Genetics of congenital hyperinsulinism: How do we know?

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Placement student

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Functional Biologist

The Exeter Centre for Hyperinsulinism Genetics

250 Km from London

RILD Building based on Hospital site

International Referral Centre for Hyperinsulinism Genetics

>6000 families from 93 countries

435 families referred to Exeter from Turkey for CHI genetic testing

Aims of the Exeter team:

1. To provide a rapid and **accurate genetic diagnosis** to enable effective medical management

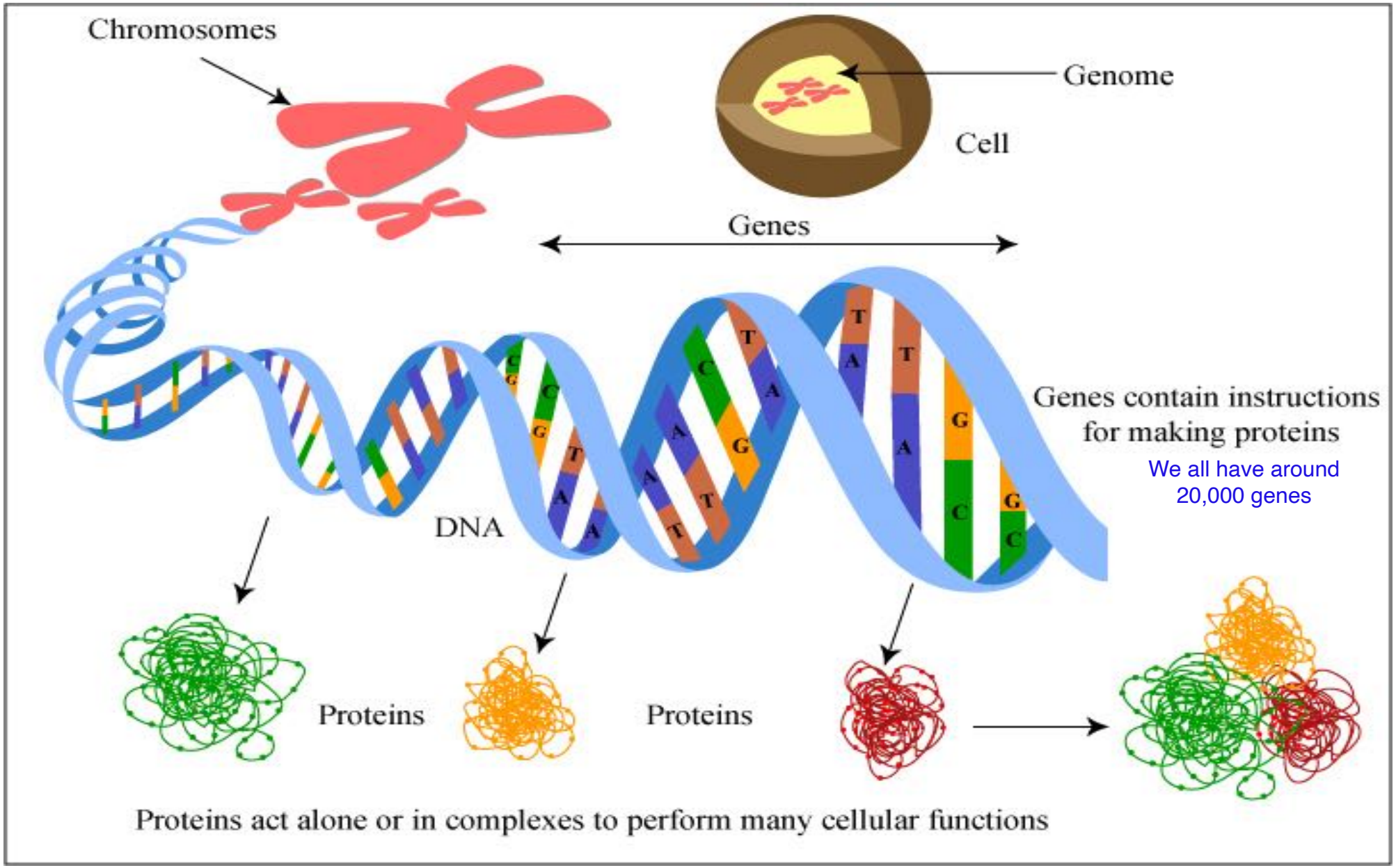
2. Research studies to **improve scientific understanding** of the condition to improve diagnosis and treatment

3. Ensure **equitable access** to genetics so that all families across the world benefit from scientific progress

The genetics of hyperinsulinism is complex: over 35 different known disease genes and lots of different ways of inheriting the condition

