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

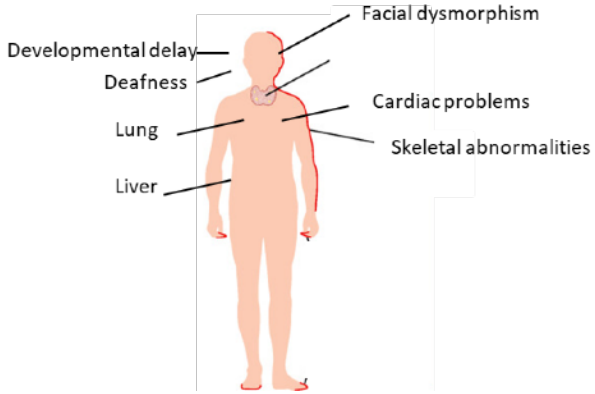
>4500 families from 93 countries

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

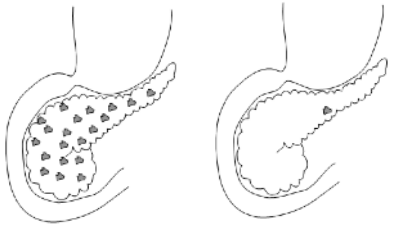
A genetic diagnosis informs of recurrence risk and can guide medical management



Monitoring for additional features (syndromic forms of HI multiple genes**)**

Advise to restrict aerobic exercise (*SLC16A1* gene)

Diffuse disease **Focal disease**



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

Dietary advice (mainly *GLUD1* gene)

Monitoring for diabetes (mainly *HNF4A, HNF1A* genes)

The Open Hyperinsulinism Genes Project: removing barriers to genetic testing

Julie Raskin

Jayne Houghton

Congenital Hyperinsulinism International

When too little sugar hurts, we help.™

NHS

Royal Devon University Healthcare

NHS Foundation Trust

University of Exeter

HI GLOBAL REGISTRY

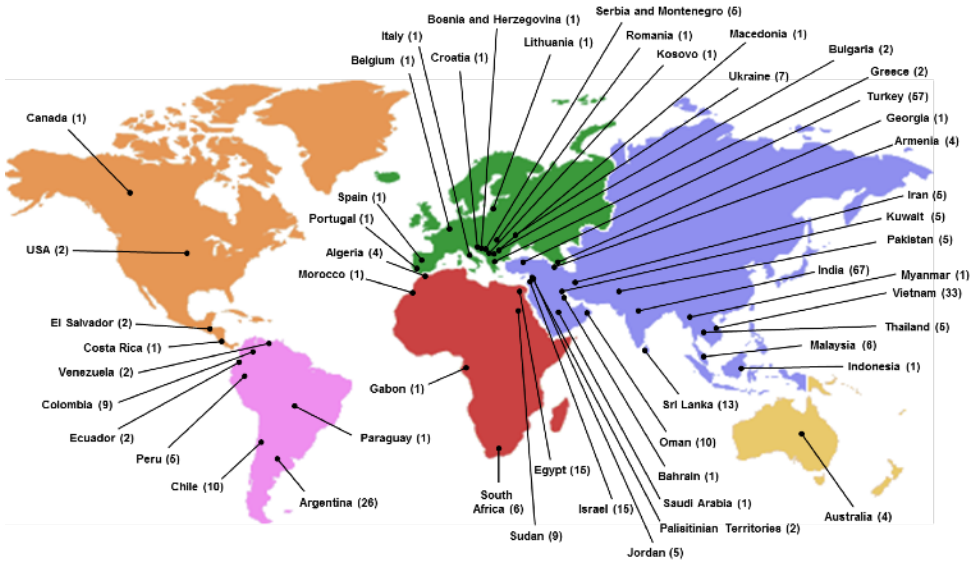
Funded comprehensive genetic testing for any individual unable to access genomics through their own healthcare system

