Implementing genomic medicine in care of patients with impaired hearing

Xue Zhong Liu1,2, Susan Blanton2, Simon Angeli1, Adrien A Eshraghi1, Fred Telisch1, Mustafa Tekin2

1) Department of Otolaryngology, University of Miami Miller School of Medicine, Miami, FL 33136, USA; 2) Dr. John T. Macdonald Department of Human Genetics, University of Miami Miller School of Medicine, Miami, FL 33136, USA.

Abstract

Objectives: The Miami OtoGenetic Program has provided a unique platform to carry out translational research on delivering genetic services to deafness patient care. Using target-enrichment/NGS, we will determine 1) the overall frequencies of different forms of genetic deafness, 2) identify new genes for ARSNHL and ADNSHL, and 3) will create important Genomic Deafness Database (GDD) and Personalized Sequence Profile (PSP) for the clinical care of deaf patients where data is ranked based on its clinical validity and utility.

Methods: We have collected a unique cohort of multiplex families derived from three unique sources from USA, China, and Turkey, suitable for determination of molecular etiology of hereditary deafness and for new gene identification using “target-enrichment” methods and next generation sequencing (NGS). Our interdisciplinary and collaborative team will conduct outcome evaluation of genetic service on deafness patient care in our diversity populations.

Results: We have established the Miami OtoGenetic Program including the research and the clinical components. The infrastructure of our multidisciplinary oto genetics team has been presented along with our utilization of testing algorithms when evaluating patients with SNHL. We have collected DNA samples from over 800 probands from multiplex families with no mutations in the common deafness genes from three unique cohorts. A total of 60% of small multiplex families are identified to have mutations in the known deafness genes in a pilot study and the remaining 40% have mutations in other yet-unidentified deafness-causing genes. We have identified several new genes for non-syndromic deafness. Hearing rehabilitation and counseling of patients with genetic causes of hearing loss are provided.

Conclusions: The combined target-enrichment/next generation sequencing (NGS) and WES is a powerful tool in the identification of new deafness genes in small multiplex families and large multi-generational families. The multidisciplinary team approach is an effective way to bring the sequencing data to clinical practice for the clinical diagnosis and management of deaf and hard-of-hearing families.

Introduction

The identification of numerous genes causing non-syndromic hearing loss (NSHL) along with recent technological advances in “target-enrichment” methods and next generation sequencing (NGS) is now making possible molecular epidemiologic studies of genetic deafness and a new wave of discoveries of the remaining genes for genetic diseases. The clinical use of high throughput sequencing has tremendous potential for changing the way we practice medicine. Because of the need to bring comprehensive genomic information of individual patients into the “real world” clinical environment, The Miami OtoGenetic Program has provided a unique platform to carry out translational research on delivering genetic services including NGS information to deafness patient care.

Methods

We have a collection of a unique cohort of multiplex families derived from three unique sources from the USA, China, and Turkey, suitable for determination of molecular etiology of hereditary deafness and for new gene identification. Using target-enrichment/NGS, we are determining: 1) the overall frequencies of different forms of genetic deafness in each of the three populations and identify ethnic differences in the distribution of genes for HL; 2) mapping/identifying genes for ARSNHL (autosomal recessive NSHL) and ADNSHL (autosomal dominant); 3) creating important Genomic Deafness Database (GDD) and Personalized Sequence Profile (PSP) for the clinical care of deaf patients. The clinical component would be responsible for identifying/categorizing patients, correlating phenotype/genotype and developing models for predicting risk. At the Human Genomics Center at the University of Miami, we have 7 NGS instruments with max capacity of 3 trillion base pairs every 2 weeks. A single run is able to produce ~4 Terabytes of raw data: 1.2 Petabyte disc storage. We have a 5,000 node computing cluster and a developed fully-automated exome capture Caliber robot with capacity of 288 exome samples per week.

Conclusions

The combined target-enrichment/next generation sequencing (NGS) and WES is a powerful tool in the identification of new deafness genes in small multiplex families and large multi-generational families. The multidisciplinary team approach is an effective way to bring the sequencing data to clinical practice for the clinical diagnosis and management of deaf and hard-of-hearing families.

References

Lu et al. 2013. Am J Hum Genet 92: 45-57
Duong et al. 2007. Association for Research in Otolaryngology, Denver, CO
Shinohara et al. 2015. Am J Hum Genet 97: 627-636
Simoes et al. 2015. Am J Hum Genet 97: 573-584
Yan et al. 2015. Am J Hum Genet 97: 230-235

Figure 1: Work flow for screening, analyses and use of clinical sequencing data in the care of patients with NSHL.

Figure 2: Diagram summarizing the Miami Molecular OtoGenetic Research Program.

Figure 3: Diagram showing the timing of the research and clinical components of the Miami OtoGenetic program.

Figure 4: Strategies for ranking gene variants: the ultimate goal of the interpretive algorithm is to determine a score that identifies the degree of “pathogenicity” versus “neutrality” for a specific gene variant. Variants of unknown significance are positioned in the central section of the scale. The pillars of the “Screening” scoring algorithm relate on computing two main categories of information, genetic and biochemical.

Figure 5: Mapped of known and novel loci of the available families

Table 1: Diagnostic algorithm for unknown cause of sensorineural hearing loss

Table 2: Variants identified in Turkish probands

Table 3: Sequence changes in Chinese and American probands

Table 4: Variants identified in Chinese probands

Table 5: Sequence changes in Chinese and American probands