series focuses on basic research ranging from evolutionary to epigenetic research. This series will also offer a platform for the exchange of current ideas in basic genetic research.

Molecular Biology of the Inner Ear Seminar Series (monthly): This seminar series brings together leading experts in all aspects of hearing research with topics ranging from molecular to medical, from sound to speech.

The Developmental Genome Anatomy Project (DGAP) Meeting (monthly): This meeting is a multi-center gathering of PI's and staff involved in DGAP, where investigators exchange updated results on DGAP patients and findings on the underlying genome structure of these cases.

BWH Biomedical Research Institute Interdisciplinary Workshops (quarterly): These workshops present a wide range of research activities ongoing at BWH and other surrounding research institutions. Attending these workshops will help expose the candidate to ideas and techniques that are relevant for this project.

American Society of Human Genetics (ASHG) and Association for Research in Otolaryngology (ARO) Meetings: These annual meetings bring together researchers to share their most recent findings in human genetics and otolaryngology, respectively. These scientific meetings present the opportunity to speak with researchers, from established experts to newest graduate students, and learn latest findings in the field allowing Dr. Boppana to present results, get feedback, and develop collaborations.

Objective 1: Strengthen candidate's knowledge and skills in molecular genetics and the genetic basis of hearing loss. Dr. Boppana will complete the following coursework, hands-on laboratory experiences and other learning activities to obtain advanced training in molecular genetics.

- Hands-on Laboratory Experience: During the 1st six-month period, the candidate will spend most of his time (except for attending course work and seminars) in the laboratory to become familiar with methodologies including comparative genomic hybridization, jumping libraries and genome sequencing (WES and WGS).
- GEN 202. Human Genetics: This weekly three-hour course provides the candidate with a comprehensive understanding of human inheritance, principles of human genetics and disease gene identification and the most recent advances in human genetics.
- BIO 508. Genomic Data Manipulation: This twice-weekly 90-minute course introduces the candidate to genomic data and computational methods for interpreting these data.
- Additional activities will include journal clubs, seminars and workshops at BWH, the Broad Institute, monthly DGAP and weekly lab meetings, and molecular biology of the inner ear seminar series organized by the Boston hearing research groups. The candidate will also attend ARO and ASHG annual meetings.
- The candidate will spend time with co-mentor, Dr. Kenna who is a pediatric otolaryngologist and an expert in the evaluation and management of hearing loss in children during the 2nd six-month block. This will provide Dr. Boppana with a better understanding of the clinical and laboratory protocols and practical clinical and ethical aspects of genetic evaluation/counseling of children/families with hearing loss.

Objective 2: Obtain advanced didactic training in molecular genetics and bioinformatics.

Although Dr. Boppana is well versed with basic biostatistics and study design, he recognizes the need for a more in-depth knowledge of statistical and bioinformatic methods pertaining to manipulation of genomic data. He will participate in the following courses and seminars to obtain the training:

- BIO 508 Genomic Data Manipulation as described above.
- BMI 714. Introduction to Next-Generation Sequencing: Methods, Analysis, and Applications. Participating in this course allows the candidate to understand and learn technical, computational, algorithmic and biomedical knowledge databases, genetic variant information systems, and related resources and tools to conduct practical genome-wide analysis, annotation and interpretation of NGS data.
- Other activities: The Broad Institute's MPG primer and the weekly MPG seminar series, HMS Department of Genetics Seminar and the monthly DGAP Meeting. The candidate will spend 3-4 weeks during the 2nd six-month block in the CLIA-certified Partners HealthCare System Laboratory for Molecular Medicine with Drs. Rehm and Shen to learn the technical and bioinformatics aspects of WGS as a clinical service.

Objective 3: Determine the genetic basis of CMV-associated hearing loss.

This will be accomplished by analyzing a subset of samples (peripheral blood and dried blood spots) from children participating in the ongoing CHIMES study as described in the Research Plan section. Having access to a well-characterized cohort of children with cCMV and the availability of the technical expertise in Boston during the sabbatical ensures the success of the project. In addition, this study will provide the candidate with very helpful hands-on experience in whole genome analysis and interpretation of the data.

Objective 4: Obtain mentored training for career enhancement from experienced, senior scientists.

The mentoring team will consist of Dr. Cynthia Morton as the primary mentor and Drs. Heidi Rehm, Jun Shen, and Margaret Kenna as co-mentors.

Primary Mentor: Dr. Cynthia C. Morton, William Lambert Richardson Professor of Obstetrics, Gynecology and Reproductive Biology and Pathology at Harvard Medical School. Dr. Morton's research interests are in molecular cytogenetics, hereditary deafness, genetics of uterine leiomyomata, and approaches to gene discovery for developmental disorders. Morton is currently funded by NIDCD, NICHD and NIGMS of the National Institutes of Health. Her laboratory has contributed to the development of diagnostic testing for chromosome studies that cross the lifespan including pre-implantation and prenatal diagnostics, perinatal and childhood studies in the evaluation of congenital and developmental disorders, infertility and pregnancy loss studies. Dr. Morton has an outstanding mentoring record and trained 10 pre-doctoral and 24 post-doctoral level trainees. The training plan has been developed with extensive feedback from Dr. Morton. She will take an active role in ensuring that the candidate's training and career development plan is implemented and objectives of the training plan are achieved. Dr. Morton will meet with Dr. Boppana weekly to review the progress and to make sure that the goals of the training program are being met.

Research Support Available

Funding Source	Complete ID Number	Title of Program	PI	Start Date	End Date	Amount
NIH	RO1DC003402	Cloning Genes Involved in Hearing	Morton, C	9/18/08	8/31/13	\$203,643
NIH	PO1GM061354	DGAP: Developmental Genome Anatomy Project	Morton, C	4/1/01	3/31/14	\$1,150,149
NIH	RO1HD060530	Genetic Studies of Uterine Leiomyomata	Morton, C	7/20/10	12/31/15	\$204,000

Sponsor's Previous Fellows/Trainees

Total number of previous predoctoral individuals previously sponsored: 10

Total number of previous postdoctoral individuals previously sponsored: 24

Name	Employer	Title
Charles Lee, Ph.D.	Brigham and Women's Hospital, Boston, MA	Associate Professor of Pathology, HMS; Director of Cytogenetics Core, DF/HCC and Associate Cytogeneticist, BWH
Natalia Leach, Ph.D.	Brigham and Women's Hospital, Boston, MA	Instructor in Pathology, HMS; Cytogeneticist, BWH
Anne Higgins, Ph.D.	UMass Memorial Medical Center, Worcester, MA	Associate Director of Cytogenetics; Assistant Professor in Pathology
Anne Giersch, Ph.D.	Brigham and Women's Hospital, Boston, MA	Assistant Professor of Pathology, HMS; Associate Cytogeneticist, BWH
Bradley Quade, M.D., Ph.D.	Brigham and Women's Hospital, Boston, MA	Associate Professor of Pathology, HMS; Pathologist, BWH

