

# Genetics of congenital hyperinsulinism: How do we know?

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[www.hyperinsulinismgenes.org](http://www.hyperinsulinismgenes.org)





# The Exeter Team



**Prof Sarah Flanagan**  
Geneticist



**Dr Jayne Houghton**  
Lead NHS Clinical Scientist



**Dr Rachel Van Heugten**  
NHS Healthcare Scientist



**Dr Matthew Wakeling**  
Bioinformatician



**Dr Pam Bowman**  
Clinical Geneticist



**Dr Matthew Johnson**  
Geneticist



**Dr Nick Owens**  
Functional Biologist



**Dr Tom Laver**  
Bioinformatician



**Dr Jonna Männistö**  
Clinician Scientist



**Dr Oguzhan Kalyon**  
Bioinformatician



**Sabrina Wright**  
Technician



**Michaelis Vasiliadis**  
PhD Student



**Dr Jasmin Hopkins**  
Geneticist



**Isabella Lazaridi**  
Placement student



**Dr Jessica Hopkinson**  
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



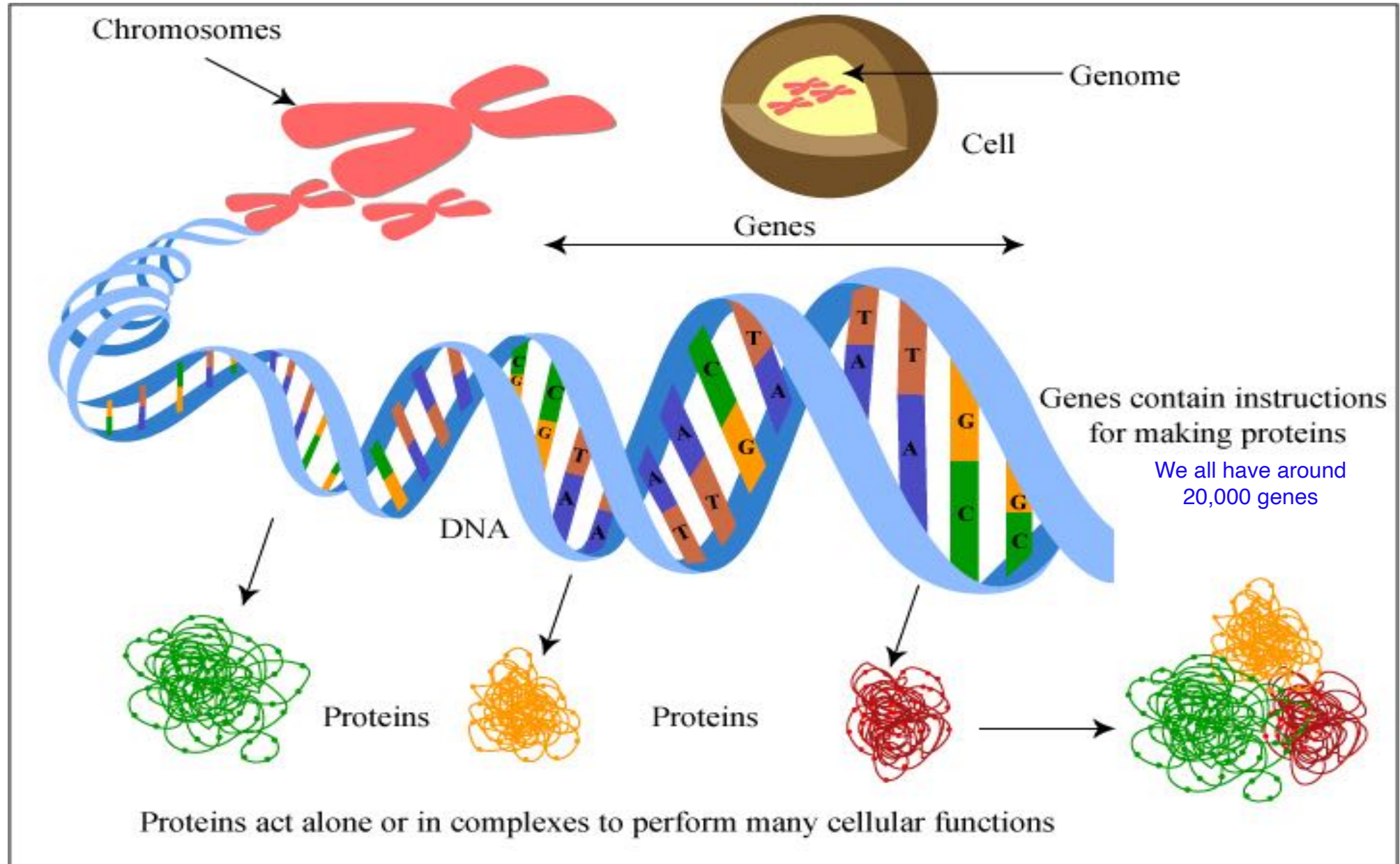
**The genetics of hyperinsulinism is complex:**  
over 35 different known disease genes and lots  
of different ways of inheriting the condition



