

## **Novel Genetic Biomarker and Microarray for Diagnosis of Hearing Loss**

### **Introduction**

Bio-Link presents a valuable product development opportunity in the field of hearing loss diagnostics. The patented technologies are based on discoveries made by researchers at the Murdoch Children's Research Institute (MCRI) in Melbourne, Australia. The technology package consists of a novel genetic biomarker that can be added to the panel of existing gene mutations known to be commonly associated with hearing loss. The addition of MCRI's new genetic marker will significantly reduce the rate of inconclusive test results, and potentially open new options for prevention, management and treatment of deafness. The package also includes an optimized microarray assay which allows highly sensitive, multiplex analysis of several mutations in genes associated with hearing loss. The combination of the novel genetic marker with the microarray provides improved diagnosis on a platform that is proven reliable, efficient, and cost-effective.

### **Background**

Deafness is one of the most common genetic disorders. Hearing loss is present at birth in approximately 1-2 per 1,000 infants and is the third most common chronic condition reported by elderly people. Universal newborn screening programs have been implemented in the US, UK, and many other OECD countries. It is believed there are more than 200 genes that can cause deafness. So far more than 40 genes have been identified that are associated with non-syndromic hearing loss (e.g. not related to damage of inner ear structures). Genetic testing for deafness is difficult due to genetic heterogeneity, and currently relies on conventional methodologies such as genotyping, PCR analysis, and bi-directional sequencing. As these methods are relatively time-consuming and expensive, current clinical testing is limited to a small number of genes and mutations.

### **Novel Genetic Biomarker for Hearing Loss**

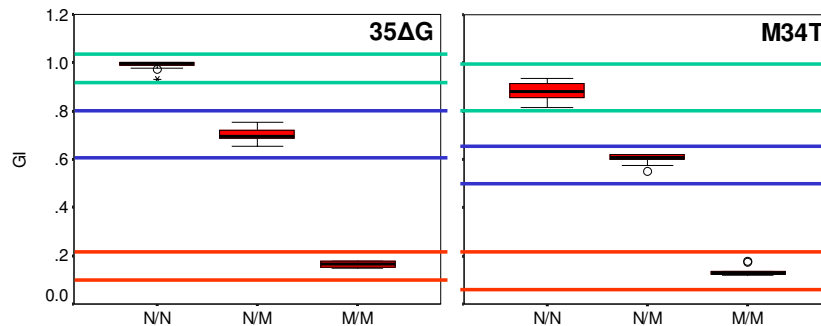
MCRI researchers Dr. Kirby Siemering and Associate Professor Henrik Dahl have discovered a novel deafness gene and have developed an animal model with a mutation in the gene for testing of agents to prevent hearing loss. Incorporation of the new marker in current panel of genetic tests being offered for hearing loss has the potential to increase the power of diagnosis thus contributing to better outcome for patients.

- Utilising an N-ethyl-N-nitroso urea (ENU) mouse model, a novel mutation was discovered which results in age-related deafness
- The mutation can be homozygous or heterozygous and may be associated with a mutation in one or more other genes such as TCMI, pendrin, myosin7a, usherin, cadherin 23 and/or connexin
- Additional work is ongoing to validate the novel biomarker in a larger cohort of human subjects that have severe or profound deafness

## Multiplexing Microarray

MCRI scientists have also developed a microarray-based hybridization assay for the detection of known mutations in hearing loss. In clinical studies, 206 DNA samples from deaf individuals were assessed with microarray technology and cross-referenced with existing sequencing technology. The test results showed a 100% success rate in detecting mutations targeted by the microarray chip. The chip performed beyond expectations, with the detection of a homozygous mutation in a person previously missed by sequencing and the detection of two mutations previously undiagnosed in three other individuals. The key advantages of the assay are:

- The assay is highly reliable and allows for parallel testing of multiple genes in a single assay that would result in substantial cost-savings and quicker turn-around time
- Proof-of-principle has been established on 15 mutations in 4 deafness genes (connexin 26, pendrin, usherin and mitochondrial 12S rRNA)
- Hybridization conditions for the detection of individual mutations are standardised which has the potential to ease the process of automation
- The assay is expandable to detect additional mutations as they are discovered.



Box and whisker plots of Genotype Index (GI) for normal (N/N), heterozygous (N/M) and homozygous patients (M/M) for 2 mutations, 35ΔG and M34T. GI values fall into distinct, non-overlapping ranges, allowing unambiguous determination of genotype.

## Intellectual Property

The technology is protected by three patent applications listed in the table below.

AU PCT Ref	Title	Subject Matter	Priority
09/000100	Diagnosis and Treatment of Sensory Defect	Novel genetic biomarkers for hearing loss	2008
03/001544	Genotyping of Deafness by Oligonucleotide Microarray Analysis	Microarray assay for genetic causes of deafness	2002
01/001643	Method for Detecting whether An Organism is Homozygous or Heterozygous Using Labelled Primers and RFLP	Background method for analysis of alleles	2000

## **Inventors**

A/Prof. Henrik Dahl has extensive experience in molecular genetics and has for several years been using microarray technology in analysis of genes and gene expression. He has authored more than 100 peer-reviewed scientific papers in international journals and is an inventor on 6 patents. Before joining MCRI in 1984, he was Head of the Biotechnology Group at Nordisk Gentoft (now Novo-Nordisk), Denmark.

Dr. Kirby Siemering (PhD, University of Melbourne) has authored more than 15 international journal articles, book chapters and patents. He has worked at senior levels in several biotechnology companies and has assisted in Victorian state policy development for the biotechnology sector.

## **Murdoch Childrens Research Institute (MCRI)**

MCRI is an independent non-profit research institute based at the Royal Children's Hospital and affiliated with the University of Melbourne in Australia. The Institute has approximately 900 staff including 100 postgraduate students, and now represents the largest research institute specialising in adolescent and child health in Australia. MCRI's areas of research include cerebral palsy, cancer, genetics, muscular dystrophy, diabetes, asthma, allergies, deafness, infectious diseases, depression and behavioural problems. MCRI also leads genetic ethics research and community debate of controversial issues such as stem cell research. The Institute receives over AUD\$65 million annually for laboratory, clinical, and public health research. Indicative of the MCRI's commitment to conduct research of the highest quality, the Institute publishes over 400 internationally peer-reviewed articles each year and holds over 60 patent applications.

## **Commercial Opportunity**

The technology provides a new genetic biomarker and a multiplex assay, which enables comprehensive analysis of mutations in a several genes linked to hereditary hearing loss. Bio-Link is seeking to license the technology to companies for clinical validation and development of advanced hearing loss diagnostics.

Interested parties please contact Christopher Boyer, Executive Director, Bio-Link:

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## **References**

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