Melbourne Genomics
Health Alliance

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Clinical utility of genomics in congenital deafness in newborns

Background

Melbourne Genomics' Clinical Flagships have been at the forefront of determining when genomic testing makes a demonstrable difference to the safety and quality of patient care.

Congenital deafness – hearing loss present at birth – is one of the 16 areas of health investigated by Melbourne Genomics.

Congenital hearing impairment can be genetic or non-genetic, but genetic factors are thought to cause more than half of all deafness. There are more than 100 genes that can cause hearing loss, many of which are associated with syndromes causing other health impacts in addition to deafness.

Identification of a specific syndrome is important for patient care, but not all syndromes are physically evident in infancy. It can be difficult to distinguish clinically whether the hearing impairment is syndromic or non-syndromic – thus management and care cannot be tailored to the patient's condition.

This Flagship team also investigated parents' preferences for additional genomic findings, unrelated to hearing loss, in their infant's test (see separate summary on the Baby Beyond Hearing study).

Publications

"A protocol for whole-exome sequencing in newborns with congenital deafness: a prospective population-based cohort", Downie, L., Halliday, J.L., Burt, R.A., Lunke, S., Lynch, E., Martyn, M., Poulakis, Z., Gaff, C., Sung, V., Wake, M., Hunter, M., Saunders, K., Rose, E., Rehm, H.L., Amor, D.J., BMJ Paediatrics Open (2017) doi: 10.1136/bmjpo-2017-000119

"Exome sequencing for isolated congenital hearing loss: a cost-effective analysis", Lilian Downie, David J. Amor, Jane Halliday, Sharon Lewis, Melissa Martyn and Ilias Goranitis, the Laryngoscope (2020) https://doi.org/10.1002/lary.29356

"Exome sequencing in infants with congenital hearing impairment: a population-based cohort study", Lilian Downie, Jane Halliday, Rachel Burt, Sebastian Lunke, Elly Lynch, Melissa Martyn, Zeffie Poulakis, Clara Gaff, Valerie Sung, Melissa Wake, Matthew F. Hunter, Kerryn Saunders, Elizabeth Rose, Sharon Lewis, Anna Jarmolowicz, Dean Phelan, Heidi L. Rehm, Melbourne Genomics Health Alliance & David J. Amor, *European Journal of Human Genetics* (2019) doi:10.1038/s41431-019-0553-8

"Exome sequencing in newborns with congenital deafness as a model for genomic newborn screening: the Baby Beyond Hearing project", Lilian Downie, Jane Halliday, Sharon Lewis, Sebastian Lunke, Elly Lynch, Melissa Martyn, Clara Gaff, Anna Jarmolowicz and David J Amor, *Genetics in Medicine* (2020) doi.org/10.1038/s41436-019-0745-1

Project description

The objective: to investigate the impact of a state-wide genomic testing approach for the diagnosis and subsequent management of children with hearing impairment detected in the newborn period.

Children found through the Victorian Infant Hearing Screening Program (VIHSP) to have moderate to profound bilateral (both ears) sensorineural hearing impairment were offered genomic testing.

As well as the VIHSP, the Flagship partnered with the Victorian Childhood Hearing Impairment Longitudinal Databank (VicCHILD, a state-wide deafness study). The Flagship also collaborated with Monash Health's established Paediatric Hearing Loss Investigation Clinic (PHLIC) and The Royal Children's Hospital's Caring for Hearing Impaired Children (CHIC) clinic, which was established alongside the Flagship to streamline the care of children diagnosed with congenital hearing loss.

The Congenital Deafness Flagship was led by Professor David Amor (The University Melbourne, The Royal Children's Hospital and the Murdoch Children's Research Institute). Key coordination was provided by Dr Lilian Downie (Murdoch Children's Research Institute); more than 20 multidisciplinary health professionals were directly involved.

Activities

Between January 2016 and December 2017, 170 eligible babies were identified through VIHSP. Of these, 155 families were contacted and 106 consented to genomic testing for their infant. All patients received chromosomal microarray and whole exome sequencing (WES), in addition to usual investigations.