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



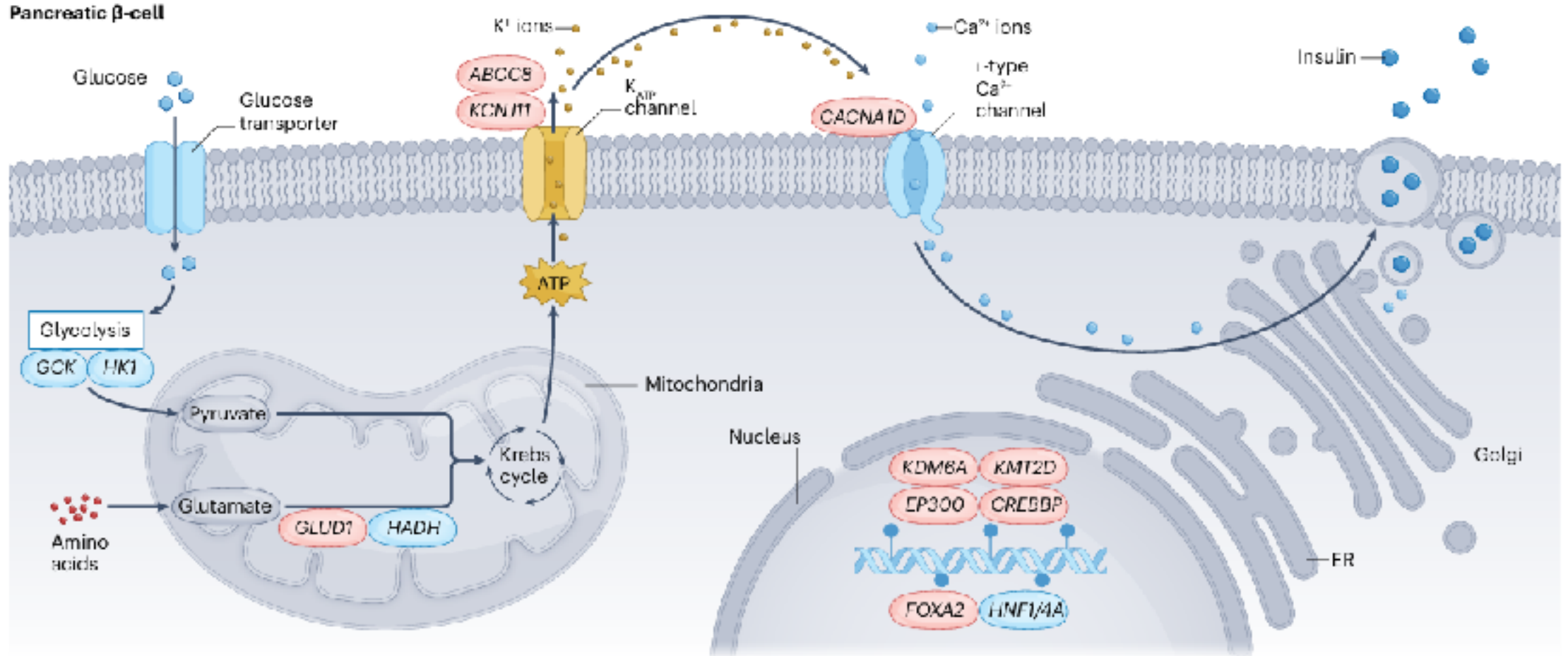
## We all have lots of changes (variants) in our DNA

### 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

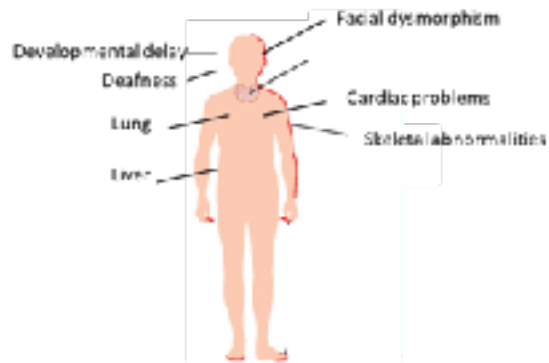


# Changes in over 35 genes are known to cause hyperinsulinism



# 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)



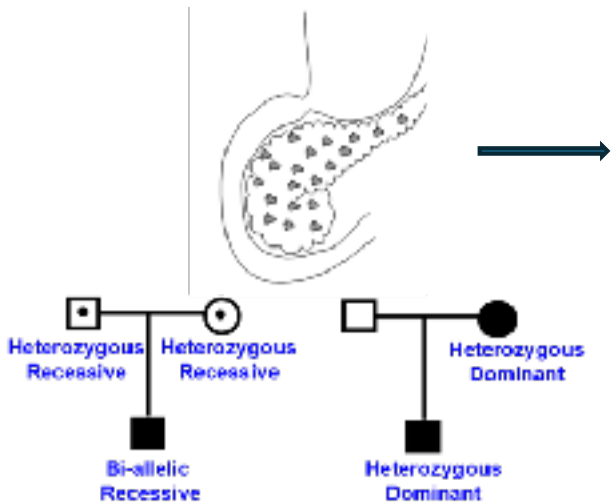
Monitoring for diabetes (e.g. *HNF4A*, *HNF1A* genes)

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

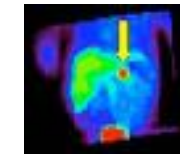
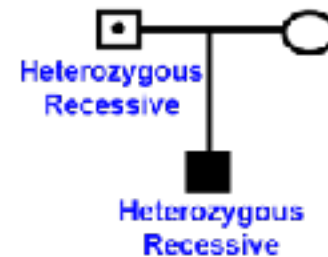
**Diffuse disease**