MOLECULAR GENETICS LABORATORY REPORT

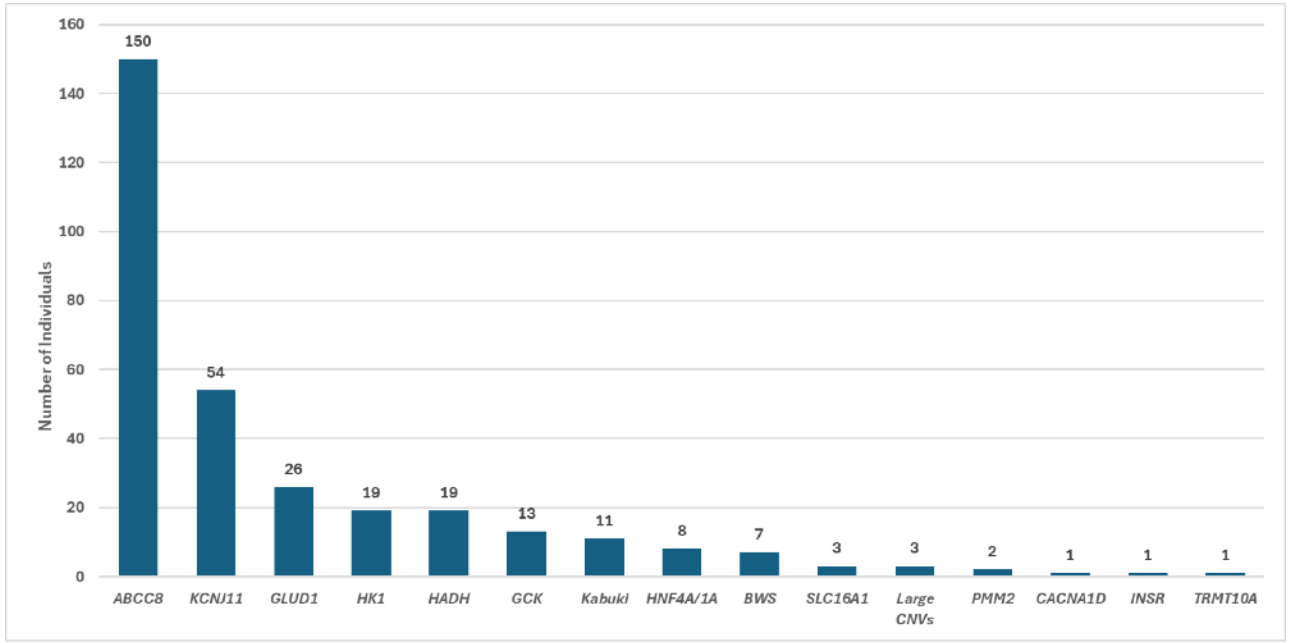
Full diagnostic report

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

Knowledge Exchange AWARDS 2022

Increasing awareness, measuring impact and disseminating knowledge

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

- 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

Jonna M. E. Männistö,[1,2] Jasmin J. Hopkins,[1] Thomas I. Hewat,[1] Fatima Nasser,[1] Joseph Burrage,[1] Antonia Dastamani,[3] Alice Mirante,[4] Nuala Murphy,[5] Jessica Rzasa,[6] Jennifer Kerkhof,[6] Raissa Relator,[6] Matthew B. Johnson,[1] Thomas W. Laver,[1] Luke Weymouth,[1] Jayne A. L. Houghton,[7] Matthew N. Wakeling,[1] Bekim Sadikovic,[6,8] Emma L. Dempster,[1,*] and Sarah E. Flanagan[1,*]

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Non-coding variants disrupting a tissue-specific regulatory element in *HK1* cause congenital hyperinsulinism

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

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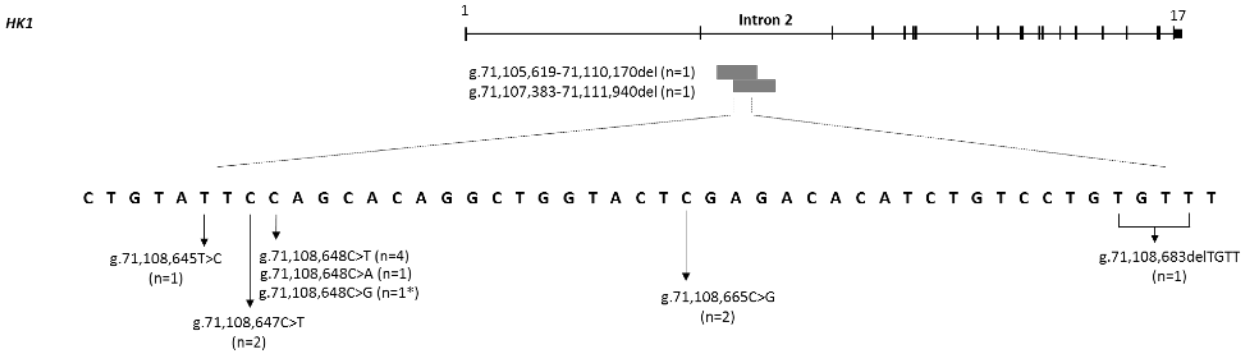
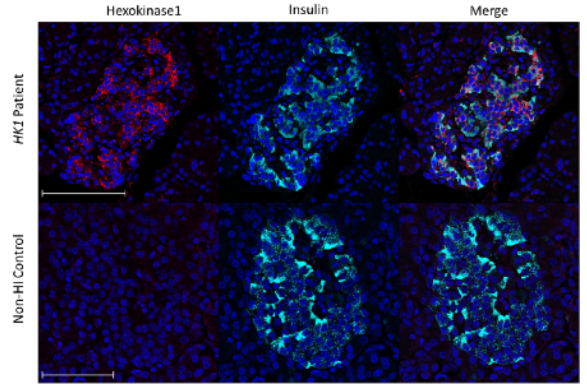
Received: November 09, 2020; Initial review: December 26, 2020; Accepted: September 10, 2021.

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

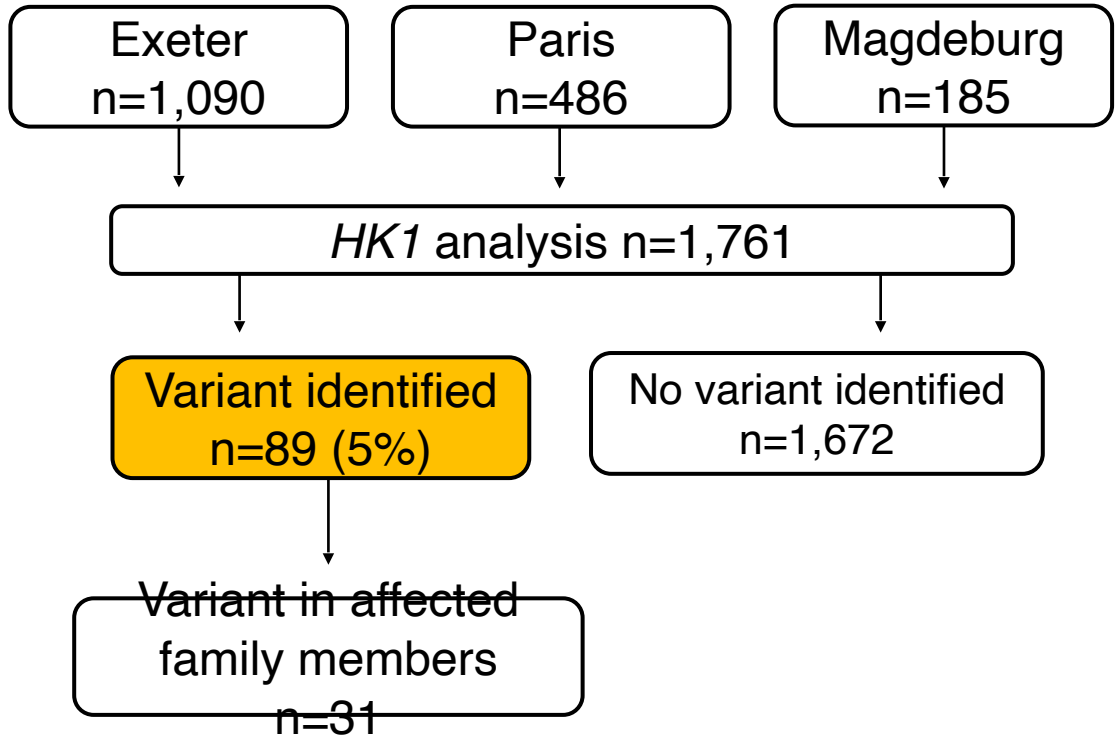
Wakeling et al (2022) Nature

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

Dr Jasmin Bennett

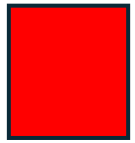
Dr Christine Bellanne-Chantelot

Dr Klaus Mohnike



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!