Your genetics are unique, advice should be tailored to each family

A gene is a segment of DNA containing the code to make a protein

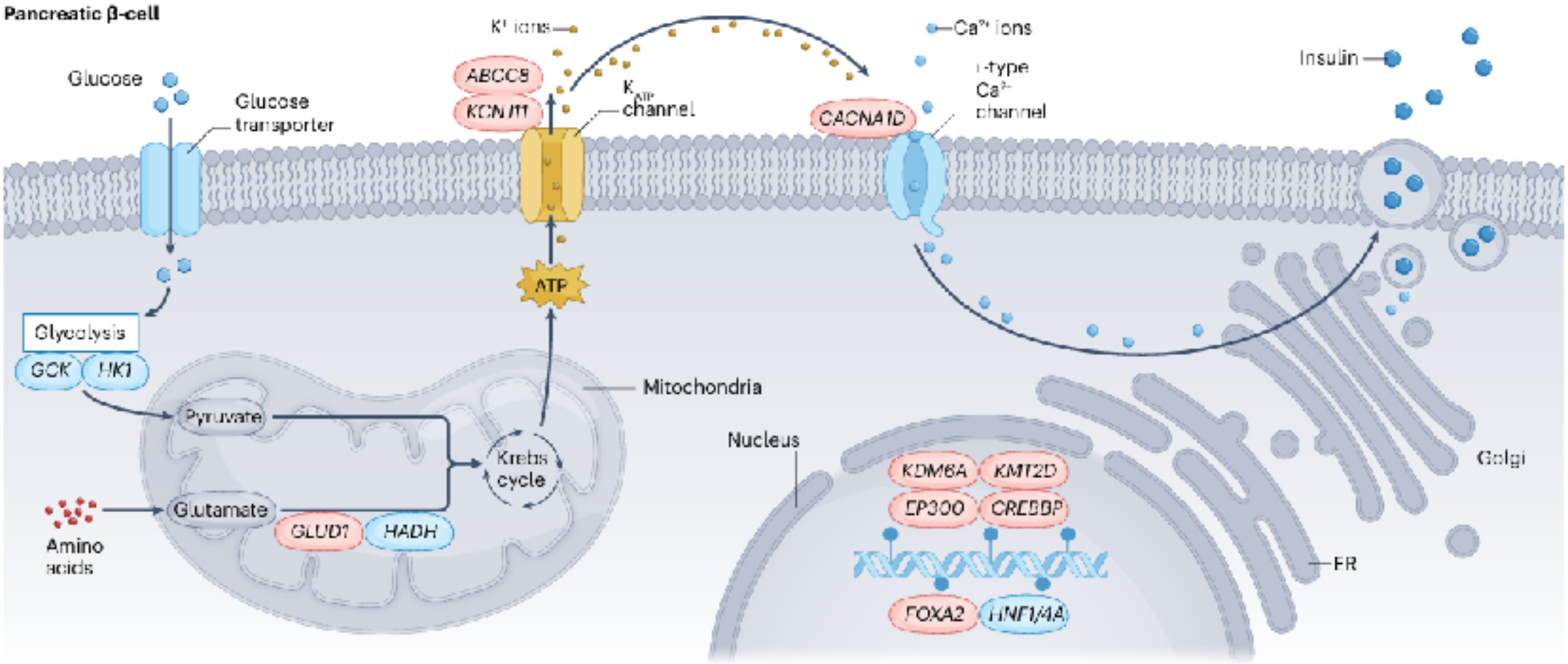


We all have lots of changes (variants) in our DNA

These changes can:

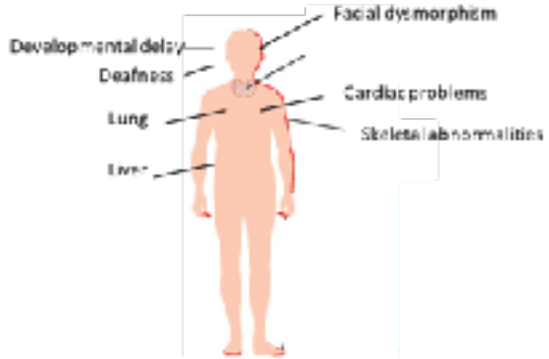
- Have no effect
- Define our characteristics (for example our eye colour, hair colour or height)
- Cause disease, when they alter how a critical protein is made or functions

Changes in over 35 genes are known to cause hyperinsulinism



Importance of understanding the genetic type of hyperinsulinism

Guide medical management



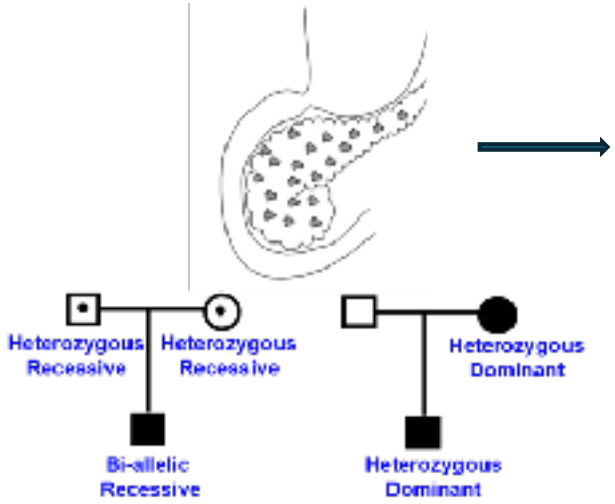
Monitoring for additional features (syndromic forms of HI *many genes*)