Co-Mentors:

- Dr. Heidi Rehm, Assistant Professor of Pathology, BWH and Harvard Medical School. Dr. Rehm is a board-certified molecular geneticist and directs the CLIA-certified Laboratory for Molecular Medicine at Partners Healthcare. Her lab provides genetic testing at a volume of over 5000 tests per year for a variety of genetic diseases. Dr. Rehm has extensive experience developing genetic tests and interpreting human genetic DNA variation identified during routine genetic testing. Dr. Rehm's laboratory uses NGS on the Illumina HiSeq platform for targeted disease testing and also performs WGS and WES interpretation services both for a clinical service as well as to support the MedSeq project, a NHGRI-funded U01 grant within the Clinical Sequencing Exploratory Research area. Dr. Rehm will provide guidance and support the candidate in developing an understanding the tools required to analyze NGS data.
- Dr. Jun Shen, Instructor of Pathology, BWH. Dr. Shen has recently joined Dr. Morton's laboratory as a junior faculty member and is interested in understanding the genetic basis of developmental disabilities and hearing loss. She also spends some of her time in LMM interpreting genetic testing results. Dr. Shen will be involved in the training plan by providing hands-on technical and intellectual input for the candidate during his time in Dr. Morton's laboratory and in LMM.
- Dr. Margaret Kenna is a leading pediatric otolaryngologist with long-standing interest in childhood deafness. Dr. Kenna will guide the applicant in selecting seminars and workshops to understand better the genetics of hearing loss and reviewing cases. The candidate will also spend time in Dr. Kenna's clinic to understand the evaluation, management and intervention strategies for infants and children with SNHL.

Training Plan (Table 1):

The proposed training plan expands upon the applicant's ongoing research efforts and extends into the field of genetics. The proposed research takes advantage of a cohort of children with cCMV participating in the CHIMES study and the biorepository that contains dried blood spots (DBS) from approximately 90,000 newborns of whom, approximately 400 infants are infected *in-utero* with CMV.

Didactics: Sequencing Techniques and Analyses: The applicant has expertise in virology and immunology and the courses proposed focus on molecular genetics. The two courses (GEN 202 and BIO 508) and the MPG Primer, described above will enhance Dr. Boppana's fundamental understanding in the field of genetics. Although the candidate is familiar with the principles behind some of the commonly used molecular biology techniques, the training plan includes courses and seminars designed to enhance his understanding of the use of the various molecular genetic technologies to investigate the genetic causes of hearing loss. During the first six-month block of sabbatical, the applicant will undertake GEN 202 and BIO 508 courses to gain insight into

the principles of genetics and manipulation of large datasets generated from the high-throughput assays. The course work also includes a laboratory component. Additionally, Dr. Boppana will attend lectures and discussions offered through the Biomedical Research Institute (BRI) at BWH and other forums. These seminars, courses, and workshops will introduce Dr. Boppana to many subjects, presented by experts in the field, which are outside of, but complementary to, the normal course of laboratory work.

Didactics: Bioinformatics: Because manipulation and analysis of large amounts of data generated from the high-throughput assays require bioinformatics knowledge and capability, the BIO 508 course is included in the 1st six-month block. The 2nd six-month period of training includes BMI 714 course in NGS.

TABLE 1. Schedule of various training activities as part of the K18 award

Activity	Year 1						Year 2					
	Jan	Mar	May	July	Sep	Nov	Jan	Mar	May	Jul	Sep	Nov
Molecular Genetics												
GEN 202												
BMI 714												
Bioinformatics												
BIO 598												
Genetics of Hearing Loss												
Hands-on lab experiences												
Training in Responsible Conduct of Research												
GRD 717												
Annual IRB training												
MPG and other seminars												
Research												
Research: Aim 1												
Research: Aim 2												
Scientific Meetings												
ARO												
ASHG												

Methodological Skills: The applicant will spend time in Dr. Morton's laboratory to acquire hands-on experience in carrying out molecular genetic techniques. During the 1st six-month period, the candidate will spend most of his time (except for attending course work and seminars) in the laboratory to become familiar with methodologies including comparative genomic hybridization, jumping libraries and genome sequencing (WES and WGS).

Seminars, Journal Clubs and Scientific Meetings: The applicant will participate in a number of seminars, journal clubs and other activities that will allow him to exchange ideas with the scientific community in the Boston area and in the international community. DGAP's monthly meetings allow the various P.I.'s, clinicians, investigators, and students involved in the project to present their latest findings and discuss the research. In 2005, BWH created the BRI, which focuses on developing research interaction within the hospital. Activities, seminars, workshops, cores, and programs are designed by the BRI to help facilitate this interaction. BWH also has several established connections to other research institutions through Partner's HealthCare System and other Harvard affiliated institutions including the Broad Institute. This community of Boston researchers sponsors many activities that help foster interdisciplinary interaction and inter-institutional collaborations. Dr. Boppana will actively participate in some of these interactions (e.g., seminar series and workshops at the Broad Institute) and will take advantage of the other presented opportunities. The applicant plans to attend the annual American Society of Human Genetics (ASHG) and Association of Researchers in Otolaryngology (ARO) meetings, which will give him the opportunity to present his work to the larger international research communities.

This training plan is designed to extend the candidate's research toolkit beyond his expertise in virology and infectious diseases and to help him venture into a new field of research, the genetics of hearing loss. This training plan is in line with, and supportive of, Dr. Boppana's desire to enhance his academic research career. Upon completion of this training plan, the candidate will have the desired training and solid foundation in molecular genetics and the genetics of hearing loss that will allow him to investigate the phenotype-genotype correlation from gene discovery to molecular pathology and to define the role of genetics in CMV-associated hearing loss. The proposed plan will equip Dr. Boppana with the necessary tools to not only become a well-trained researcher in the field of genetics of hearing but also to enhance the hearing research capacity at UAB.

Specific Aims

Congenital CMV infection (cCMV) is the most frequent intrauterine infection in the post-rubella era and a leading non-genetic cause of sensorineural hearing loss (SNHL) in children worldwide prompting the Institute of Medicine to rank the development CMV vaccine as a priority to prevent disabilities from cCMV¹⁻³. Between 20,000 and 30,000 babies born each in the United States are congenitally infected with CMV and approximately 10%-15% of these children develop SNHL¹. It is estimated that cCMV accounts for ~20% of all SNHL at birth and at least 25% of all SNHL in children at 4 years of age⁴. CMV-associated hearing loss can be present at birth but a majority of infected children with SNHL have normal hearing at birth^{5,6}. In addition, hearing loss in children with congenital CMV infection is frequently progressive during the first few years of life^{5,7}. Further, there is wide variability in audiologic profiles of children with CMV-associated SNHL with respect to severity, laterality and timing of onset. Therefore, it is not possible to identify children with cCMV at increased risk for SNHL early in life because predictors or risk factors for CMV-associated SNHL have not been identified. The pathogenesis of CMV-associated hearing loss and the basis for the variable disease presentation are not known.