**Or**

**Focal disease**



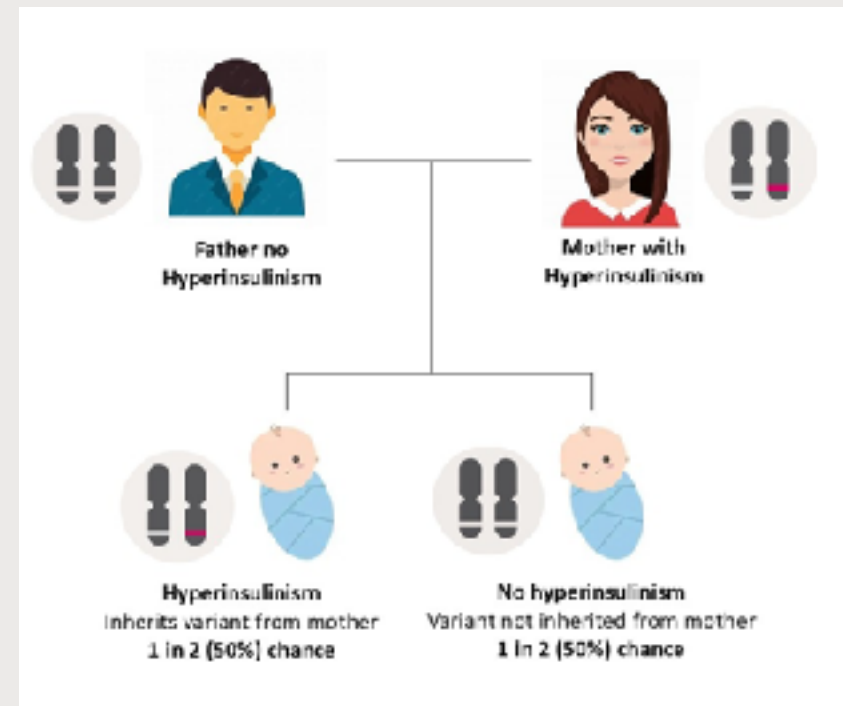
**Near total pancreatectomy**  
Insulin dependent diabetes and exocrine insufficiency



**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



University of Exeter



**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 <sup>1\*</sup>, Henrik Thybo Christesen<sup>2</sup>, Michael Bau Mortensen<sup>3</sup>, Jayne A. L. Houghton<sup>4</sup>, Anne Lerberg Nielsen<sup>5</sup>, Sönke Detlefsen<sup>6</sup> and Sarah E. Flanagan<sup>7</sup>

<sup>1</sup>Ukrainian Scientific and Practical Center of Endocrine Surgery, Transplantation of Endocrine Organs and Tissues of MUIH of Ukraine, Kyiv, Ukraine; <sup>2</sup>Herz Christien Andersen Children's Hospital, Odense University Hospital, Odense, Denmark; <sup>3</sup>Department of Surgery, Upper GI and HPB Section, Odense University Hospital, Odense, Denmark; <sup>4</sup>The Cancer Research UK Royal Devon University Healthcare NHS Foundation Trust, Exeter, United Kingdom; <sup>5</sup>Department of Nuclear Medicine, Odense University Hospital, Odense, Denmark; <sup>6</sup>Department of Pathology, Odense University Hospital, Odense, Denmark; <sup>7</sup>Department of Clinical and Biomedical Science, University of Exeter Medical School, Exeter, United Kingdom



Dr Evgenia Globa, Ukraine



Dr Henrik Christesen, Denmark

**nature**

Correspondence

<https://doi.org/10.1038/s44363-026-0019-9>

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

 Check for updates

# Genetic testing involves searching for variants in the known hyperinsulinism genes



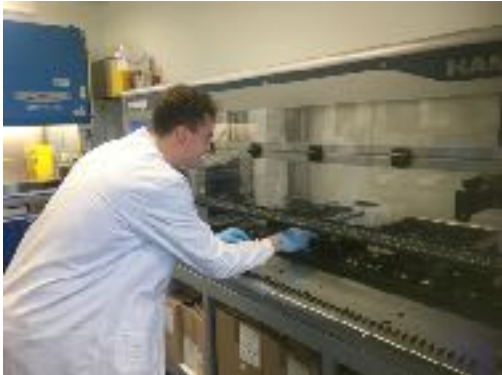
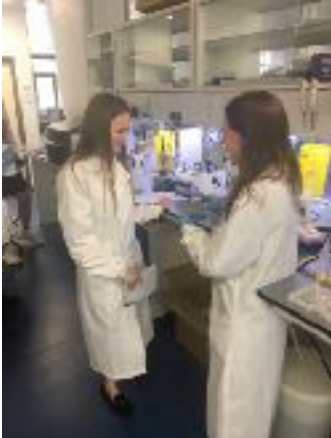
Blood sample sent to laboratory