the orphan disease center

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MDBR • CHI Feb 1

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

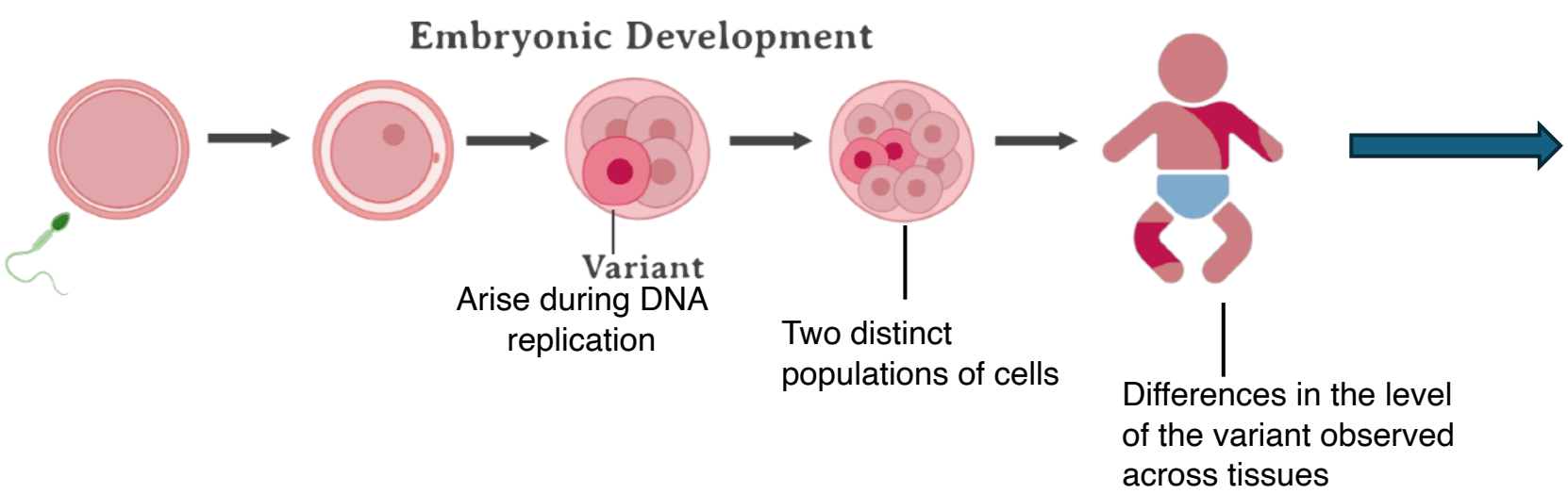
Awardee: Sarah Flanagan

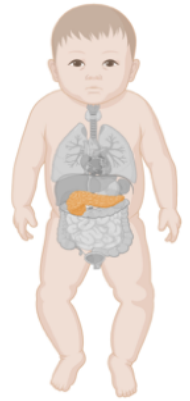
Institution: University of Exeter Medical School

Grant Amount: $70,920.00

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

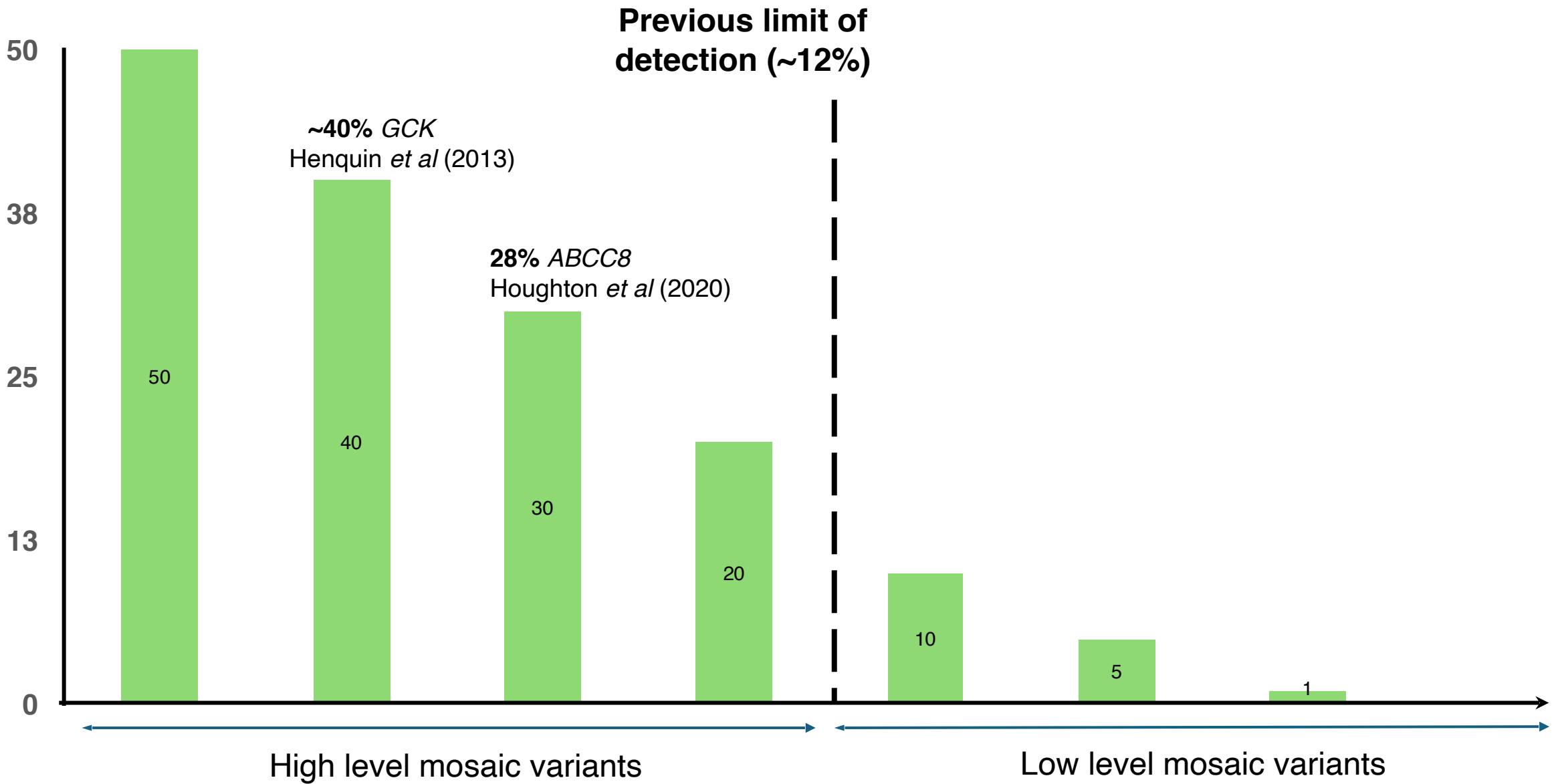
Mosaicism is the presence of two or more populations of genetically distinct cells in an individual