Dietary modifications (e.g. *GLUD1, HADH* gene)

Monitoring for diabetes (e.g. *HNF4A, HNF1A* genes)

Identifying a *ABCC8* or *KCNJ11* (K-ATP channel) variant in drug-unresponsive hyperinsulinism can inform surgery

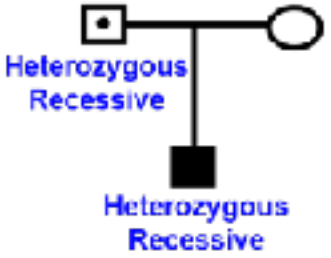
Diffuse disease



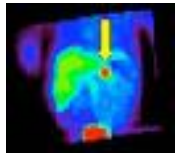
Near total pancreatectomy

Insulin dependent diabetes and exocrine insufficiency

Or



Focal disease

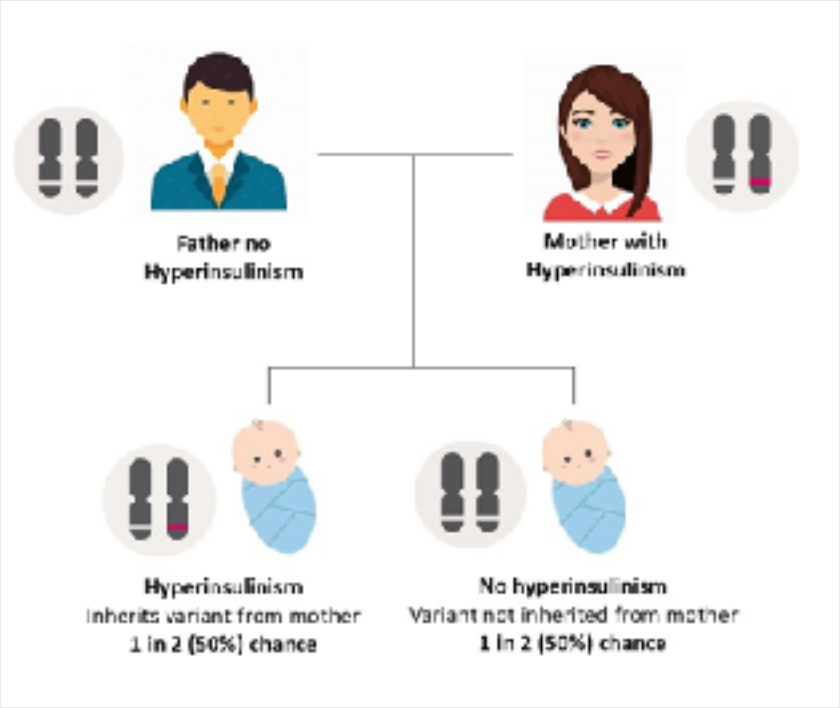


18F-Dopa PET-CT scan and lesionectomy

Curative in >98% of cases

Provides families with information on recurrence risk:

How likely future children within the family are to be affected with congenital hyperinsulinism



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

CONGENITAL HYPERINSULINISM

HI GLOBAL REGISTRY

Funded genetic testing for all individuals unable to access genomics

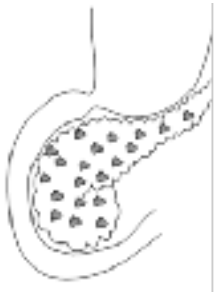
Full diagnostic report

Opportunities to enrol in research studies

Ensures geography and economic status are not barriers to genetic testing

The program has funded genetic testing for >1100 families from 63 countries

Genetic diagnosis achieved for 52% of families: results have informed on management



Diffuse disease (n = 384)

Focal disease (n = 139)

Focal Hyperinsulinism (n =14)

↓

18F-DOPA PET-CT Scan (n=14)

↓

Curative lesionectomy (n=14)

Congenital hyperinsulinism in the Ukraine: a 10-year national study

Evgenia Globa, Henrik Thybo Christesen, Michael Bau Mortensen, Jayne A. L. Houghton, Anne Lerberg Nielsen, Sönke Detlefsen and Sarah E. Flanagan

nature

Correspondence

https://doi.org/10.1038/s41360-026-00199

The Open Hyperinsulinism Genes Project bridges global disparities in access to genomic medicine

Check for updates

Dr Evgenia Globa, Ukraine

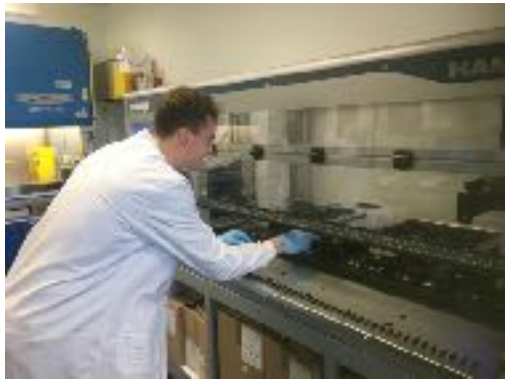
Dr Henrik Christesen, Denmark

Genetic testing involves searching for variants in the known hyperinsulinism genes