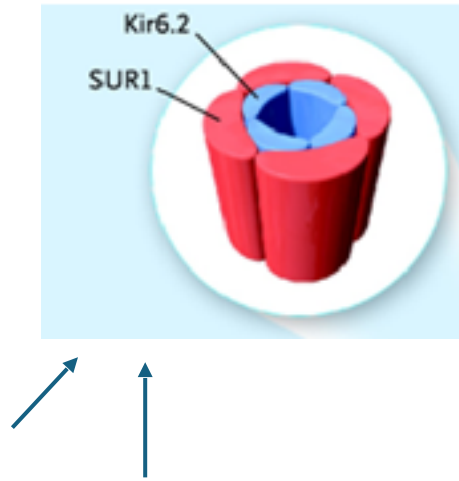
DNA is extracted



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%)

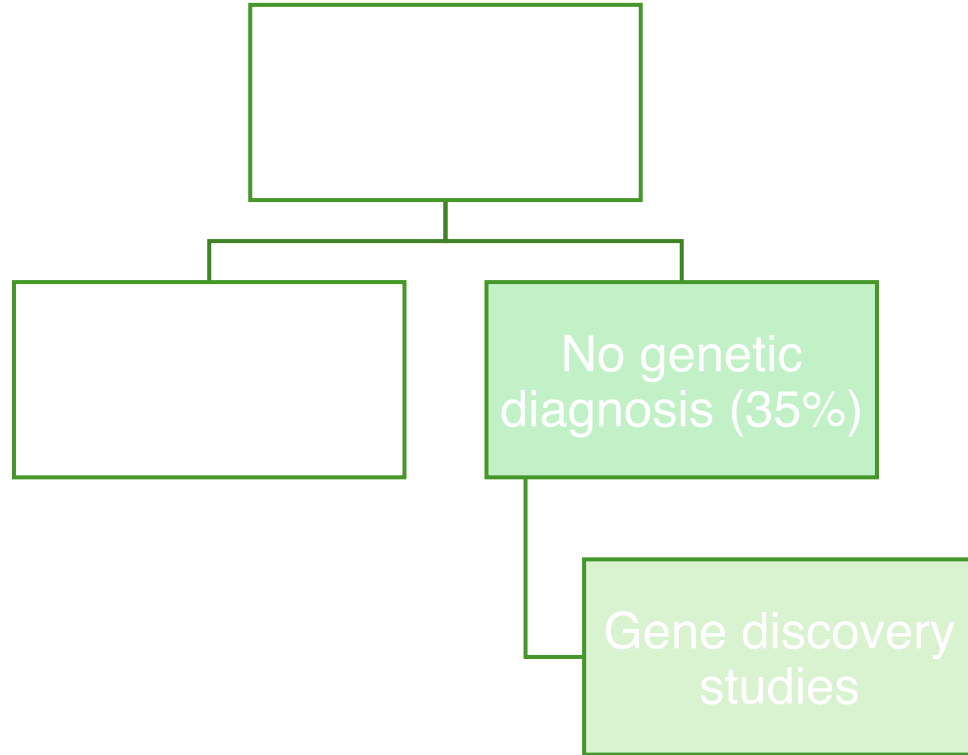
- ABCC8***: 143
- KCNJ11***: 31
- HADH***: 29
- GLUD1***: 9
- GCK***: 4
- HK1***: 3
- HNF4/1A***: 3
- Other**: 9



# 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.diabetes.org.uk/content/genetic-beta-cell-research-bank](http://www.diabetes.org.uk/content/genetic-beta-cell-research-bank)

**DiabetesGenes**

Search for:  In Current Research

About - What Type Of Diabetes? MODY - Neonatal Diabetes - Rare Types - Tests For Diabetes Subtypes - Current Research - Training & Events - Donate

## Genetic Beta Cell Research Bank

[View other Diabetes Studies](#)

GenC Home Patients Professionals

### Lead Site, Exeter

University of Exeter Medical School,  
Royal Devon University Healthcare  
NHS Foundation Trust

**Overall Responsibility:**

Dr Kevin Coldough  
Dr Jayne Houghton  
Principal Clinical Scientists  
Exeter Genomics Laboratory  
Royal Devon University Healthcare  
NHS Foundation Trust  
Barnack Road  
Exeter EX2 2DW

[k.coldough@ex.ac.uk](mailto:k.coldough@ex.ac.uk)  
[j.houghton@ex.ac.uk](mailto:j.houghton@ex.ac.uk)

**Nursing Management:**

Dr Maggie Shepherd  
Senior Research Nurse  
NHS Exeter Clinical Research  
Facility  
Royal Devon University Healthcare  
NHS Foundation Trust  
Barnack Road  
Exeter  
EX2 2DW

[m.shepherd@ex.ac.uk](mailto:m.shepherd@ex.ac.uk)  
Tel: 01392 428374

Responsible for overseeing recruitment of new volunteers and samples donated specifically for research purposes.

### Research Reference Numbers

IRMS:  
310560

REC:  
Fores Research Ethics Committee 5  
22/19/0298

CRP:  
1/1

**The Genetic Beta Cell Research Bank (GenCRB) is a Tissue Bank With Over-arching Ethics To Carry Out Research Into The Mechanisms And Genetic Causes Of Diabetes And Other Beta Cell Disorders.**

The Genetic Beta Cell Research Bank (GenCRB) is a tissue bank with over-arching ethics to carry out research into the mechanisms and genetic causes of diabetes and other beta cell disorders. It stores samples from diagnostic archives and residual samples from research activity where enduring consent has been given. The GenCRB ensures effective guardianship of these samples, with a Steering Committee that review all requests to use samples and associated data to ensure they are sensibly used to improve the diagnosis, care and treatment of genetic diabetes.

