HYPERINSULINISM GENES

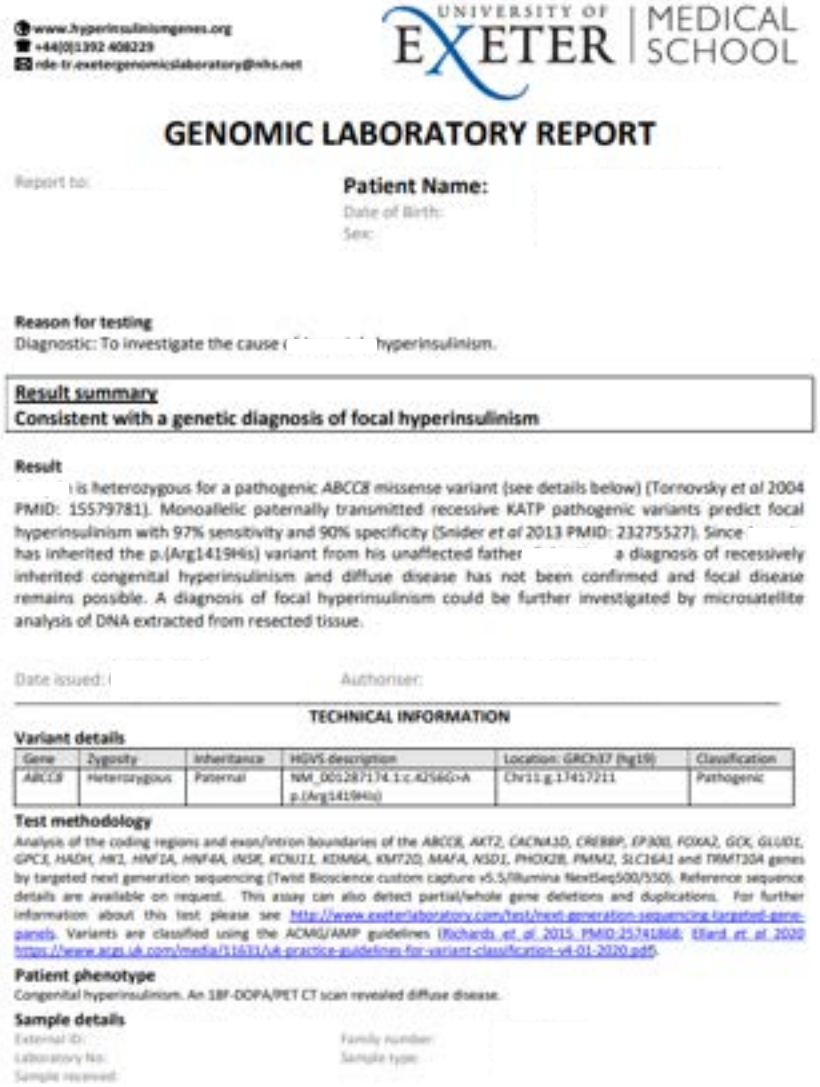
Learning about the genetic causes of HI and understanding your genetic report

Sarah Flanagan

@flanagan_se

Aim of the presentation

- DNA and genetic variation
- Known genetic causes of congenital hyperinsulinism
- The importance of a genetic diagnosis
- Opportunities for families without a genetic diagnosis



www.hyperinsulinismgenes.org
+44(0)1392 408229
rde-tr.exetergenomicslaboratory@nhs.net

UNIVERSITY OF EXETER | MEDICAL SCHOOL

GENOMIC LABORATORY REPORT

Report to:

Patient Name:
Date of Birth:
Sex:

Reason for testing
Diagnostic: To investigate the cause (hyperinsulinism.