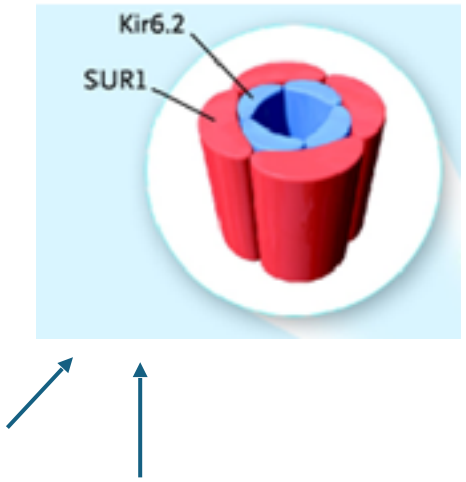
Blood sample sent to laboratory

DNA is extracted

We read the DNA sequence of the 35 known HI genes and look for changes



Routine testing identifies the genetic cause of HI in 65% of children



Data shown for **n=2,943** individuals who have undergone testing of all known genes

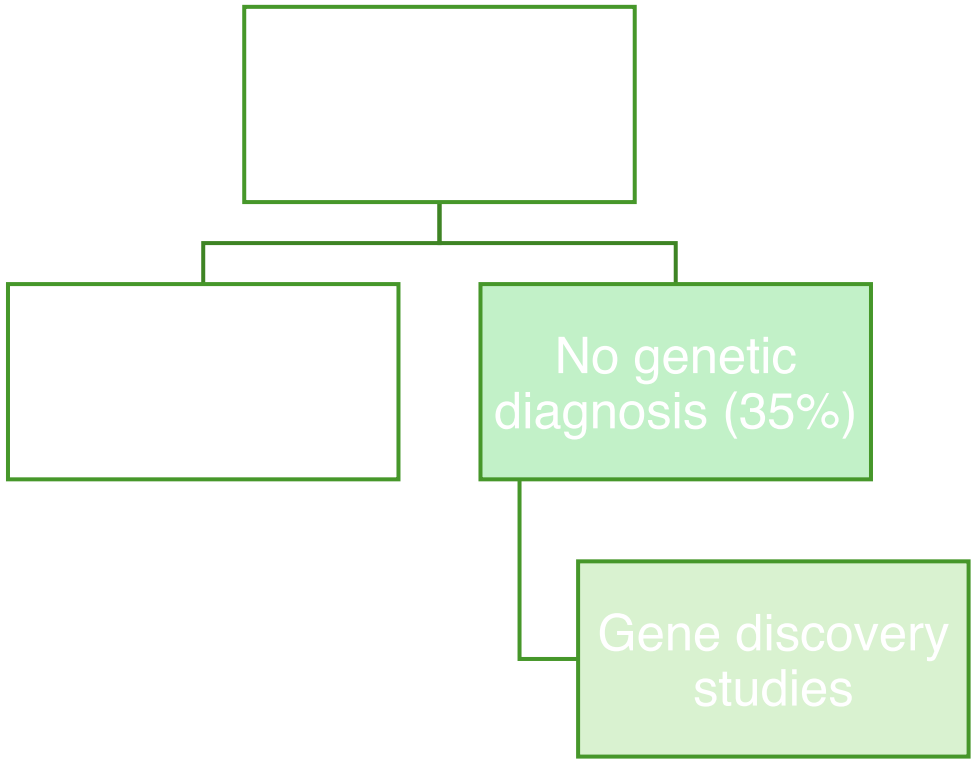
Genetic diagnosis provided for 53% of Turkish Referrals

- Disease causing variant identified
  n = 231/435 (53%)

- ***ABCC8*:** 143
- ***KCNJ11*:** 31
- ***HADH*:** 29
- ***GLUD1*:** 9
- ***GCK*:** 4
- ***HK1*:** 3
- ***HNF4/1A*:** 3
- **Other:** 9

Research studies to discover new genes and improve understanding of congenital hyperinsulinism

Research Opportunities for Families Living with Congenital Hyperinsulinism



Consent

1. We understand that our samples and clinical information will be used only for diagnostic and research purposes relevant to ourselves and others in my family. Please Tick ☐
2. We also consent for our samples and clinical information to be saved in the Genetic Beta Cell Bank for use in future research into all forms of hyperinsulinism and other beta cell conditions, whether or not it is of direct clinical benefit to us. Please Tick: Yes ☐ No ☐
3. We are also happy to be contacted about research into hyperinsulinism and you may contact me directly at:

Name: Address: Telephone: E-mail:

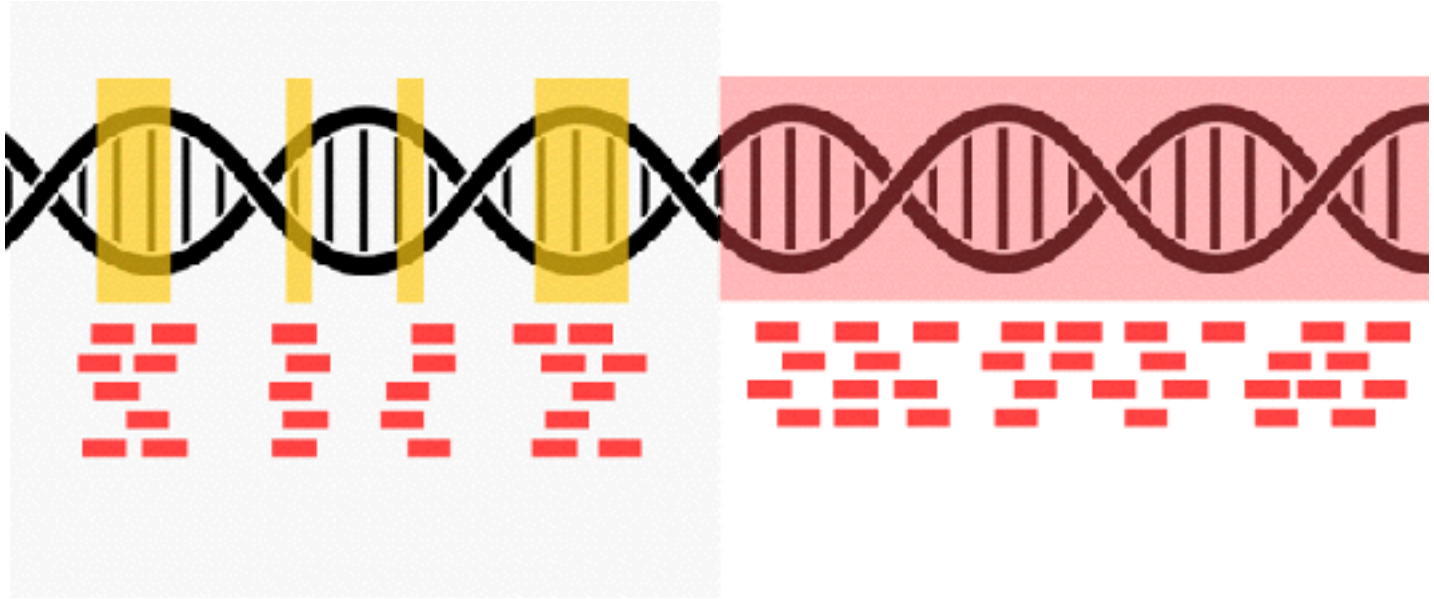
Signed by patient/ guardian/advocate: ..... Date: .....

For more information (and patient information sheets) please see www.diabetesgenes.org/content/genetic-beta-cell-research-bank

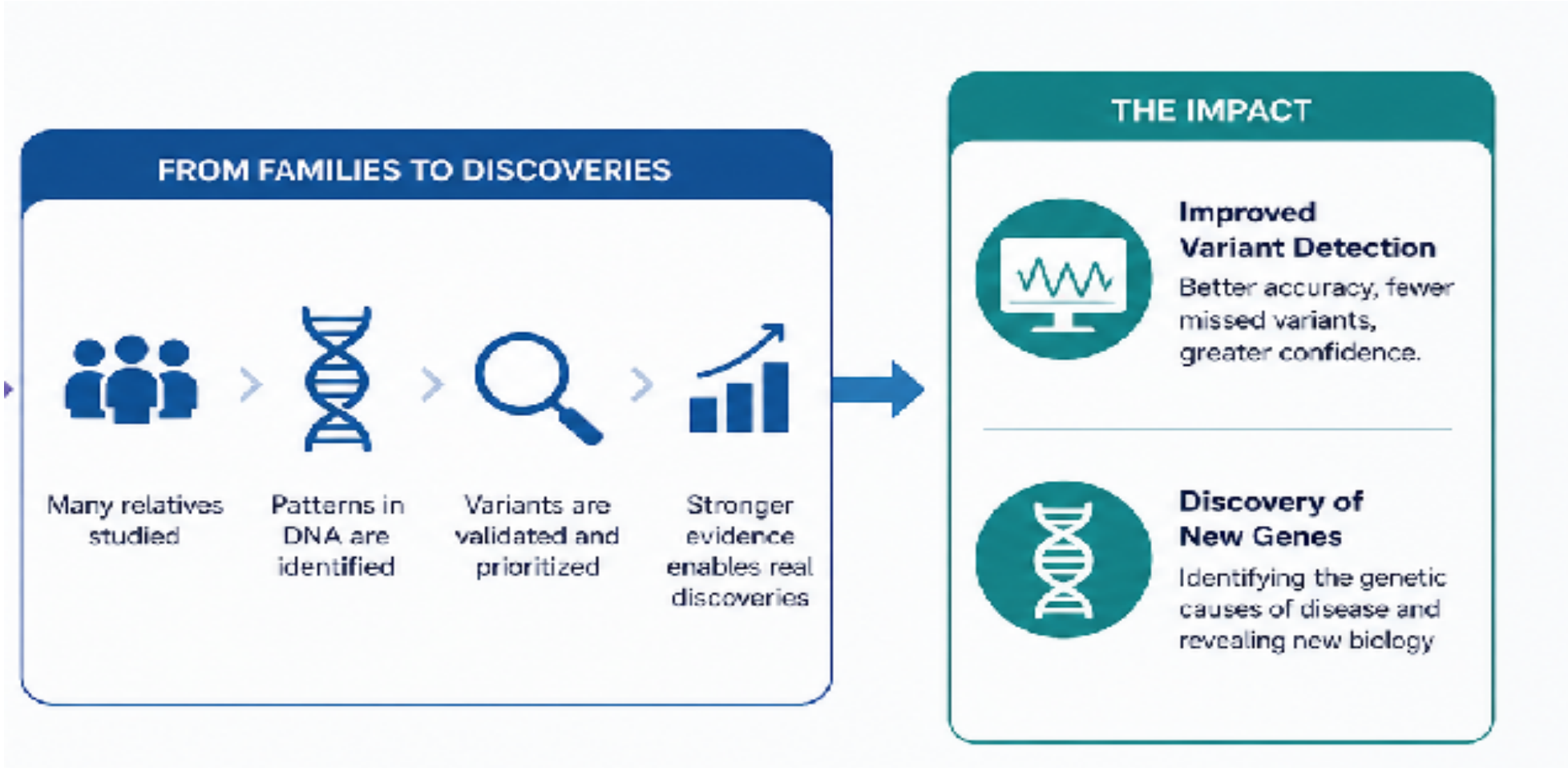
Whole genome sequencing to search for new genetic causes of congenital hyperinsulinism