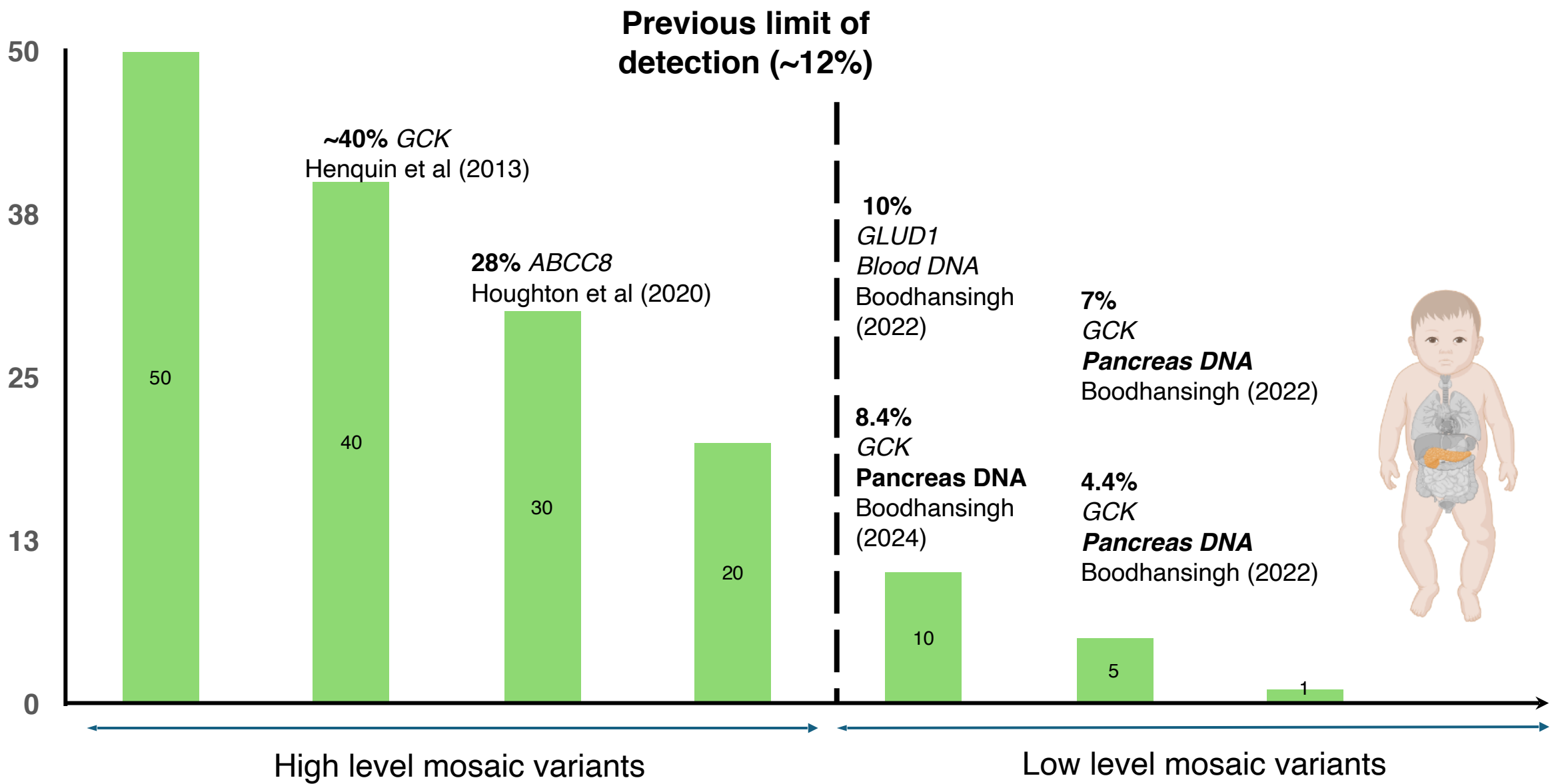


Low level mosaic variant (<10%): may only be present in some tissues or present in multiple tissues but at a low level