The Royal Devon University Healthcare NHS Foundation Trust Molecular Genetics Laboratory is a world leader in monogenic diabetes diagnosis and receives samples from over 10 countries. Patients referred to the service currently provide consent for their samples to be analysed to determine the genetic cause of their diabetes. A genetic diagnosis is found for around 33% of patients tested. If however, a genetic cause is not found, suggesting a new causative gene or a non-monogenic form of diabetes, the analysis of samples becomes part of a research question. If no clear diagnosis is found, DNA samples are usually stored and re-analysed in the future when new genes have been discovered. Samples in these storage areas may fall between research and diagnostic governance procedures.

### Eligibility And Inclusion Criteria

1. Any person may donate samples originally taken for diagnostic purposes. In such cases there are no exclusion criteria as the burden to the donor is minimal.
2. Samples primarily for research purposes will be collected with consideration to minimise burden. Where possible, saliva samples or buccal swabs will be used to obtain DNA from children or adults lacking capacity to consent.

### Informed Consent For Samples/Data To Be Stored In This Research Bank

- 1. Use Of Excess Diagnostic Samples For Research Purposes
- 2. Use Of Excess Research Samples For Future Research Purposes
- 3. Use Of Samples Specifically Collected For Research Purposes
- Tissue Donor Privacy And Confidentiality

### Patients

If you are a patient and would like more information, please click [here](#)

### Professionals

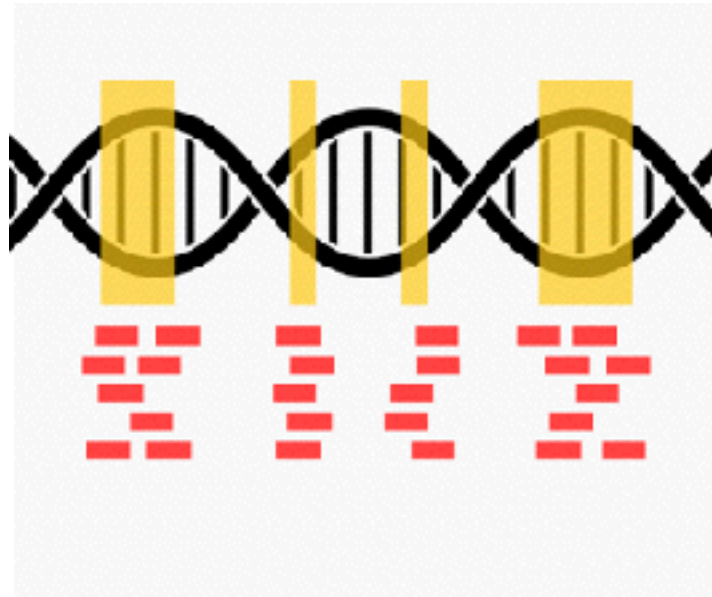
Our referral form includes informed consent/assent statements.

For information about referring to the Genetic Beta Cell Research Bank and patient information sheets, please click [here](#).

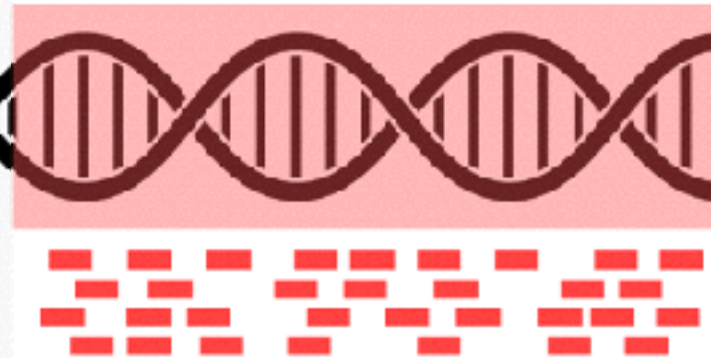
It is accepted that these are not as detailed as a research study consent form, but aims to provide sufficient evidence of informed consent and/or assent by the patient and/or consent from a guardian or consultant, without burdening the patient and their clinician with excessive administration during a time limited clinical appointment.