Routine testing: screen for variants in the genes known to cause hyperinsulinism

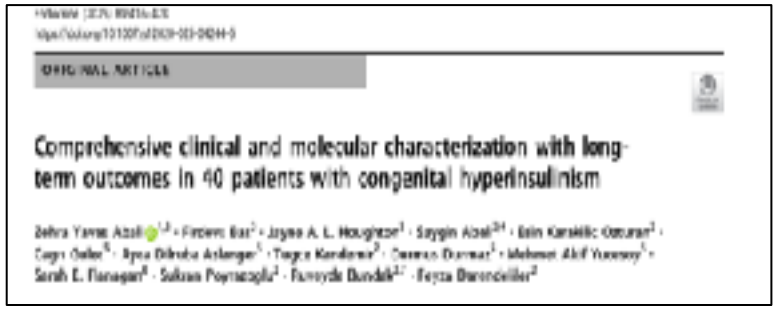
Research studies: screen all 20,000 genes to search for disease-causing variants



Many Turkish families have contributed to recent genetic discoveries



Working together to improve scientific knowledge: Exeter–Turkey Partnership



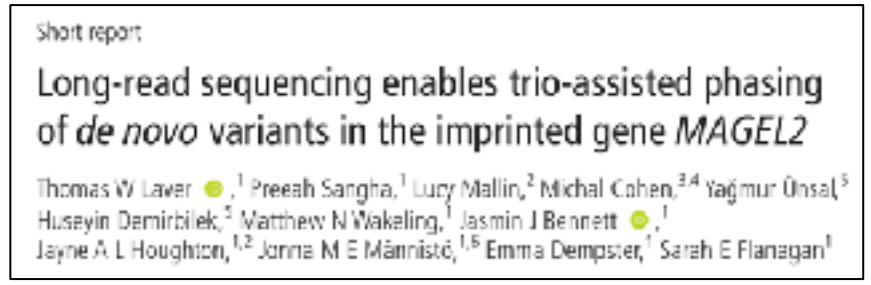
ORIGINAL ARTICLE

Comprehensive clinical and molecular characterization with long-term outcomes in 40 patients with congenital hyperinsulinism

Genome Medicine

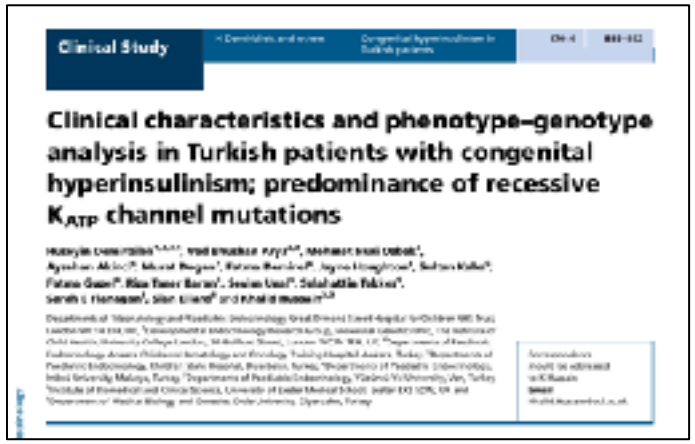
RESEARCH Open Access

Non-coding *cis*-regulatory variants in *HK1* cause congenital hyperinsulinism with variable disease severity