The extensive variability in disease expression suggests that there are co-factors other than direct viral-mediated damage these could include genetic causes that play an important role in CMV-associated SNHL. In a previous study to determine importance of connexin mutations in children with cCMV and those with CMV-associated SNHL, the presence gap junction protein beta-2 (GJB2) and a large deletion in gap junction protein beta-6 (GJB6) variations were examined in 149 children with cCMV and 380 uninfected neonates⁸. The study population was predominantly African American, and 4.3% of the subjects were carriers of GJB2 variations. The overall frequency of GJB2 variations was significantly higher in children with CMV-associated hearing loss (21%) compared with those with cCMV and normal hearing (3%, $p=0.017$) and uninfected newborns (3.9%, $p=0.016$). None of the study children had the common GJB2 variation, 35delG or the GJB6 deletion. Eight previously reported and four novel variations were observed in GJB2. Although the importance of these variations is not clear, the significantly increased frequency of GJB2 variations in children with CMV-associated SNHL is intriguing and raises the possibility that genetic factors may play an important role in hearing loss in children with cCMV.

The objective of the proposed research career enhancement award application is for the candidate to undergo advanced training to acquire knowledge and tools that will enable him to investigate whether there is genetic basis to SNHL in children with cCMV and those with SNHL of undetermined etiology. To achieve the objectives of the proposal, the candidate will undertake a sabbatical in the laboratory of Dr. Cynthia Morton at the Brigham and Women's Hospital. As part of the application, a research project is proposed to investigate whether genetic factors play a role in CMV-associated SNHL by analyzing a subset of children participating in the ongoing CMV and Hearing Multicenter Screening Study with and without hearing loss. The availability of the patient population with defined hearing outcomes and environment at BWH, Broad Institute and other Harvard-affiliated institutions ensures that the study objectives can be achieved. In addition, the feasibility of utilizing newborn dried blood spot (DBS) specimens from study children for known genomic variation associated with non-syndromic SNHL and the presence of infectious genomes will be explored. Ongoing research in Dr. Morton's laboratory and at the Broad Institute has developed and optimized protocols for whole exome sequencing (WES) of the human genome in cord blood and peripheral blood specimens^{9,10}. However, it is unclear whether DBS will provide adequate DNA yield of satisfactory quality to perform WES. Furthermore, it is not known whether WES of DBS will identify infants with congenital CMV infection.

Aim 1. Genomic analysis to identify pathogenic variations associated with SNHL in children with cCMV

The studies in this aim will be accomplished by diagnostic sequencing using WES and OtoGenome testing to identify pathogenic variations associated with SNHL in a subset of children participating in the CHIMES study.

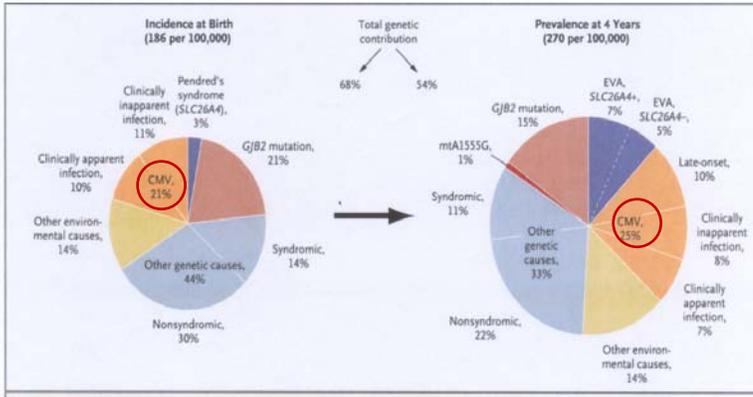
Aim 2. Determine the feasibility of utilizing newborn DBS from the CHIMES cohort for WES

Aim 2.1 Identify pathogenic genomic variations associated with SNHL by analyzing newborn DBS.

Aim 2.2 Explore whether infectious genomes can be identified in newborn DBS

Congenital CMV infection (cCMV) is a leading non-genetic cause of sensorineural hearing loss (SNHL) in children in the United States and worldwide¹⁻⁴. It is estimated that between 20,000 and 30,000 infants are born each year in the U.S. with cCMV and CMV-associated SNHL accounts for 25% to 40% of all childhood SNHL (Figure 1)³. The Institute of Medicine has identified the poor audiologic outcome due to cCMV as a leading area of unmet medical need⁵. Most infants (~90%) with cCMV have no detectable clinical abnormalities at birth (asymptomatic infection), approximately 70% of CMV-associated SNHL occurs in asymptomatic infants⁶⁻¹².

Figure 1. Estimates of causes of deafness at birth and at four years of age in the U.S.³. Congenital CMV accounts for about one-quarter of all childhood deafness.



CMV-associated SNHL is highly variable with respect to severity, age of onset, laterality, and continued progression^{7,10-12}. Approximately 65-75% of children with CMV-associated SNHL have severe or profound loss. About 50% of all children with CMV-associated SNHL and about 75% of asymptomatic children with SNHL have normal hearing at birth (delayed onset SNHL)^{7,11}. Predictors of CMV-associated SNHL, especially in children with asymptomatic cCMV are not known and the basis for the variability in disease presentation is unclear.

Pathogenesis of CMV-associated SNHL is poorly understood. Study of limited number of human temporal bones from children with cCMV

and fetal tissues showed the presence of viral antigens or inclusions in the cochlea and/or the vestibular apparatus¹³⁻¹⁶. However, this finding has not been consistently observed and only a limited number of specimens, mostly from children/fetuses with severe congenital infection were examined. Although CMV-associated SNHL could occur as a result of infection of the sensory epithelia, the variable disease presentation, delayed and/or progressive losses, and the absence of viral antigens in a significant proportion suggests that direct virus mediated damage alone cannot readily explain hearing deficit in many of the affected children. Also, a somewhat surprising observation in the series of temporal bone studies was the lack of a significant inflammatory infiltrate in the majority of specimens^{14,15}. Although guinea pig model has been used to study cCMV infection and more recent study demonstrated asymmetrical and progressive losses in congenitally infected pups, this model does not recapitulate human cCMV disease and this lack of a small animal model is a major barrier to understanding the pathogenesis of CMV-associated SNHL¹⁷⁻¹⁹. Therefore, we propose that genetic factors also play an important role in CMV-associated SNHL.