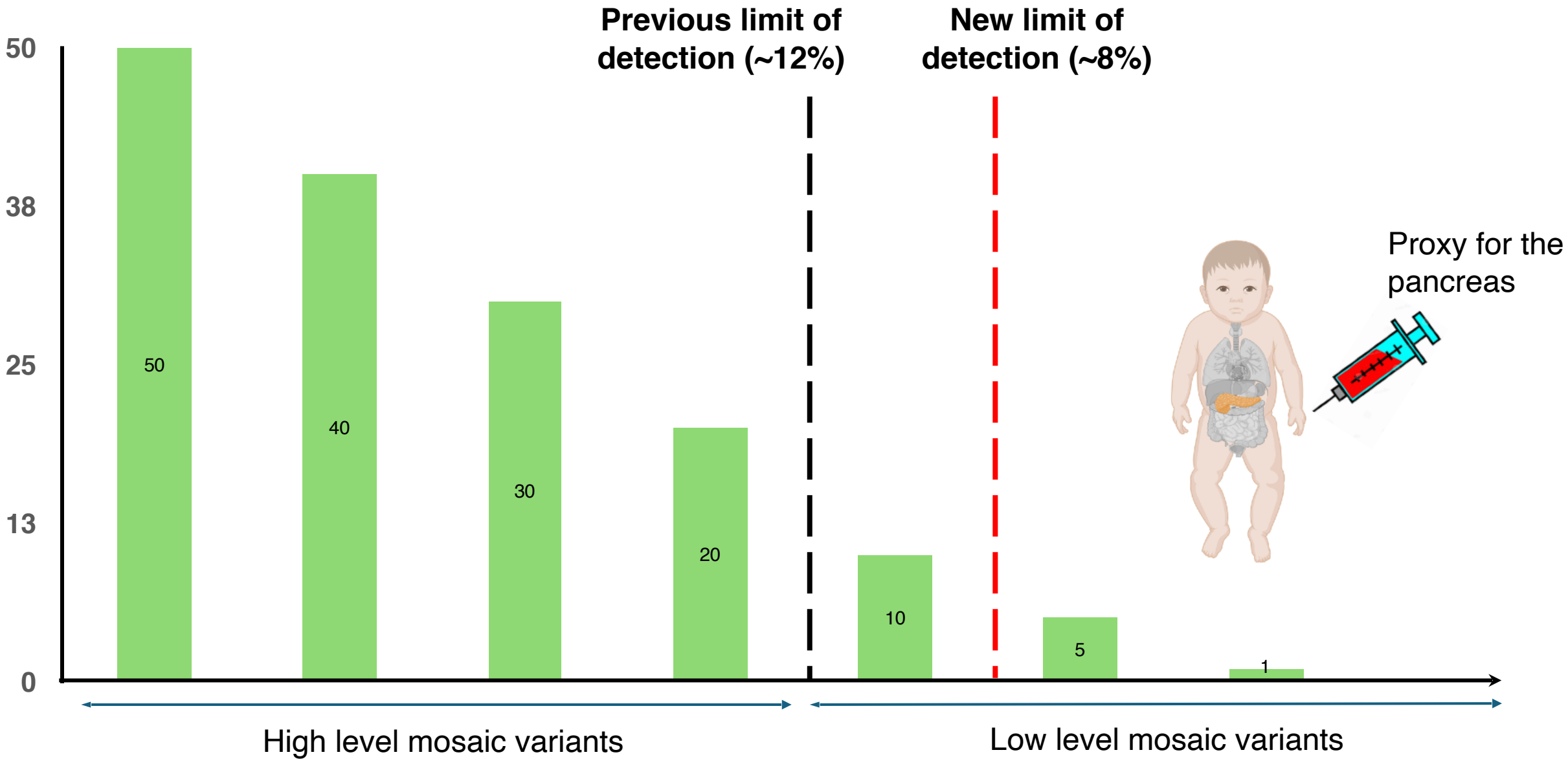
Mosaic variants are well reported in congenital hyperinsulinism



New technology allows for detection of low-level mosaic variants



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

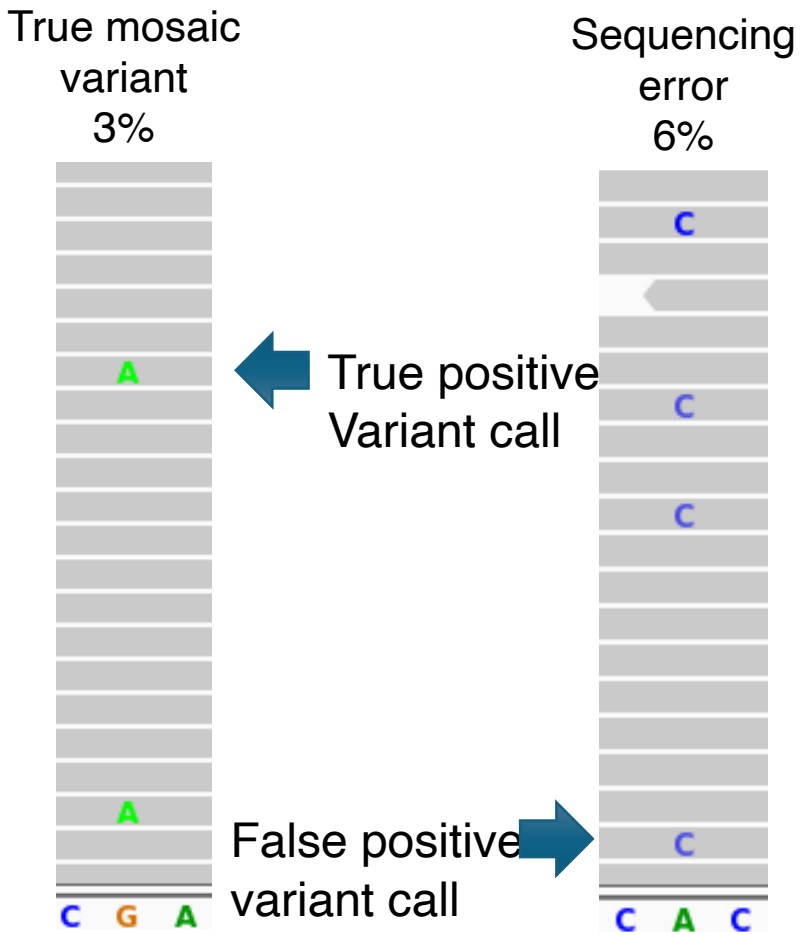


High number of false calls when searching for variants below 8%

Genetically unsolved following tNGS
n=1,036

Initial screening for low-level variants (<8%)

~14,500's low level variants across genes on panel
(~14 variants per sample!)