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

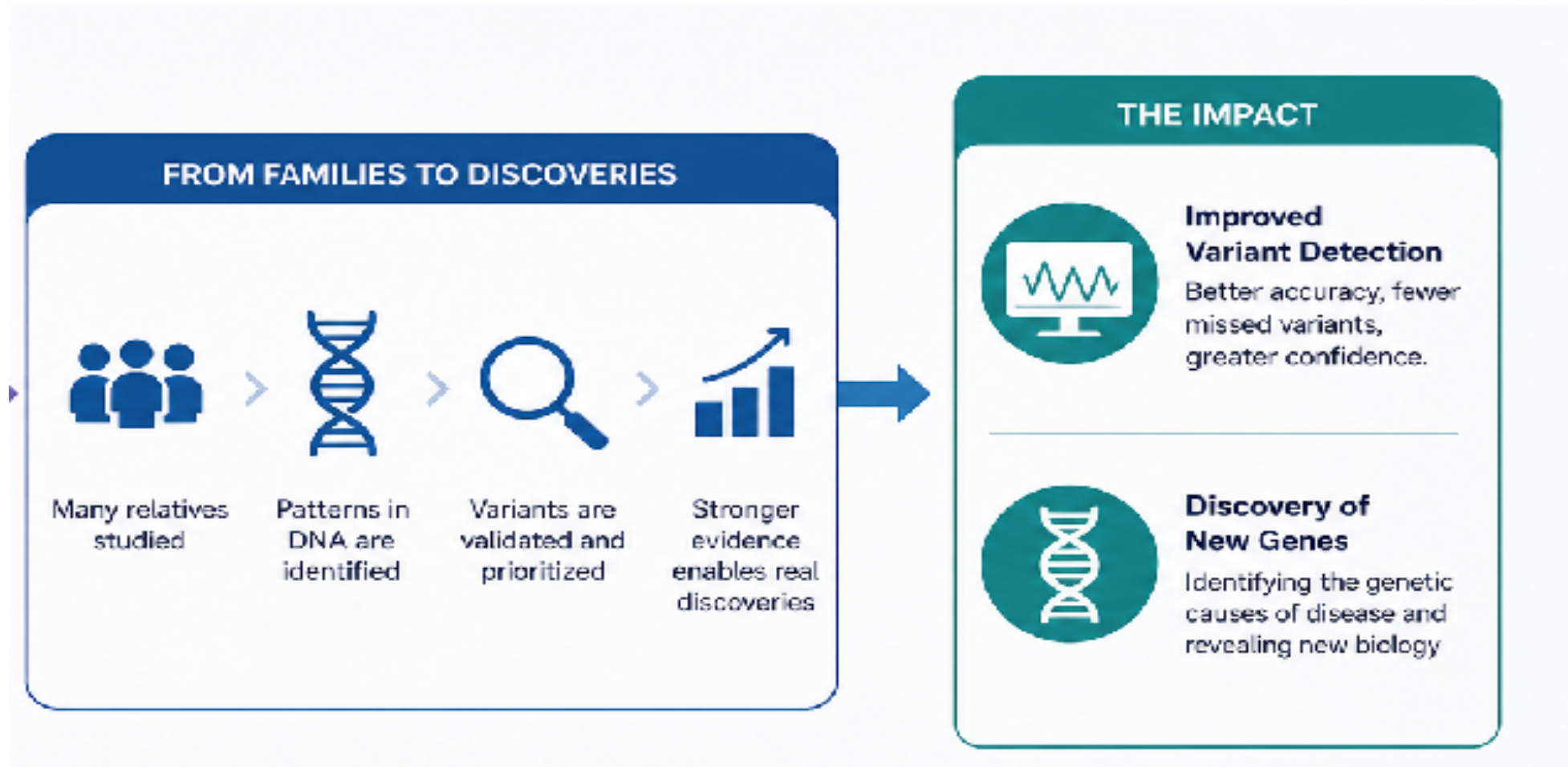
**Routine testing:** screen for variants in the genes known to cause hyperinsulinism



**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

Waller JM, Wakeling N, Sangha P, et al. *Diabetologia* 2019;62:144–52

**ORIGINAL ARTICLE**

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

Belma Yanik Azal<sup>1,2</sup>, Fırat Bar<sup>1</sup>, Jayne A. L. Houghton<sup>1</sup>, Saygin Akal<sup>2,1</sup>, Ekin Karadöküç Öncü<sup>1</sup>, Çağrı Güler<sup>1</sup>, Ayşe Dilsaba Arslanlar<sup>1</sup>, Tugçe Karadöküç<sup>1</sup>, Çarman Duman<sup>1</sup>, Mehmet Akif Yücey<sup>1</sup>, Sarah E. Flanagan<sup>1</sup>, Sükran Poymazoğlu<sup>1</sup>, Feryde Dundak<sup>2</sup>, Feyza Darendeliler<sup>2</sup>

Waller JM, Wakeling N, Sangha P, et al. *Genome Medicine* 2019;11:116

**RESEARCH** **Open Access**

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

Jayne A. L. Houghton<sup>1</sup>, Lucie Saint-Martin<sup>2</sup>, Bianca Naumann<sup>3</sup>, Zeynep M. E. Mönke<sup>1,4</sup>, Jayne A. L. Houghton<sup>1</sup>, Susan Empting<sup>5</sup>, Matthew W. Johnson<sup>6</sup>, Thomas W. Laver<sup>1</sup>, Jonathan M. Laska<sup>7</sup>, Benjamin Sparrow<sup>8</sup>, Matthew N. Wakeling<sup>9</sup>, Andrew Ranejee<sup>10</sup>, Antaria Dastanov<sup>11</sup>, Hüseyin Demirbilek<sup>12</sup>, John Mitchell<sup>13</sup>, Markus Storgel<sup>14</sup>, Inesational Congenital Hyperinsulinism Consortium<sup>15</sup>, Klaus Mohnik<sup>16</sup>, Jean-Baptiste Amouk<sup>17</sup>, Nick D. L. Owen<sup>18</sup>, Martin Zenker<sup>19</sup>, Christine Bellard-Chazelot<sup>20</sup> and Sarah E. Flanagan<sup>1</sup>

Short report

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

Thomas W Laver<sup>1</sup>, Preetah Sangha<sup>1</sup>, Lucy Mallin<sup>2</sup>, Michal Cohen<sup>3,4</sup>, Yağmur Ünsal<sup>5</sup>, Hüseyin Demirbilek<sup>6</sup>, Matthew N Wakeling<sup>1</sup>, Jasmin J Bennett<sup>7</sup>, Jayne A. L. Houghton<sup>1,2</sup>, Jonna M E Männistö<sup>1,5</sup>, Emma Dempster<sup>1</sup>, Sarah E Flanagan<sup>1</sup>