SIGNIFICANCE: Deafness is the most common sensory deficit and cCMV is a major non-genetic cause. Yet, little is known about the pathogenesis of CMV-associated SNHL. Higher prevalence of cCMV in the offspring of young, urban African American women demonstrates that most of the disease burden from this infection is seen in the low-income minority population. The majorities of children with cCMV and SNHL including ~75% of those with asymptomatic infection and SNHL have normal hearing at birth but develop deficits during early childhood. Although antiviral therapy has shown some benefit in decreasing SNHL, it is only recommended for infants with symptomatic cCMV. Early identification of children with cCMV at increased risk for SNHL is not possible currently because of the extensive variability in SNHL, lack of predictors (clinical or laboratory) of outcome. Therefore, most children with CMV-associated SNHL do not receive appropriate interventions during critical stages of speech and language development to prevent permanent disabilities. Determining the genetic basis of CMV-associated SNHL could enable timely identification of children with cCMV at increased risk for SNHL early in life. In addition, the proposed studies will also examine the prevalence of genetic factors in hearing loss in predominantly African American children. Significant advances have been made in understanding the genetic basis of syndromic and non-syndromic SNHL. In addition, high throughput sequencing (HTS) methods are being applied to provide insight into the basis of genetic disorders²⁰⁻²³. Dr. Morton and her collaborators at the Broad Institute have established the first in-solution whole exome sequencing (WES) methods. The analysis of specimens from children in the CHIMES cohort will take place during the 2nd 6-month block of the sabbatical and it is expected by that time, WES and whole genome sequencing (WGS) methods will have been further refined allowing us to explore the genetic basis of SNHL in children with cCMV.

INNOVATION: Although an earlier study showed increased frequency of heterozygous mutations in connexin 26 in children with CMV-associated SNHL, it is not known whether genetic causes play a role as co-factors in CMV-associated SNHL²⁴. Therefore, the proposed study not only attempts to address an important gap in our knowledge but also explore the use of highly innovative technology including exome-capture and WGS for the analysis of specimens from the study children. Further, the feasibility of utilizing DBS for WES will provide important information and if successful, will significantly advance the field of newborn screening. Determining the underlying genetic basis for SNHL in cCMV will allow the stratification of infected children that will permit targeted monitoring and intervene during critical stages of speech and language development.

APPROACH: The **overall objective** of the proposed research career enhancement award application is for Dr. Boppana to undergo advanced training and acquire skills and tools that will enable him investigate genetic causes of SNHL in children with cCMV and those with hearing loss of undetermined etiology by undertaking a sabbatical in the laboratory of Dr. Cynthia Morton at BWH. As part of the application, an exploratory project is proposed to investigate whether genetic causes are co-factors in CMV-associated SNHL and to investigate the feasibility of analyzing DBS from newborns with and without cCMV (from the CHIMES biorepository) for known genomic variants associated with SNHL and for the presence of infectious genomes. Ongoing research in Dr. Morton's laboratory and her collaborators' at the Broad Institute has developed and optimized protocols for WES of the human genome in cord blood and peripheral blood specimens. In addition, pipelines have been developed to distinguish non-human sequences such as viral integrations. However, it is unclear whether DBS will provide adequate DNA yield of required quality to perform WES.

Preliminary Data:

GJB2 and GJB6 variations in children with cCMV (Table 2): In a previous study to determine whether connexin mutations are factors in CMV-associated SNHL, variation in GJB2 and GJB6 were examined using nucleotide sequencing and PCR methods, respectively in 149 children with cCMV (19 with SNHL) and 380 uninfected neonates²⁴. The study population was predominantly African American, and 4.3% were carriers GJB2 mutations. The overall frequency of GJB2 variations was higher in children with CMV-associated SNHL (21%), compared with cCMV children with normal hearing (3%, p=.02) and uninfected children (3.9%, p=.02). Eight previously reported (M34T, V27I, R127H, F83L, R143W, V37I, V84L, G160S) and four novel variations (V167M, G4D, A40T, and R160Q) were detected. The overall allele frequency for each variation in the SNHL group was 0.026 (1/38) and in the group with normal hearing was 0.0038 (1/260). None of the study children had the 342kb deletion in GJB6. These findings coupled with the phenotypic variability in CMV-associated SNHL raises the possibility of genetic causes as co-factors in CMV-associated SNHL.

Table 2. Clinical characteristics and the type of GJB2 variations in cCMV children with and without SNHL²⁴.

Patient	Nucleotide change*	Protein change	Symptomatic cCMV	Hearing outcome
1	101T → C	M34T	Petechiae, microcephaly, and intracranial calcifications	Bilateral moderate to severe loss
2	250G → C	V84L	No	Mild to moderate loss in right ear
3	478G → A	G160S	Microcephaly	Progressive loss in left ear
4	499G → A	V167M	Petechiae, microcephaly, and intracranial calcifications	Delayed mild loss in left ear
5	11G → A	G4D	No	Normal
6	79G → A	V27I	No	Normal
7	250G → C	V84L	No	Normal
8	380G → A	R127H	No	Normal

* All variations were heterozygous.

Disease burden from cCMV in resource-poor settings: Data from studies in India and Brazil show that cCMV is a major cause of SNHL even in highly seropositive populations from resource-poor settings demonstrating the global disease burden from cCMV^{4,25,26}.

Study population and specimens: The subjects will be derived from the ongoing NIDCD CHIMES study at UAB and the DBS specimens from the study repository. The CHIMES network of seven academic pediatric medical centers in the United States has screened 100,605 newborns for cCMV^{27,28}. Of those screened, 462 (0.5%) were CMV-infected and 52 (11%) had symptomatic cCMV. The prevalence of cCMV was significantly higher for non-Hispanic black infants (0.99%) compared to non-Hispanic white (0.28%), Hispanic white (0.30%) and Asian infants (0.14%). Significantly more CMV-infected infants (7.1%) did not pass their newborn hearing screen (NHS) compared with only 0.9% of CMV-negative babies. Overall, 7.6% (35/462) of CMV-infected

cohort in the CHIMES had SNHL at birth. The follow-up is ongoing and additional children with SNHL are being identified. It is expected another 7%-8% of cCMV cohort will develop SNHL by 4 years of age. Although CHIMES is a multicenter study, we plan to enroll only children participating at UAB into the proposed study. Of the 35 with SNHL at birth, 11 were identified from the cohort at UAB and additional 10-15 will develop SNHL during follow-up. We plan to enroll 15 children with SNHL and a similar number of age and race-matched children with normal hearing from the cohort as a comparison group. Peripheral blood specimens will be collected after obtaining informed consent. If genomic variations of clinical significance are identified, these children and their parents will be seen by Dr. Nathaniel Robin in the UAB genetics clinic for discussion of test results and appropriate counseling (letter attached).