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

Genetically unsolved following routine testing
(n=1,036)

Candidate HI variants
(predicted to cause HI)

Individuals with a variant 1-8% (n=25)
14 different variants

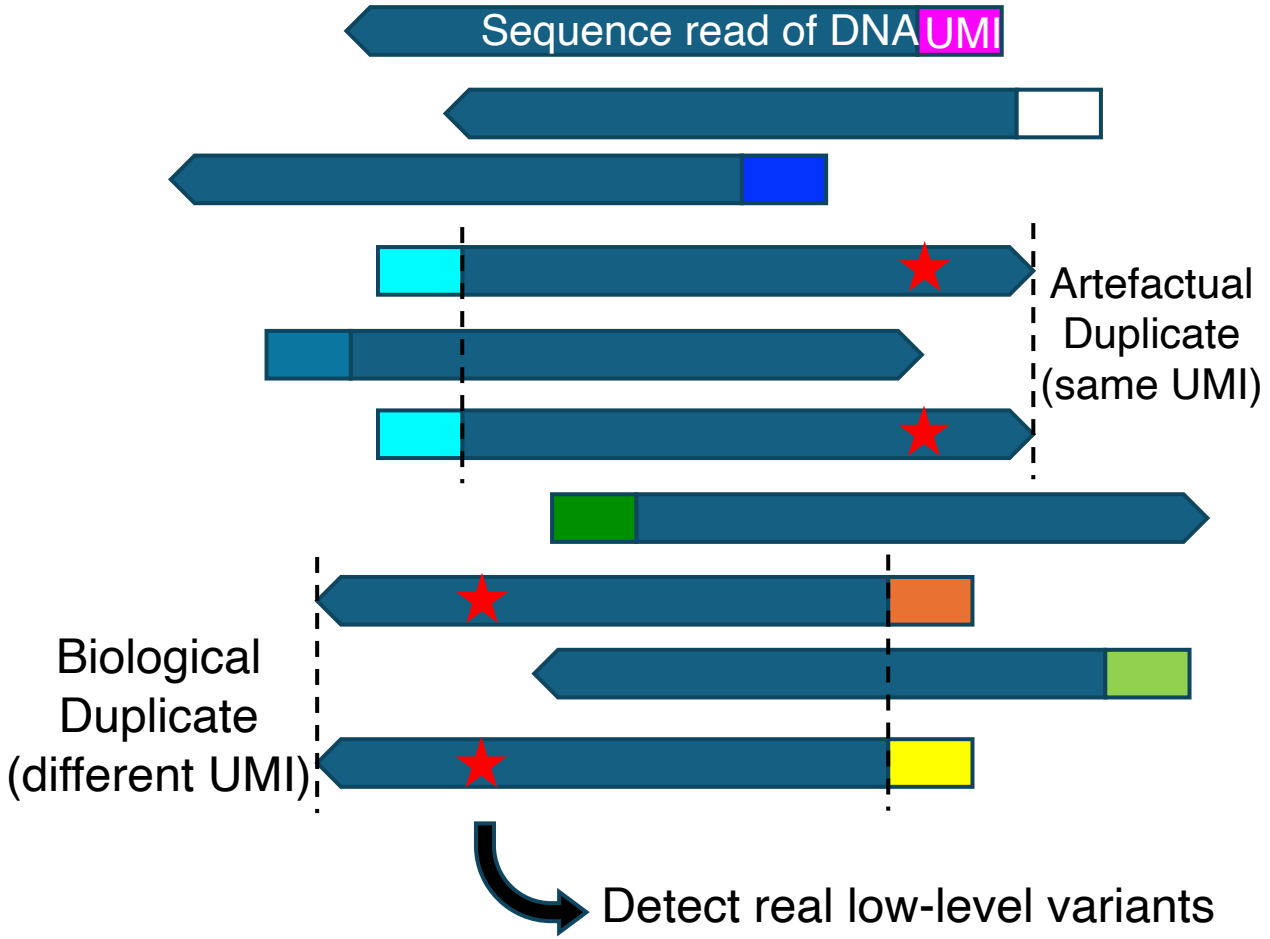
Control variants
(not predicted to cause HI)