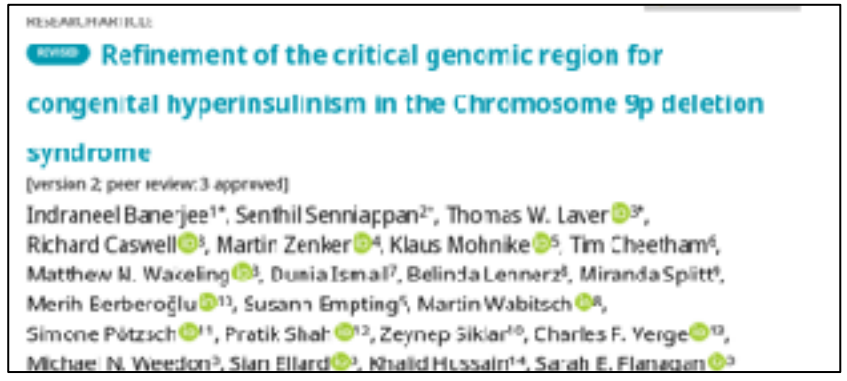
Short report

Long-read sequencing enables trio-assisted phasing of *de novo* variants in the imprinted gene *MAGEL2*



Clinical Study

Clinical characteristics and phenotype–genotype analysis in Turkish patients with congenital hyperinsulinism; predominance of recessive K_{ATP} channel mutations

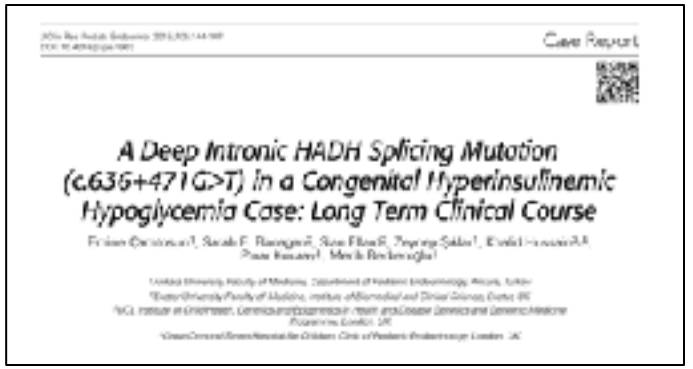


RESEARCH ARTICLE

REVISED Refinement of the critical genomic region for congenital hyperinsulinism in the Chromosome 9p deletion syndrome

[version 2; peer review: 3 approved]

Indraneel Banerjee[1*], Senthil Senniappan[2*], Thomas W. Laver[3*], Richard Caswell[4], Martin Zenker[5], Klaus Mohnike[6], Tim Cheetham[7], Matthew N. Wakeling[8], Dunia Ismail[9], Belinda Lennerz[8], Miranda Splitt[8], Merih Berberoğlu[10], Susann Empting[6], Martin Wabitsch[11], Simone Pötzsch[11], Pratik Shah[12], Zeynep Siklar[10], Charles F. Verge[13], Michael N. Weedon[3], Sian Ellard[3], Khalid Hussain[14], Sarah E. Flanagan[3]



Case Report

A Deep Intronic HADH Splicing Mutation (c.636+471G>T) In a Congenital Hyperinsulinemic Hypoglycemia Case: Long Term Clinical Course

CASE REPORT

Congenital Hyperinsulinism and Evolution to Sulfonylurea-responsive Diabetes Later in Life due to a Novel Homozygous p.L171F *ABCC8* Mutation

HORMONE RESEARCH IN PAEDIATRICS

Novel Insights from Clinical Practice

Coexistence of Mosaic Uniparental Isodisomy and a *KCNJ11* Mutation Presenting as Diffuse Congenital Hyperinsulinism and Hemihypertrophy

REPORT

Next-Generation Sequencing Reveals Deep Intronic Cryptic *ABCC8* and *HADH* Splicing Founder Mutations Causing Hyperinsulinism by Pseudoexon Activation

Clinical characteristics of recessive and dominant congenital hyperinsulinism due to mutation(s) in the *ABCC8/KCNJ11* genes encoding the ATP-sensitive potassium channel in the pancreatic beta cell

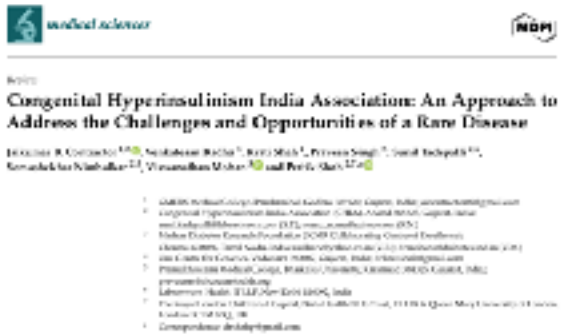
Supporting the development of genomic testing services for hyperinsulinism worldwide