Aim 1. Genomic analysis to identify pathogenic variations associated with SNHL in children with cCMV

Significantly higher frequency of variation in GJB2 was observed in children with CMV-associated SNHL. However, the significance of this variation is unclear. In this aim, we propose to conduct a pilot study to analyzing a small subset from the CHIMES cohort to identify pathogenic variations causing SNHL. We will utilize whole exome sequencing (WES) approach because it is universally available, has been developed and optimized at the Broad Institute and provides the best yield for identifying pathogenic variations. In addition, WES is probably the most efficient means of identifying genes responsible for specific cellular or organismal perturbations. The specimens will be processed in Dr. Morton's laboratory and submitted to the Broad Institute taking advantage of the WES workflow established for congenital hearing loss. Investigators at the Broad developed a novel solution-based protocol that involves generating tens of thousands of 120-mer oligonucleotides on solid arrays (Agilent), cleaving them from the array and converting them into single-stranded, biotin-labeled RNA 'baits' to drive hybridization through high concentration²⁹. This protocol was licensed to Agilent and has been used in >200 publications. The fingerprinting of the DNA samples and WES processes has been optimized and require 50 ng to 100 ng of input DNA. The exome capture will be performed using the SureSelect system; libraries will be quantified via pigogreen for normalization and pooling into batches. The resulting pools will be qPCR assayed and loaded on to HiSeq 2500 flowcells for cluster amplification as part of the Broad's standard Illumina construction process.

The findings from WES studies will be confirmed by analyzing samples in the CLIA certified Partner's Healthcare Laboratory for Molecular Medicine by OtoGenome testing that examines variation in 100 genes known to be associated with hearing loss during the 2nd 6-month block of the sabbatical. In children for whom a pathogenic cause has not been identified by WES and OtoGenome approach, we plan to utilize emerging technologies that are being developed in the laboratory including detection of structural variation by array CGH and whole-genome jumping libraries. As these processes and techniques are being developed and optimized for diagnostic testing in Dr. Morton's and her collaborators' laboratories, this is an exciting time to be part of this group to not only to understand better the technologies but also to gain hands-on experience.

Aim 2. Determine the feasibility of utilizing newborn DBS for identifying pathogenic variations

Aim 2.1 Identify pathogenic genomic variants associated with SNHL by analyzing newborn DBS.

The current protocols and pipelines for human WES in the sponsor's laboratory and at the Broad are utilizing peripheral blood specimens because of the quantity and the quality of the input DNA required. It is not known whether sufficient quantity of DNA of high quality can be derived from newborn DBS. Since DBS are routinely collected from all newborns in the nursery, an ability to utilize these for WES will be a significant advance in the field of newborn screening for detecting underlying genetic causes for congenital SNHL and other disorders. The availability of newborn DBS from children in the CHIMES cohort with defined hearing outcome enables us to explore whether it will be possible to carry out WES on DBS. Current WES protocols at Broad requires 100 ng of input DNA for a target sequence of 33 Mb and achieves 120X coverage. In our studies of DBS testing for detecting CMV DNA by real-time PCR as part of the CHIMES study, two 3mm punches of the filter paper were used to extract DNA, which yielded 40 ng to 50 ng of DNA. Most DBS samples in our archive contain at least two additional circles filled with blood. Therefore, sufficient DNA can be extracted from DBS. Although the DBS specimens from CMV-infected children were stored at -20°C with desiccant, it is not known whether the extracted DNA from these spots will yield DNA of high quality. The technical processes and protocols for performing WES on the extracted DNA from DBS will be similar to that used to analyze peripheral blood specimens. Having paired DBS and peripheral blood specimens will allow us to compare the findings to determine whether DBS can be utilized for WES.

Aim 2.2 Explore whether infectious genomes can be identified in newborn DBS

Congenital CMV infection is the leading non-genetic cause of SNHL and accounts for at least 20-25% of all childhood deafness. By interrogating non-aligned sequences against the vast datasets of infectious genomes, it may be possible to gain new insights into infectious causes of SNHL. For the studies in this aim, SV sequencing will be performed by jumping libraries in small subset of study children with cCMV (~10) and an equal number of specimens from uninfected children. This approach offers a unique opportunity to isolate and localize integration of non-human sequences into the genome, particularly viral sequences. Dr. Morton and collaborators have previously published methods in which transgene integration sites were isolated in transgenic models and showed that these can have significant impact on host genome rearrangement and local gene expression³⁰. A similar pipeline for viral integrations has been established. In a pilot study to measure the relative abundance of viral genomic material in an autism cohort, Dr. Morton and colleagues aligned sequencing reads against the NCBI meta-genome reference database of 4,328 viral genomes, finding ~0.67% of all reads uniquely aligned to one of these viral genomes, with particular enrichment for herpesviridae family. In addition, this pipeline appends the viral genomes to the hg19 reference. The methods and protocols have been previously published³¹. In brief, the genome is fragmented and the DNA fragments are retained at a user specified size. Fragments are circularized around a custom designed biotinylated oligonucleotide and the circles are then fragmented, the circularization junction is retained by binding the biotinylated oligo to streptavidine beads, followed by ligation of customized bar coded adaptors for multiplexed paired-end sequencing. This will generate ~100X coverage of the genome per subject.

Potential pitfalls/Alternative plans. The proposed study will attempt to identify genetic causes as co-factors for SNHL in children with cCMV. A significant limitation of the study is the small sample size and therefore, it may not be possible to identify genetic factors in some or even majority of children. However, the findings from the study will still provide important preliminary data that could form the basis of future investigations on detecting co-factors for SNHL in children with cCMV. Additionally, even when genetic variation has been identified, it may be difficult to determine the significance of these variants and therefore, may not impact the clinical care for the children. The studies proposed in aim 2, exploring the feasibility of utilizing DBS for WES analysis could have significant impact on newborn screening for disease identification. Although the small sample size is a major limitation, carrying out the proposed studies will achieve one of the important objectives of the application, providing the candidate with hands-on experience with a variety of novel technologies and data analyses from analyzing specimens from study subjects.

Future Studies. Currently, it is not possible to identify children at risk for developing hearing loss in children with cCMV early in life. In addition, the available antiviral therapy for cCMV does not prevent all SNHL because is only recommended for a minority of infants with cCMV (those with symptomatic infection). Understanding genetic factors associated with SNHL will allow early identification of children at increased risk for targeted monitoring and intervene during critical stages of acquisition of speech and language skills. Therefore, more definitive studies with sufficient sample size can be undertaken to address and validate the findings of our study. An expanded study with larger sample size that also includes testing of parents to provide definitive information about the role of genetic factors in CMV-associated SNHL will be feasible because of our access to the CHIMES cohort. Further, if our hypothesis about the role of genetic variation as co-factors in SNHL is confirmed, it will be possible to target the children at increased risk for aggressive intervention measures to prevent or reduce permanent disabilities.

Timeline

Approval of the study protocol by UAB IRB will be accomplished during the first 2 months of the award. Enrollment of study subjects and collection of specimens will take place during the 1st 6 months of year 1. Execution of a material transfer agreement (MTA) between UAB and BWH will also take place during the 1st six months of year for the transport of specimens to the mentor's laboratory. The 1st 6-month block of sabbatical (2nd half of year 1) will be devoted to gain in-depth knowledge of molecular genetics by undertaking course work and hand-on laboratory experiences to become familiar and proficient in various laboratory protocols. Analysis of specimens by WES and other high throughput protocols will take place in the 1st half of the 2nd 6-month block of the sabbatical. During the final 3 months of the sabbatical, specimens will be analyzed in the CLIA-certified LMM to compare the results of OtoGenome testing with WES.

