

The Genetic Causes of HI and Novel Approaches to Genetic Discovery

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Presentation overview

- Update on current knowledge of the genetics of HI in Exeter
- The Open Hyperinsulinism Genes project update
- Strategy to increase number of families receiving a genetic diagnosis
 - Gene discovery studies
 - Improved detection of variants
 - Rescreening historic cohorts

Exeter : international referral centre for HI genetic testing







VERSITY OF

'ER

MEDICAL SCHOOL



>4500 families from 93 countries

Routine screening of 22 different genes identifies the cause of HI in 65%

Data shown for **n=2,943** individuals who have undergone comprehensive genetic testing through NHS laboratory



Dr Jayne Houghton

A genetic diagnosis informs of recurrence risk and can guide medical management





genes

Advise to restrict aerobic exercise (SLC16A1 gene)



Dietary advice (mainly GLUD1 gene)



Monitoring for diabetes (mainly HNF4A, HNF1A genes)

Diffuse Focal disease disease



Determines the extent of pancreas affected, informing on surgery when drug-unresponsive (mainly ABCC8, KCNJ11 genes)

The Open Hyperinsulinism Genes Project: removing barriers to genetic testing



Julie Raskin



Jayne Houghton



Funded comprehensive genetic testing for any individual unable to access genomics through their own healthcare system



~	ETERISCHOOL
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Full diagnostic report

Opportunities to enrol in research studies

The project has funded genetic testing for 942 families living with HI around the globe





Genetic testing performed on 942 families from 63 countries

Genetic diagnosis provided for 494 families (52%)

The project is gratefully acknowledged by the families and clinicians

"We want you to know that the contribution you make to us is invaluable. There is only gratitude towards you and your team." Clinician, Argentina

"Thank you for your laboratory's kindness and promptness in helping us doing the genetic tests. The facilities available here are embryonic at best and the costs are prohibitive for poor families." Clinician, India

"Thank you, we really appreciate your and the CHI Association's kindness." Mum, Israel



Increasing awareness, measuring impact and disseminating knowledge

Publish project model as an exemplar for genetic testing in other rare diseases (Q1: 2025)

The Open Hyperinsulinism Genes Project



Summary of project data (incl. summary genetic data, clinical data)

• Follow-up questionnaires to measure impact

Families have already contributed to new genetic findings/discoveries

Congenital Hyperinsulinism and Novel *KDM6A* Duplications -Resolving Pathogenicity With Genome and Epigenetic Analyses

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Molecular Characterization and Management of Congenital Hyperinsulinism: A Tertiary Centre Experience

RAJNI SHARMA,¹ KAKALI ROY,¹ AMIT KUMAR SATAPATHY,² ANIL KUMAR,¹ PAMALI MAHASWETA NANDA,¹ NISHIKANT DAMLE,³ JAYNE AL HOUGHTON,⁴ SARAH E FLANAGAN,⁵ VENKATESAN RADHA,⁶ VISWANATHAN MOHAN,⁶ VANDANA JAIN¹ From ¹Division of Pediatric Endocrinology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India; ²Department of Pediatrics, All India Institute of Medical Sciences, Bhubaneswar, Orissa, India; ³Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India; ⁴Genomics Laboratory, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK; ⁵Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK; ⁶Department of Molecular Genetics, Madras Diabetes Research Foundation, Chennai, Tamil Nadu, India. Correspondence to: Prof Vandana Jain, Division of Pediatric Endocrinology, Room no.3058, Teaching Block, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110 029. drvandanajain@gmail.com Received: November 09, 2020; Initial review: December 26, 2020; Accepted: September 10, 2021.