**Clinical Study**

### Clinical characteristics and phenotype–genotype analysis in Turkish patients with congenital hyperinsulinism; predominance of recessive *K<sub>ATP</sub>* channel mutations

Hüseyin Demirbilek<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000</sup>

**RESEARCH PAPER**

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

[version 2; peer review: 3 approved]

Indraneel Banejee<sup>1\*</sup>, Senthil Senniappan<sup>2</sup>, Thomas W. Laver<sup>3\*</sup>, Richard Caswell<sup>4</sup>, Martin Zenker<sup>5,6</sup>, Klaus Mohnik<sup>7,8</sup>, Tim Cheetham<sup>9</sup>, Matthew N. Wakeling<sup>10</sup>, Dumia Ismail<sup>11</sup>, Belinda Lennerz<sup>12</sup>, Miranda Spitt<sup>13</sup>, Merih Berberoğlu<sup>14,15</sup>, Susann Empting<sup>16</sup>, Martin Wabitsch<sup>17,18</sup>, Simone Pötzsch<sup>19,20</sup>, Pratik Shah<sup>21,22</sup>, Zeynep Sikiar<sup>23</sup>, Charles F. Yerge<sup>24,25</sup>, Michael N. Weedon<sup>26</sup>, Sian Ellard<sup>27</sup>, Khalid Hussain<sup>28</sup>, Sarah E. Flanagan<sup>29</sup>

**Case Report**

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

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**CASE REPORT**

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

Emine Gültekin<sup>1</sup>, Sükran Poymazoğlu<sup>2</sup>, Feyza Darendeliler<sup>3</sup>, Jayne A. Houghton<sup>4</sup>, Sian Ellard<sup>5</sup>, Sarah E. Flanagan<sup>6</sup>, Khalid Hussain<sup>7</sup>

**HORMONE RESEARCH IN PEDIATRICS**

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

Pinar Kocaay<sup>1</sup>, Zeynep Sikiar<sup>2</sup>, Sian Ellard<sup>3</sup>, Aydin Yağmurlu<sup>4</sup>, Emine Gültekin<sup>5</sup>, Eric Erdem<sup>6</sup>, Merih Berberoğlu<sup>7</sup>, Sarah E. Flanagan<sup>8</sup>

**REPORT**

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

Sarah E. Flanagan<sup>1</sup>, Merih Berberoğlu<sup>2</sup>, Sian Ellard<sup>3</sup>, Aydin Yağmurlu<sup>4</sup>, Emine Gültekin<sup>5</sup>, Feyza Darendeliler<sup>6</sup>, Pinar Kocaay<sup>7</sup>, Çağrı Güler<sup>8</sup>, Hüseyin Demirbilek<sup>9</sup>, Mustafa Şahin<sup>10</sup>, Andrew Green<sup>11,12</sup>, Peter E. Claverie<sup>13</sup>, Fabrice Gaudin<sup>14,15</sup>, Peter E. Claverie<sup>16</sup>, Khalid Hussain<sup>17,18</sup>, Michael N. Weedon<sup>19</sup> and Sarah E. Flanagan<sup>1</sup>

**RESEARCH PAPER**

### 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

Mustafa Şahin<sup>1</sup>, Sükran Poymazoğlu<sup>2</sup>, Merih Berberoğlu<sup>3</sup>, Zeynep Sikiar<sup>4</sup>, Sian Ellard<sup>5</sup>, Sarah E. Flanagan<sup>6</sup>, Khalid Hussain<sup>7</sup>, Aydin Yağmurlu<sup>8</sup>

# Supporting the development of genomic testing services for hyperinsulinism worldwide



India



Ukraine



Finland

## Host Laboratory Visits and Placements



Support variant interpretation



Share laboratory protocols

# Patient resources under development

- Types of Inheritance
- Genetic subforms
- Understanding genetic reports

Introduction of Focal Congenital Hyperinsulinism (FCH) 

First version: Amanda Rowland, Anne Mowbray, Sarah Parnham, Gill Bergeron  
Updated: 05-05-2024

### Inheritance of Focal Congenital Hyperinsulinism

**Genes, chromosomes and genetic variation**

We all have thousands of **genes**. Genes are small parts of **DNA** (DNA is the body's instruction manual). Each person has two copies of each gene. One copy is from their mother, and the other copy is from their father.



Genes provide a code to make **proteins**. Proteins help the body grow, function and stay healthy. It is normal to have some variations in this genetic code between individuals, this is what makes us all different.

However, sometimes a change (or **variant**) in a gene can cause a protein not to function properly, leading to health problems. Disorders caused by genetic variants are often called **genetic**, **congenital**, or **inherited** conditions.

**What is inheritance?**

Inheritance describes how an individual's characteristics are passed from parents to their children through variants in their genes. Congenital hyperinsulinism is often caused by genetic variants that have been inherited from parents. Some variants cause disease when they are in one copy of a gene inherited from one parent, these are called **dominant** variants. Other variants only cause disease when present in both copies of a gene. These are called **recessive** variants. Someone who has a recessive variant in one copy of a gene is referred to as a **carrier** and will not have the condition.