SUMMARY STATEMENT
(Privileged Communication)

Release Date: 07/16/2014

PROGRAM CONTACT:
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Application Number: 1 K18 DC014289-01

Principal Investigator

BOPPANA, SURESH B MD

Applicant Organization: BRIGHAM AND WOMEN'S HOSP., INC.

Review Group: CDRC
Communication Disorders Review Committee

Meeting Date: 06/12/2014
Council: OCT 2014
Requested Start: 01/01/2015

RFA/PA: PAR13-186
PCC: HR20

***Project Title:* Genetic causes as co-factors in cytomegalovirus associated hearing loss**

***SRG Action:* Impact Score:**

***Next Steps:* Visit http://grants.nih.gov/grants/next_steps.htm**

Human Subjects: 30-Human subjects involved - Certified, no SRG concerns

Animal Subjects: 10-No live vertebrate animals involved for competing appl.

***Gender:* 1A-Both genders, scientifically acceptable**

***Minority:* 1A-Minorities and non-minorities, scientifically acceptable**

***Children:* 2A-Only Children, scientifically acceptable**

Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
1		
2		
<hr/>		
TOTAL		

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the **COMMITTEE BUDGET RECOMMENDATIONS** section.

1K18DC014289-01 Boppana, Suresh

RESUME AND SUMMARY OF DISCUSSION: This NIDCD Research Career Enhancement Award for Established Investigators (K18) application requests two years of support for a candidate to acquire advanced scientific knowledge and tools in the field of genetics, focusing on hearing loss in children. This is a strong application with many strengths, including this well-established and productive principal investigator (PI) as the candidate, the outstanding mentorship plan proposed, and the well thought-out training plan which is carefully documented with letters of support. The proposal to learn interpretation and application of whole exome sequence (WES) studies - an important emerging field - dovetails well with the PI's current supported research in hearing loss in congenital cytomegalovirus (CMV) infected infants and children. Weaknesses noted in the discussion include no stated plan for balancing support of the PI's current projects with time away during the K18 portion of the study and the research plan lacks a general pipeline for analysis of the WES data and does not consider how it would be applied to the patient samples. This concern is compensated by the excellent mentorship plan.

DESCRIPTION (provided by applicant): Congenital cytomegalovirus (CMV) infection is the most common viral infection and a leading non-genetic cause of sensorineural hearing loss (SNHL) and other neurological sequelae. Despite the high disease burden, little is known about the pathogenesis and mechanisms of CMV-associated hearing loss. In addition, only about 15% of children with congenital CMV infection develop hearing and in those who develop these deficits, the losses are quite variable with respect to severity, laterality and timing. A previous study showed increased frequency of GJB2 mutations in children with CMV-related SNHL raising the possibility that genetic factors may explain the variability in hearing loss in congenital CMV infection. The overall goal of this NIDCD Research Career Enhancement Award (K18) application by an established investigator is to acquire advanced scientific knowledge and tools in the field of genetics, focusing on hearing loss in children. The candidate is a clinician scientist with a proven track record for extramural funding and scientific productivity in the area of congenital cytomegalovirus (CMV) infection and CMV-associated hearing loss over the past two decades. Specific objectives of this proposal include: 1) Strengthening his knowledge and skills in molecular genetics and genetic basis of hearing loss, 2) Undergo advanced didactic training in molecular genetics and bioinformatics, 3) Conduct a study to determine whether genetic causes are co-factors in CMV-associated hearing loss by analyzing a subset of samples (peripheral blood and dried blood spots) from the cohort participating in the ongoing CHIMES study, 4) Continue to make scholarly contributions in area of CMV-associated deafness, and 5) Develop collaborations and seek extramural funding to carry out studies to elucidate mechanisms of CMV-associated hearing loss. The training plan proposed consists of a sabbatical in Dr. Cynthia Morton's laboratory at the Brigham and Women's Hospital for hands-on training in molecular genetics, formal coursework, and participating in a variety of learning opportunities including seminar series at the Broad Institute and other Harvard affiliated institutions, lab meetings and attending national meetings. A research project to examine a subset of children participating in the CHIMES study to determine genetic basis for CMV-associated hearing loss is also proposed. In addition, the feasibility of whole exome sequencing using dried blood spots will be explored. The availability of excellent resources to complete the training at BWH and other Harvard affiliated institutions, patient population from CHIMES with defined hearing outcomes, and specimens ensures successful completion of the proposed training and research. In addition to Dr. Morton as the primary mentor, three other leading experts (Drs. Rehm, Kenna and Shen) have agreed to participate in the program as co-mentors for the candidate. The proposed studies will not only improve our understanding of the mechanisms of CMV-associated hearing loss but also prepare the candidate to expand his research program to investigating genetic basis of hearing loss and to enhance hearing research capacity at UAB.

PUBLIC HEALTH RELEVANCE: The objective of this NIDCD Research Career Enhancement Award (K18) application by an established investigator is to acquire advanced scientific knowledge and tools in the field of genetics, focusing on hearing loss in children. The applicant is a clinician scientist with a

proven track record for extramural funding and scientific productivity in the area of congenital cytomegalovirus (CMV) infection and CMV-associated hearing loss. However, he lacks training and expertise in investigating the role of genetic causes as co-factors in CMV-associated hearing loss. In addition, the applicant is interested in forming a multi-disciplinary group for an integrated hearing research program that will bring individualized approaches in the evaluation and management of children with hearing loss at UAB. The proposed career development plan will enable the applicant to develop and enhance his skillset and provide him with tools to refocus his career to the genetics of hearing loss. The proposed training plan consists of a combination of coursework, hands-on laboratory experience in Dr. Cynthia Morton's laboratory at Brigham and Women's Hospital, and a variety of other learning opportunities including seminar series, lab meetings and attending national meetings. In addition to Dr. Morton as the primary mentor, three other leading experts (Drs. Rehm, Kenna and Shen) have agreed to participate in the program as co-mentors for the candidate. The application also includes a research project to examine a subset of children participating in the CHIMES study to determine the genetic basis for CMV-associated hearing loss.

CRITIQUE 1:

Candidate:

Career Development Plan/Career Goals /Plan to Provide Mentoring:

Research Plan:

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Environment Commitment to the Candidate:

Overall Impact: The candidate is proposing to retrain in genomic analysis of patients with hearing loss, especially as it relates to congenital Cytomegalovirus (CMV) infection. He has put together a superb mentoring team at a premier location. The plan is ambitious but the appropriate resources are well documented. He will learn new skills for analysis of whole exome sequence data and he plans to bring that expertise back to the University of Alabama Birmingham (UAB) where he will establish an integrated clinical care pathway for evaluation and management of hearing impaired patients. Collaborations developed during this training will be invaluable to Dr. Boppana's research agenda.