For the period of the Flagship, families involved could choose to attend one of the integrated paediatric hearing impairment and genetics clinics or a related regional service.

Outcomes

- More than half the children (56%) received a genetic diagnosis for their hearing loss through genomic testing, compared to one fifth who would have been diagnosed using standard approaches (21%).
- Almost half of the 38 children diagnosed with an isolated hearing impairment would not have been identified using standard testing (17, 44%). All these children were released from ongoing surveillance for syndromic features and their parents could be reassured that their child's hearing impairment was not part of a syndrome.
- Ten of the 21 children diagnosed with a syndromic form of hearing impairment had a tailored care plan put in place following diagnosis. Two children have had a specific treatment offered as a result of their genomic diagnosis – one offered laser eye therapy to prevent vision loss, and the other a bone marrow transplant. Seven of these 21 children were initially thought to have an isolated form of deafness. This change in diagnosis has allowed surveillance and monitoring to be put in place for 5.
- Genomic testing also provided value to families: 51 couples know the chance of the condition occurring again in another child and have the option of prenatal testing or pre-implantation genetic diagnosis. Two relatives have received a genetic diagnosis from Flagship results – with a further seven currently considering whether to accept the offer of testing.
- Genomic testing enables more efficient use of medical monitoring: across the 106 children tested, health costs associated with screening and surveillance were reduced by at least $38,640.
- Genomic testing is cost-effective for infants with isolated hearing loss. An incremental cost-effectiveness analysis was undertaken to assess the cost and outcomes of genomic sequencing for newborns with congenital hearing loss compared to usual testing. Usual care incurs a total cost of $3,200 per child over the entirety of their paediatric care (18 years), with 22% of children tested receiving a diagnosis. Genomic sequencing costs a total of $4,200 per child over the same period but results in an additional 30 diagnoses per 100 children tested, with over half (52%) receiving a diagnosis.

Lessons learnt

- Specialist integrated hearing loss clinics were preferred by families, with all families from rural and regional Victoria choosing to attend one of the integrated clinics in Melbourne in preference to a regional genetics clinic appointment.

Impact

The evaluation and experience gained from the Congenital Deafness Flagship directly informed the recommended genetic and genomic testing pathways made by a national expert group[1].

Clinical Flagship team

Name	Organisation	Role
David Amor	MCRI/VCGS	Clinical geneticist
Lilian Downie	MCRI/VCGS	Clinical genetics fellow
Anna Jarmolowicz	MCRI/VCGS	Genetic counsellor
Belinda Creighton	Monash Health	Genetic counsellor
Elizabeth Rose	RCH	Otolaryngologist
Elly Lynch	Melbourne Genomics	Project manager
Gemma Brett	MCRI/VCGS	Genetic counsellor
Georgia Paxton	RCH	Paediatrician
Jane Halliday	MCRI	Researcher
Kerryn Saunders	Monash Health	Paediatrician
Libby Smith	MCRI	Researcher
Martin Delatycki	MCRI/VCGS	Clinical geneticist
Matthew Hunter	Monash Health	Clinical geneticist
Melissa Wake	RCH	Paediatrician
Rachel Burt	MCRI	Researcher
Sam Ayres	MCRI/VCGS	Genetic counsellor
Sharon Lewis	RCH	Researcher
Valerie Sung	RCH	Paediatrician
Yael Prawer	Monash Health	Genetic counsellor
Yana Smagarinsky	MCRI/VCGS	Genetic counsellor
Zeffie Poulakis	RCH	Psychologist

This Clinical Flagship collaborated with the Boston-based Genome Sequence-Based Screening for Childhood Risk and Newborn Illness ('BabySeq') Project and the North Carolina Newborn Exome Sequencing for Universal Screening team.

[1] Sung, V., et al, (2019) *Journal of Paediatrics and Child Health*, 2019, https://doi.org/10.1111/jpc.14508