Result summary
Consistent with a genetic diagnosis of focal hyperinsulinism

Result
is heterozygous for a pathogenic *ABCC8* missense variant (see details below) (Tornovsky *et al* 2004 PMID: 15579781). Monoallelic paternally transmitted recessive KATP pathogenic variants predict focal hyperinsulinism with 97% sensitivity and 90% specificity (Snider *et al* 2013 PMID: 23275527). Since has inherited the p.(Arg1419His) variant from his unaffected father a diagnosis of recessively inherited congenital hyperinsulinism and diffuse disease has not been confirmed and focal disease remains possible. A diagnosis of focal hyperinsulinism could be further investigated by microsatellite analysis of DNA extracted from resected tissue.

Date issued: Authoriser:

TECHNICAL INFORMATION

Variant details

Gene	Zygosity	Inheritance	HGVS description	Location: GRCh37 (hg19)	Classification
ABCC8	Heterozygous	Paternal	NM_001287174.1:c.4256G>A p.(Arg1419His)	Chr11:g.17417211	Pathogenic

Test methodology
Analysis of the coding regions and exon/intron boundaries of the *ABCC8, AKT2, CACNA1D, CREBBP, EP300, FOXA2, GCK, GLUD1, GPC3, HADH, HK1, HNF1A, HNF4A, INSR, KCNJ11, KDM6A, KMT2D, MAFA, NSD1, PHOX2B, PMM2, SLC16A1* and *TRMT10A* genes by targeted next generation sequencing (Twist Bioscience custom capture v5.5/Illumina NextSeq500/550). Reference sequence details are available on request. This assay can also detect partial/whole gene deletions and duplications. For further information about this test please see http://www.exeterlaboratory.com/test/next-generation-sequencing-targeted-gene-panels. Variants are classified using the ACMG/AMP guidelines (Richards et al 2015 PMID:25741868; Ellard et al 2020 https://www.acgs.uk.com/media/11631/uk-practice-guidelines-for-variant-classification-v4-01-2020.pdf).

Patient phenotype
Congenital hyperinsulinism. An 18F-DOPA/PET CT scan revealed diffuse disease.

Sample details
External ID: Family number:
Laboratory No: Sample type:
Sample received:

Important notes

- Methods for genetic testing will differ between laboratories
- Style of the genetic reports will differ between laboratories

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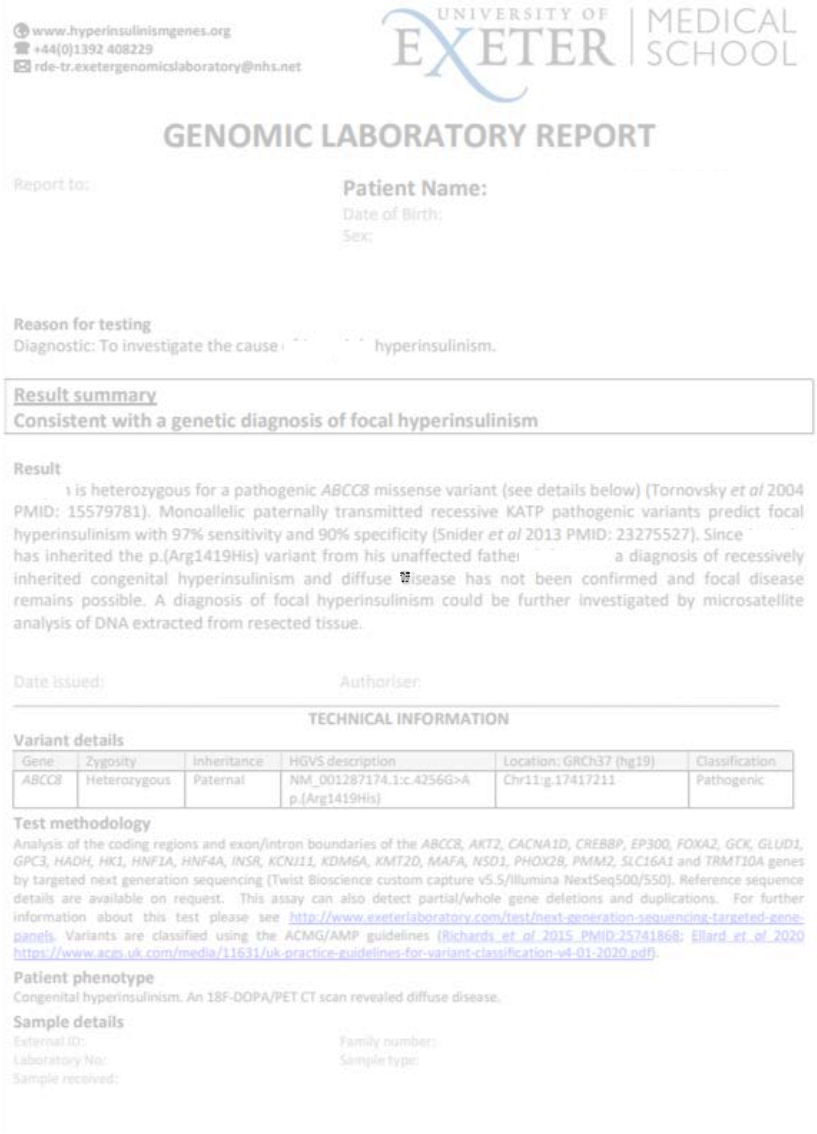