1. Candidate:

Strengths

- Has produced paradigm shift in understanding of the role of reinfection with CMV to production of congenital CMV infection
- Has a demonstrated record in continuous NIH funding
- Director of the CMV and Hearing Multicenter Screening Study (CHIMES) repository which will allow him to secure appropriate well characterized samples
- Developed a test for detecting CMV infection in newborns
- The PI, Dr. Boppana, has shown a deep commitment to understanding the correlates between deafness and congenital CMV infection. There is confidence that he will continue to contribute significantly to this important area.

Weaknesses

- None noted by the reviewer

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring:

Strengths

- The goal to produce and analyze whole exome sequencing data in relation to hearing is timely and requires significant training to adequately process the large amount of data this technique generates.

- Goals are admirable and well defined. The PI plans to use his newly acquired skills to help evaluate and manage treatment for hearing impaired patients.
- He has identified an appropriate combination of formal classes, workshops and seminars uniquely available in the Boston area, in addition to superior laboratory exposure provided by the Morton and Rehm laboratories and clinical experiences with Dr. Kenna.

Weaknesses

- None noted by the reviewer

3. Research Plan:

Strengths

- Access to well characterized patient population
- Access to exceptionally strong sequencing and analysis facility in association with the Broad Institute
- The proposed research is a good vehicle for developing the research skills this PI seeks.
- Developing the use of dried blood spots for whole genome sequence analysis and virus detection is relatively innovative.

Weaknesses

- Small sample set (acknowledged by the investigator)
- While the technical aspects of the application are good, the genetic interpretation is not well described on the other hand and the application is designed to retrain in an excellent human genetics environment.
- There is no clear description of how the WES data will be analyzed.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- This is an exceptionally strong mentoring team. Dr. Morton is a world recognized expert on genetic disease, and more recently on next gen sequence analysis. The rest of the team is well chosen to provide both clinical exposure for DNA testing and hands-on laboratory work. The facilities at the Broad Institute are top notch.
- The mentor and co-mentors have provided excellent letters detailing the expected interactions with the applicant and the expected outcomes. The nature and extent of the mentorship is appropriate.

Weaknesses

- None noted by the reviewer

5. Environment and Institutional Commitment to the Candidate:

Strengths

- The facilities for training and research at Brigham and Women's Hospital, the Lab of Molecular Medicine and the Broad Institute are all state of the art and uniquely suited for the proposed research
- There is a strong letter from the PI's chair at UAB pledging support of his career plan.

Weaknesses

- None noted by the reviewer

Protections for Human Subjects: Acceptable Risks and Adequate Protections

- This research will involve patients ascertained through the UAB CHIMES project. They will have been enrolled in that project which allows recontact for additional research. The patients will be recalled and invited to participate in the whole exome sequencing project described in the present application. An additional blood sample will be required. There is little risk in obtaining

this sample. If genomic variations that could cause hearing loss are identified, the result will be discussed with the parents by a geneticist.

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C2A - Only Children, Acceptable

- The participants will be children. The parents will provide consent and if the child is old enough he/she will be asked to assent. Selection is based on hearing status and an equal number of boys and girls will likely be enrolled. The study will include congenitally infected children who are participating in the CHIMES study. Subjects are enrolled without regard to minority status and will reflect the composition of the study population participating in the CHIMES study. All will be under 21 since this study is intended to look at children with hearing loss.

Vertebrate Animals: Not Applicable (No Vertebrate Animals)

Biohazards: Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research: Acceptable

Comments on Format:

- Formal course plus IRB training

Comments on Subject Matter:

- Ethical issues and principles in the practice of science.
- Among topics discussed are the nature, extent, and causes of fraud in science; UAB policies on fraud; ideals of good science; the responsibilities of authorship and peer review; potential problems raised by the commercialization of research; scientists are public policy advisors; and ethical issues in animal experimentation and in clinical trials

Comments on Faculty Participation: Not applicable

Comments on Duration:

- Ten 2 ½ hours sessions

Comments on Frequency:

- One semester in 2 year period

Select Agents: Not Applicable (No Select Agents)

Resource Sharing Plans: Acceptable

Budget and Period of Support: Recommend as Requested

CRITIQUE 2:

Candidate:

Career Development Plan/Career Goals /Plan to Provide Mentoring:

Research Plan:

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Environment Commitment to the Candidate:

Overall Impact: The application is for the PI, Suresh Boppana, to spend two six-month windows over a two-year period in the laboratory of Professor Morton. The goal of this sabbatical is to enhance the PI's knowledge and skills in the areas of molecular genetics and bioinformatics. The PI plans to apply this

knowledge and newly acquired skills to further focus his ongoing work related to congenital hearing loss associated with the cytomegalovirus (CMV). The training plan proposed involves didactic education, laboratory training, and general mentorship from a team of mentors lead by Professor Cynthia Morton. The areas of instruction and laboratory training would enhance the PI's ongoing work and allow him to begin understanding the existence of genetic variation in congenital CMV related hearing loss. The training plan and the associated research project are well conceived and appear to be the appropriate next step given the PI's career and research goals. The enthusiasm for the application is dampened slightly by the numerous typographical and construction errors. For example, some support letters at the end of the package were not visible to this reviewer.

1. Candidate:

Strengths

- The PI has a sustained and successful history of contributions to the area of CMV-related hearing loss. Evidence of excellence comes from his history of publications and successful attempts at obtaining extramural funding.
- The fact that the PI has identified the next steps in his research trajectory and is willing to act on them is a sign of commitment.
- The training or enhancement plan builds on the PI's program of research and will allow his work to have a more comprehensive and deeper impact on CMV and CMV-related hearing loss.

Weaknesses

- It is unclear how the PI will maintain oversight of his ongoing work at UAB during his six-month stints at the Morton laboratory.

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring:

Strengths

- The career development plan constitutes several dimensions, including didactic instruction, laboratory rotations, and general mentorship from scientific leaders in their specific domains.
- All aspects of the career development plan dovetail nicely with the PI's existing work and his vision of the next steps.
- The PI has not hesitated to engage with junior scientists with specific expertise when necessary.
- The PI's existing work will be ongoing and will contribute to the database and materials that can be used during the training period.

Weaknesses

- Are the didactic courses unique and do they have to be taken at the sabbatical institution? If similar courses were available at the home institution, the PI could focus more time on laboratory work during his sabbatical stints.

3. Research Plan:

Strengths

- The work proposed will be the initial steps necessary for understanding the variations in expression of CMV-related hearing loss and their genetic bases.
- The research plan is focused and limited, consistent with the time limits associated with this application.
- It appears as though the successful use of dried blood spots in conducting whole exome sequencing will be an important step in the field.

Weaknesses

- It may be complicated for the PI to maintain his current research load at his home institution and focus on the new work at the sabbatical institution during the two 6-month spans.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- Dr. Morton is a recognized leader in the field and has a demonstrated history of high impact research in the area. She will be the primary mentor and is perfectly suited given the expressed goals of this application.
- The other members of the mentorship team bring specific skills that form parts of the training plan.