Individuals with a variant <8% (n=25)
12 different variants

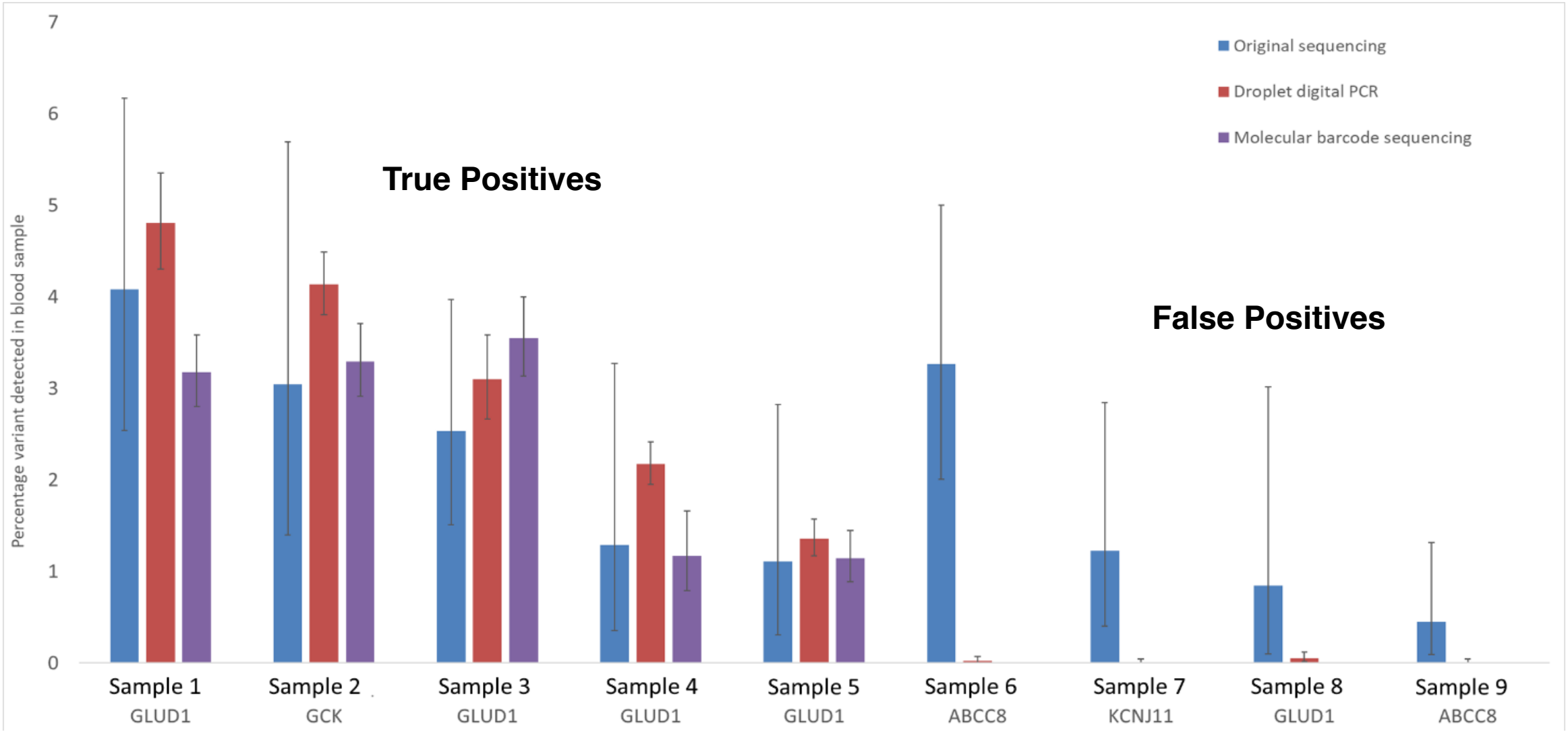
Development of new high-throughput sequencing method differentiates between true variants and sequencing artefacts

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

Dr Matthew Johnson



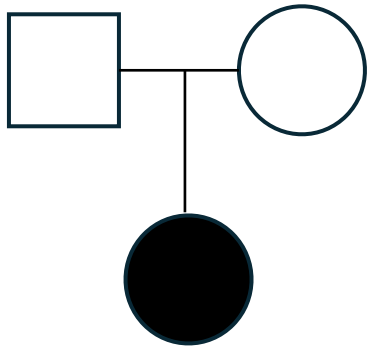
Molecular barcoded sequencing reliably calls low-level mosaic variants



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**

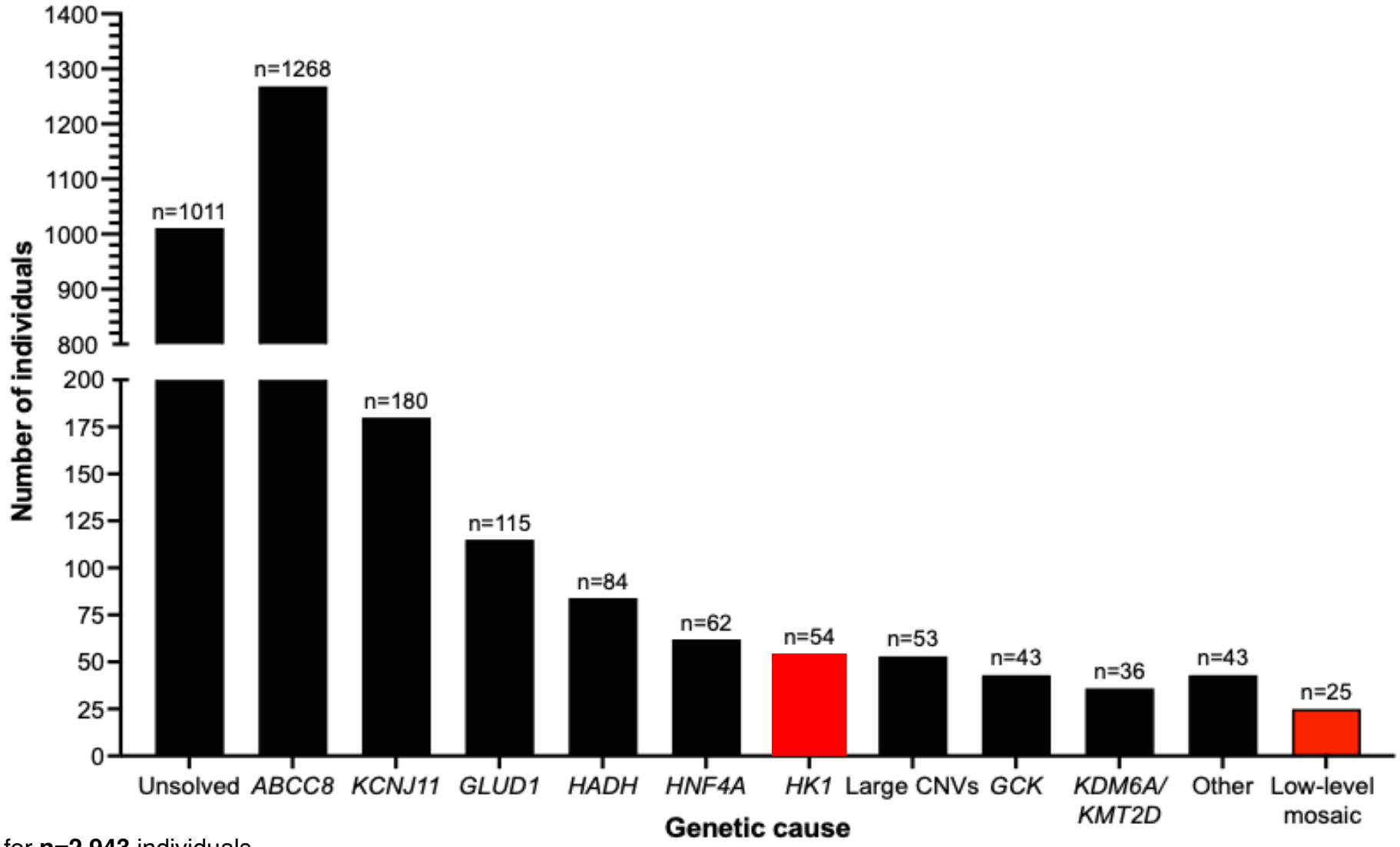
Initially referred for testing >20 years ago