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The Human Genome

- An instruction manual stored in each cell to create, maintain and repair a human being from conception to the end of life

- The human genome is made up of 3 billion nucleotides of DNA (ATGC)

- Genome sequencing allows us to read the entire DNA sequence.

- Each individual has two copies of DNA (one inherited from their mother and one inherited from their father).

Genes code for proteins

- There are approximately 20,000 genes in the human genome

ABCC8 gene

ATG **CCC** **CTG** **GCC** **TTC**

Met Pro Leu Ala Phe

SUR1 protein

Met Pro Leu Ala Phe

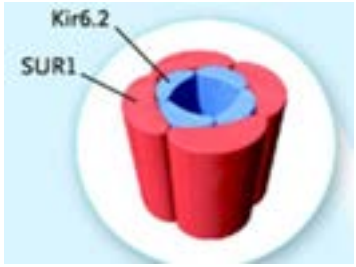
Nucleotides (building blocks of DNA contained within a ‘gene’)

⇩

Amino acids (building blocks of proteins)

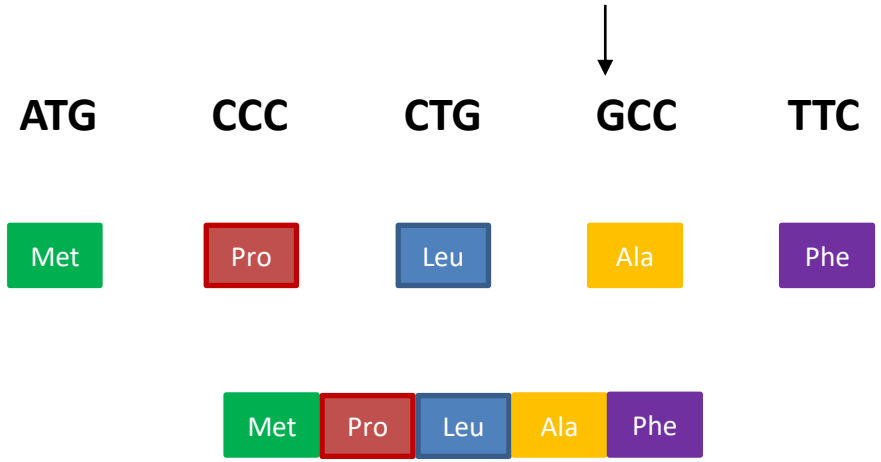
⇩

Proteins (e.g. GCK, SUR1, Kir6.2, GDH, HNF4A)



Every human genome differs by 4-5 million variants

New variants occur during DNA replication. If they arise in the germ cells (sperm/oocytes (egg)) they can be inherited by offspring and passed on through the generation