Weaknesses

- None noted.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- The Morton laboratory and the general scientific environment surrounding it are ideal for the purposes of this application.

Weaknesses

- None noted.

Protections for Human Subjects: Acceptable Risks and Adequate Protections

- The PI describes their ongoing processes which appear to be appropriate.

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C2A - Only Children, Acceptable

- By necessity the application focuses on children only.

Vertebrate Animals: Not Applicable (No Vertebrate Animals)

Biohazards: Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research: Acceptable

Comments on Format:

- Appropriate

Comments on Subject Matter:

- Appropriate

Comments on Faculty Participation: Not applicable

Comments on Duration:

- Appropriate

Comments on Frequency:

- The current design breaks up the sabbatical into two separate time windows.

Select Agents: Not Applicable (No Select Agents)

Resource Sharing Plans: Acceptable

- Small data set will be obtained and the results shared through traditional channels.

Budget and Period of Support: Recommend as Requested

CRITIQUE 3:

Candidate: 2

Career Development Plan/Career Goals /Plan to Provide Mentoring:

Research Plan:

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Environment Commitment to the Candidate:

Overall Impact: The overall goal of this application is for Dr. Bopanna to retool his skills towards sophisticated genomic and exomic analyses in order to lead a major research program on the genetic mechanisms that underlie CMV-induced pathologies. Specifically, his goal is to understand the population variability in neurosensory deafness that arises from congenital cytomegalovirus infection. The training plan is very specifically and extensively developed with coursework and seminars in population and molecular genetics and the supporting computational analyses. The candidate is an accomplished clinician and infectious disease researcher. The training he will acquire through this support will permit him in the long run to decipher complex interactions between infection and innate hereditary predisposition leading to a basis for the pathophysiological mechanisms for hearing loss stemming from infection.

1. Candidate:

Strengths

- The candidate's clinical training and credentials are outstanding.
- The candidate has an excellent record of clinical investigation particularly in the areas of pathologies arising from CMV and other viral infections. His recent research emphasis has refocused his interests towards hearing losses that may arise from congenital CMV exposure.
- Referees and mentors are uniformly positive about the PI's drive and insightful selection of training opportunities in the service of enhancing his research capabilities.
- The candidate maintains R01 funding as PI and also as co-Investigator on additional grants.

Weaknesses

- None noted by the reviewer

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring:

Strengths

- The training plan is very well developed. He will acquire extensive training in molecular and population genetics including a didactic and practical informatics courses, journal clubs and seminars.
- Colleagues and research personnel at the Broad Institute will equip the candidate with expanded familiarity with a breadth of genetics strategies beyond the immediate ones he will be trained for.

Weaknesses

- None noted by the reviewer

3. Research Plan:

Strengths

- The candidate's earlier research on congenital CMV infection leading to hearing loss is extensive. His observation of variability of hearing loss following infection has suggested an underlying genetic basis of susceptibility. In particular, a gap junction subunit shows high association. The research project will test this premise using an NIDCD-sponsored large cohort (CHIMES).
- Only a subset of children from the CHIMES cohort, those enrolled at the candidate's home institution will be enrolled, enhancing the feasibility of longitudinal and interventional studies based on the outcomes of the initial research.

Weaknesses

- The specific features to be extracted from the whole genome and whole exome analyses are not well elaborated. In particular, there is limited discussion of the computational strategies used to associate genomic or exomic polymorphisms with hearing deficits.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- An outstanding team of mentors has been selected, all of whom appear to be enthusiastic about their role in Dr. Boppana's training.
- Cynthia Morton is an acknowledged leader in the genetic basis of hearing defects approached through a wide range of experimental strategies. Her association with the Broad Institute ensures access to state-of-the art sequencing technologies and informatics support.

Weaknesses

- None noted by the reviewer

5. Environment and Institutional Commitment to the Candidate:

Strengths

- Facilities are outstanding as expected, and there are several overlapping groups of research foci that will expand the candidate's capabilities when he returns to his home institution.
- The Broad Institute's intellectual resources are a powerful complement to the technological and research focus of Dr. Morton's laboratory.

Weaknesses

- None noted by the reviewer

Protections for Human Subjects: Acceptable Risks and Adequate Protections

- Direct risks are few as genetic analyses will be conducted on dried blood spot samples.

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C2A - Only Children, Acceptable

- Studying congenital CMV infection requires recruitment of child participants. The study population is a subset of the CHIMES cohort with parental consent on record. Ethnic, economic and racial diversity standards are in place. Later follow-up analyses will require new informed consent. Parents of the subjects identified as being at risk will be referred for genetic counseling.

Vertebrate Animals: Not Applicable (No Vertebrate Animals)

Biohazards: Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research: Acceptable

Comments on Format:

- Annual seminars (just once per year) for IRB investigators. Plus classroom sessions.

Comments on Subject Matter:

- Human subject protection as well as appropriate areas in science such as authorship, peer review etc.

Comments on Faculty Participation: Not applicable

Comments on Duration:

- Semester long course

Comments on Frequency:

- IRB retraining annually

Select Agents: Not Applicable (No Select Agents)

Resource Sharing Plans: Applicable

- PI indicates that HIPAA concerns and possibility of deductive identification of individuals in the small population guide them to NOT share data. The specific decisions will be discussed with NIDCD staff and local IRB officials once results and analyses are completed.

Budget and Period of Support: Recommend as Requested

- There is some concern whether sufficient time is allocated. The PI's total commitment of 6 calendar months corresponds to 6 months in the Morton lab. Will there be sufficient research time during the two 6-month stints at home institution to continue these analyses as described?

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS: ACCEPTABLE

The protocol features minimal risk to subjects and employs adequate protection against risks.

INCLUSION OF WOMEN PLAN: ACCEPTABLE

The study population is expected to include both male and female subjects, which is scientifically acceptable. A Targeted/Planned Enrollment Table is included and reflects this gender breakdown.

INCLUSION OF MINORITIES PLAN: ACCEPTABLE

The study population is expected to reflect the demographics of the catchment area, an appropriately diverse population; this is scientifically acceptable. A Targeted/Planned Enrollment Table is included and reflects this minority breakdown.

INCLUSION OF CHILDREN PLAN: ACCEPTABLE

The study is expected to include children only, which is scientifically acceptable.

VERTEBRATE ANIMALS: NOT APPLICABLE

BIOHAZARD COMMENT: The committee cites no concerns.

SELECT AGENTS: The committee cites no concerns.

RESOURCE SHARING PLANS: The committee cites no concerns.

RESPONSIBLE CONDUCT OF RESEARCH: The committee cites no concerns.

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html>. The impact/priority score is calculated after discussion of an application by

averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

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NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS
CDRC
June 12, 2014 - June 13, 2014**

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* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

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