**Congenital Hyperinsulinism**

In congenital hyperinsulinism the pancreas releases too much insulin causing low blood sugar (**hypoglycaemia**). In some cases, people have **diffuse** disease, where the whole pancreas releases too much insulin. Other people have **focal** disease, where too much insulin is released from a smaller area of the pancreas. **This information sheet is about focal hyperinsulinism, which is caused by recessive variants.**



**Changes in the KCNJ11 and KCNJ12 genes cause focal disease**

Focal congenital hyperinsulinism involves changes in one of two genes, **KCNJ11** and **KCNJ12**. These genes code for proteins that make the potassium channel, also called the **KATP channel**. The **KATP** channel acts as an on/off switch or gate in one pancreas and controls when insulin is released into one blood.

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In congenital hyperinsulinism, changes in these genes can cause the channel to stop working properly. As a result, cells in the pancreas release insulin even when blood sugar (glucose) levels are low, leading to repeated episodes of hypoglycaemia.

**How does a focal lesion develop?**

Focal disease happens when two separate genetic events come together.

**Genetic event 1:** First, a child inherits a single recessive variant in one copy of the **KCNJ11** or **KCNJ12** gene from their unaffected father. This variant on its own does not cause congenital hyperinsulinism, which is why the father does not have the condition.

**Genetic event 2:** The second event occurs during the baby's development in the womb. A cell in the pancreas loses the mother's copy of the same gene and the father's copy of the gene is duplicated. The cell then has two identical copies of the father's gene, both of which have the variant. This is a random event that happens by chance within a cell in the pancreas.

This situation has two consequences within the pancreas: (1) the cell starts to multiply more than normal, producing lots of cells or even a tumour, as all these cells seem one tumour have two copies of the variant causing them to release too much insulin.

**What is the likelihood of having focal hyperinsulinism?**

If an unaffected father carries a recessive variant in one copy of the **KCNJ11** or **KCNJ12** gene, there is a 50% chance that he will pass it on to his child (**genetic event 1**). Most children who inherit the variant will be healthy carriers and will not have congenital hyperinsulinism.

A child develops focal congenital hyperinsulinism only if **genetic event 2** also happens during pregnancy. This second event is estimated to happen in about 1 in 170 pregnancies.

Overall, this means the chance of a father with a recessive **KCNJ11** or **KCNJ12** variant having a child with focal hyperinsulinism is about 1 in 340 (less than 1%).



Map the variant to identify a pQTL site on the chromosome.

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**What is the likelihood that someone with focal disease will have a child with hyperinsulinism? Most children of affected parents will not develop hyperinsulinism.**

If the father has focal hyperinsulinism each child has a 50% (1 in 2) chance of inheriting the variant and being a healthy carrier (**genetic event 1**). For the child to develop focal hyperinsulinism **genetic event 2** must occur. The likelihood of this is 1 in 170 (less than 1%). If the child's mother carries a recessive variant in her same gene there is an increased chance of the child having diffuse congenital hyperinsulinism.

If the mother has focal hyperinsulinism each child has a 50% (1 in 2) chance of inheriting the variant and being a healthy carrier. If the child's father carries a recessive variant in the same gene there is an increased chance of the child having diffuse congenital hyperinsulinism.

The likelihood that a parent with focal hyperinsulinism will have a child with **diffuse** hyperinsulinism is generally low. However, the likelihood increases in two specific situations: 1. The partner and the person with focal hyperinsulinism are related by blood or 2. Congenital hyperinsulinism is particularly common in the population that the two parents are from.

**Getting individualised information and accessing genetic counselling services**

This leaflet gives a general explanation of how focal hyperinsulinism can be passed on in families. It is essential to get individualised information from a specialist genetic counsellor for genetic counselling for you or your family.

If congenital hyperinsulinism runs in your family, it may be helpful to speak to your local clinical genetics service. To arrange an appointment, you will usually need a referral from your family doctor (GP) or the UK or from a specialist doctor. They can talk through what thoughts mean for you, your children, and other family members, and answer any questions you may have. Because every family is different, the information and advice you receive will be based on your own family history and circumstances. This can help you understand your options, make informed choices, and plan for the future.

**Additional Resources**

- **UKH website** <https://www.hyperinsulinism.org.uk/about-us/ukh-ukh/>
- **Genes explained** <https://www.genesis.org.uk/genes-explained/>
- **The role of the KCNJ11 gene** <https://www.genesis.org.uk/genes-explained/kcnj11/>
- **Genes (Genetics explained)** <https://www.genesis.org.uk/genes-explained/genes-explained/>
- **Class 3 or 4 KCNJ11 mutation often happens in the inherited form of hyperinsulinism and not of focal hyperinsulinism** <https://www.genesis.org.uk/genes-explained/kcnj11/>



The leaflet was developed after a focus group on hyperinsulinism with The Children's Hyperinsulinism Study. It replaces the previous leaflet, Congenital Hyperinsulinism.

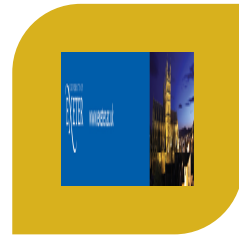


*Translate into different languages*

# 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

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**Turkey**



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

# Teşekkür ederim



**The Open Hyperinsulinism  
Genes Project**

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