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

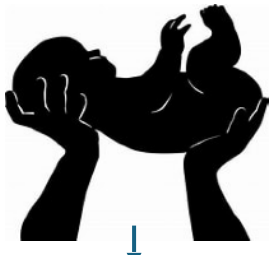
- Presented age 14 months
- Insulin 8.2 mu/L, glucose 2.6 mmol/L
- Diazoxide responsive
- Hyperammonaemia, 93umol/L

Low-level mosaic variants are an important cause of HI



Data shown for **n=2,943** individuals

Applying new knowledge to historic cases



Improved genetic technology

Improved knowledge of the genetic causes of congenital hyperinsulinism

1954
First description of hyperinsulinism

No genetic diagnosis

1996
First genes identified

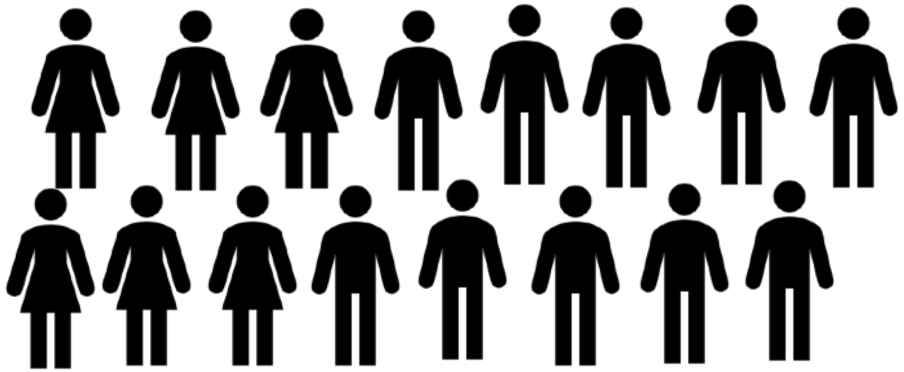
2024

>30 different genes identified for CHI better detection of variants

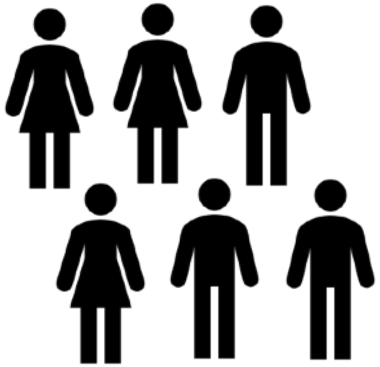
Genetic diagnosis possible for >65% of children

Systematic rescreening of an historic cohort using current knowledge of genetics

Diagnosed with CHI between 1972-2023



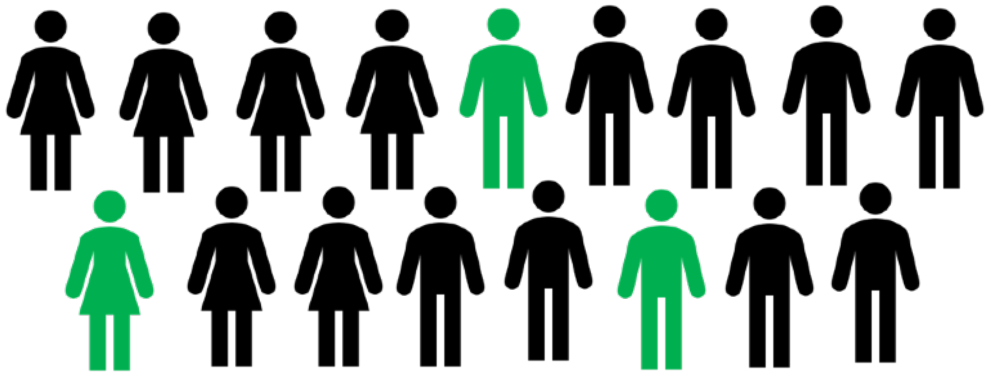
Negative on testing in Finnish laboratory n=17



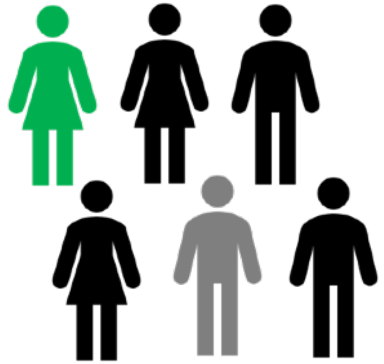
Inconclusive genetics n=6

Dr Jonna Männistö

Five families (22%) received new genetic results



Negative genetics
n=3/17



Inconclusive genetics
n=2/6

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

Summary

- 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

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wellcome trust

TEAM CHIbra
The Million Dollar Bike Ride

Collaborators, clinicians, the families

HYPERINSULINISM GENES

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

CHI
Congenital Hyperinsulinism International

Children's HYPERINSULINISM Charity

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