India

Ukraine

Finland

Host Laboratory Visits and Placements



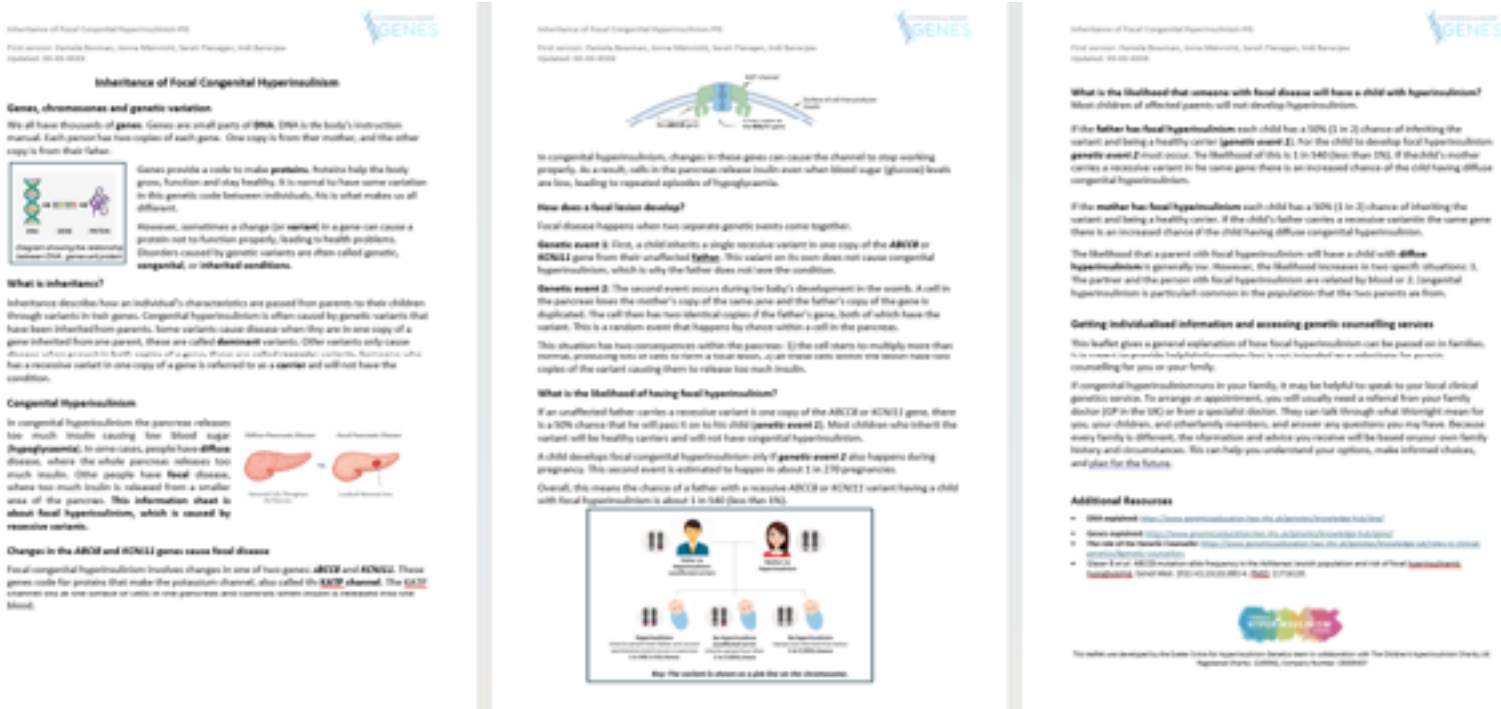
Congenital Hyperinsulinism India Association: An Approach to Address the Challenges and Opportunities of a Rare Disease

Support variant interpretation

Share laboratory protocols

Patient resources under development

- **Types of Inheritance**
- **Genetic subforms**
- **Understanding genetic reports**



Translate into different languages

www.hyperinsulinismgenes.org

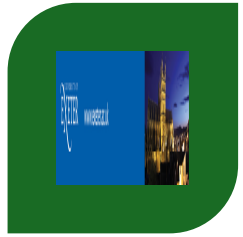
Summary

GENETIC TESTING FOR CONGENITAL HYPERINSULINISM IS IMPORTANT AS IT CAN INFORM MEDICAL MANAGEMENT

ROUTINE TESTING IDENTIFIES A DISEASE-CAUSING CHANGE IN ~65% OF PEOPLE

EACH FAMILY'S GENETICS ARE UNIQUE – REQUIRE TAILORED ADVICE

RESEARCH UNDERWAY TO SEARCH FOR NEW GENES IN THE PEOPLE WITHOUT A GENETIC DIAGNOSIS



SUPPORTING LABORATORIES IN DEVELOPING THEIR OWN GENETIC TESTING SERVICES AND IMPROVE RESOURCES

Acknowledgments

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

Families and clinicians

Dr Huseyin Demirbilek, Turkey

CHI Congenital Hyperinsulinism International

Science is a gradual accumulation of small advances, each one building on the last.

Teşekkür ederim

HYPERINSULINISM
GENES

The Open Hyperinsulinism Genes Project

The Exeter Centre for Hyperinsulinism Genetics at the University of Exeter and Congenital Hyperinsulinism International