Severe congenital hyperinsulinism caused by variants in the *HK1* gene





Variants cause the HK1 gene to be inappropriately switched on in the pancreas

Variants identified in 17 individuals prioritised for gene discovery studies because they had a severe persistent congenital hyperinsulinism



Wakeling et al (2022) Nature

International collaboration to assess the clinical features and prevalence of *HK1*-hyperinsulinism in individuals not selected for by clinical features







Dr Jasmin Bennett Dr Christine Bellanne- Dr Klaus Mohnike Chantelot



Bennett et al under review

HK1 variants identified in ~2% of individuals with HI in the Exeter cohort



Improved detection of low-level mosaic variants in the known genes using state-of-the art technology



Thank you!



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MDBR • CHI Feb1

Implementing detection of low-level mosaic variants from blood samples in hyperinsulinism to improve diagnosis

Awardee: Sarah Flanagan

Institution: University of Exeter Medical School

Grant Amount: \$70,920.00

Funding Period: February 1, 2023 - January 31, 2024



Mosaicism is the presence of two or more populations of genetically distinct cells in an individual



Low level mosaic variant (<10%): may only be present in some tissues or present in multiple tissues but at a low level

Mosaic variants are well reported in congenital hyperinsulinism



High level mosaic variants

Low level mosaic variants

New technology allows for detection of low-level mosaic variants



High level mosaic variants

Low level mosaic variants

Can we accurately detect variants that are present in pancreas but at an extremely low level in the blood?



High level mosaic variants

Low level mosaic variants

High number of false calls when searching for variants below 8%



Aim: to develop a method to confirm which variants are real and which are false calls



Development of new high-throughput sequencing method differentiates between true variants and sequencing artefacts

- Molecular barcoded sequencing
- Identify true DNA variants
- Allows for ultra-deep, high accuracy sequencing of a large set of genes (rapid highthrough put screening)





Dr Matthew Johnson

Molecular barcoded sequencing reliably calls low-level mosaic variants



Candidate variants

Control variants

Low level mosaic variants identified in the blood in 25 people so far

- ABCC8: 1 variant identified in 1 proband
- GCK: 2 different variants identified in 3 probands
- GLUD1: 7 variants identified in 13 probands
- HK1: 5 variant identified in 8 probands

Initially referred for testing >20 years



GLUD1 965G>A, ~2.5%, molecular barcoded sequencing

- Presented age 14 months
- Insulin 8.2 mu/L, glucose 2.6 mmol/L
- Diazoxide responsive
- Hyperammonaemia, 93umol/L

Low-level mosaic variants are an important cause of HI



Data shown for n=2,943 individuals

Applying new knowledge to historic cases



1954 First description of hyperinsulinism

No genetic diagnosis

1996 First genes identified



>30 different genes identified for CHI better detection of variants

2024

Genetic diagnosis possible for >65% of children

Systematic rescreening of an historic cohort using current knowledge of genetics



Diagnosed with CHI between 1972-2023





Negative on testing in Finnish laboratory n=17 Inconclusive genetics n=6



Dr Jonna Männistö

Five families (22%) received new genetic results





1 x Low level mosaic GCK variant
1 x SLC16A1 non-coding variant
1 x HK1 non-coding variant
1 x ABCC8 splicing variant (missing variant)

1 x KCNJ11 variant reclassified

New genetic diagnosis

Variant reclassified as not-disease causing



- Knowledge of the genetics of hyperinsulinism has increased at pace
- New genomic technologies are improving our ability to detect genetic variants that are causative of hyperinsulinism
- New knowledge of the genetics of hyperinsulinism also needs to benefit individuals who have undergone historic testing and are without a genetic diagnosis

Acknowledgements





Dr Jayne Houghton Dr Jasmin Bennett Dr Jonna Mannisto Dr Jessica Hopkinson Dr Matthew Johnson Dr Evgenia Globa Dr Tom Laver Dr Matthew Wakeling Dr Nick Owens



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Collaborators, clinicians, the families



Dr Antonia Dastamani Dr Indi Banerjee Dr Christine Bellanne-Chantelot Dr Cecile Saint Martin Dr Klaus Mohnike Dr Martin Zenker