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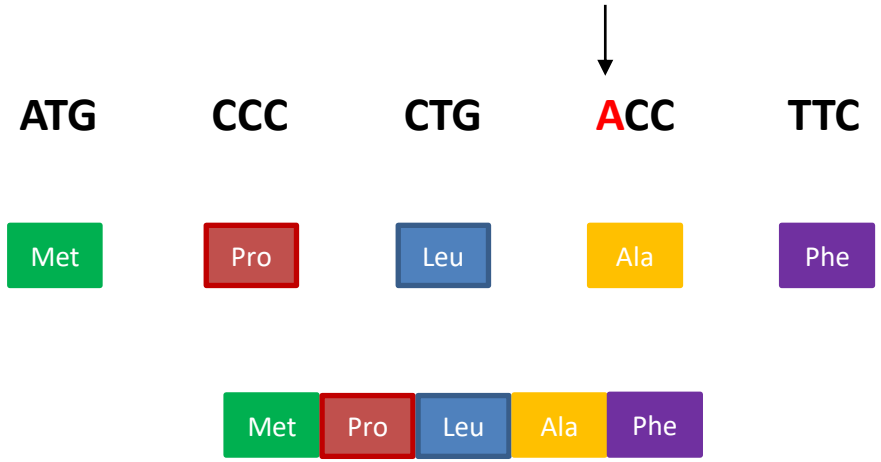

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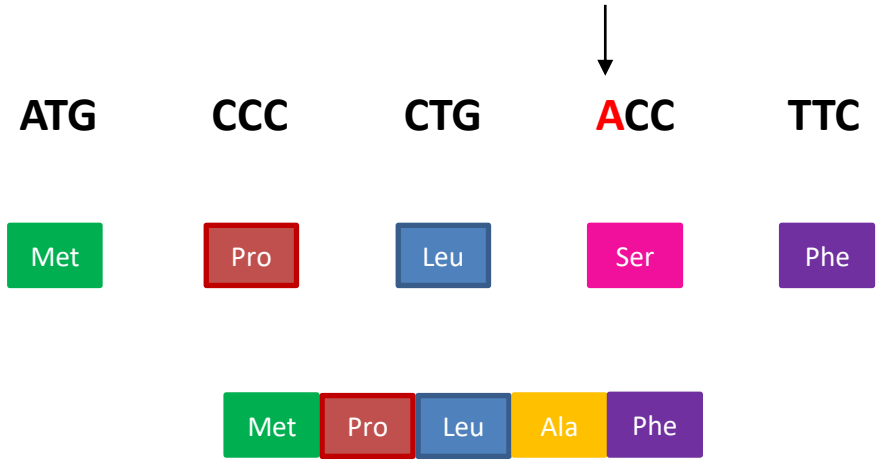

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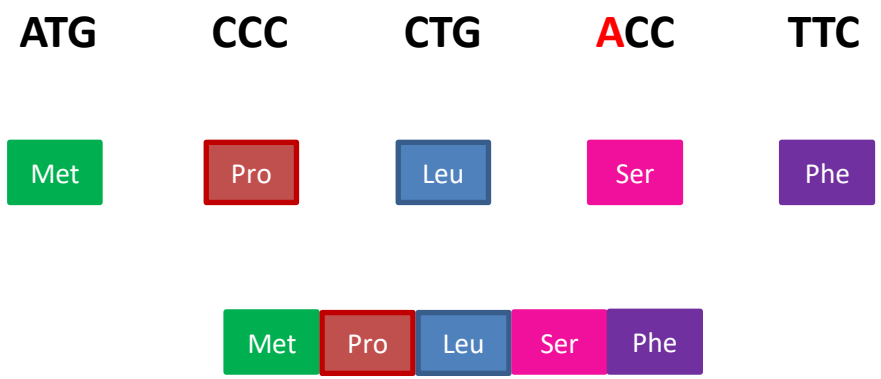

The impact of genetic variation

- No effect
- Define characteristics like eye colour
- Or cause disease when the variant is present in a region of DNA that is critical for normal function of protein

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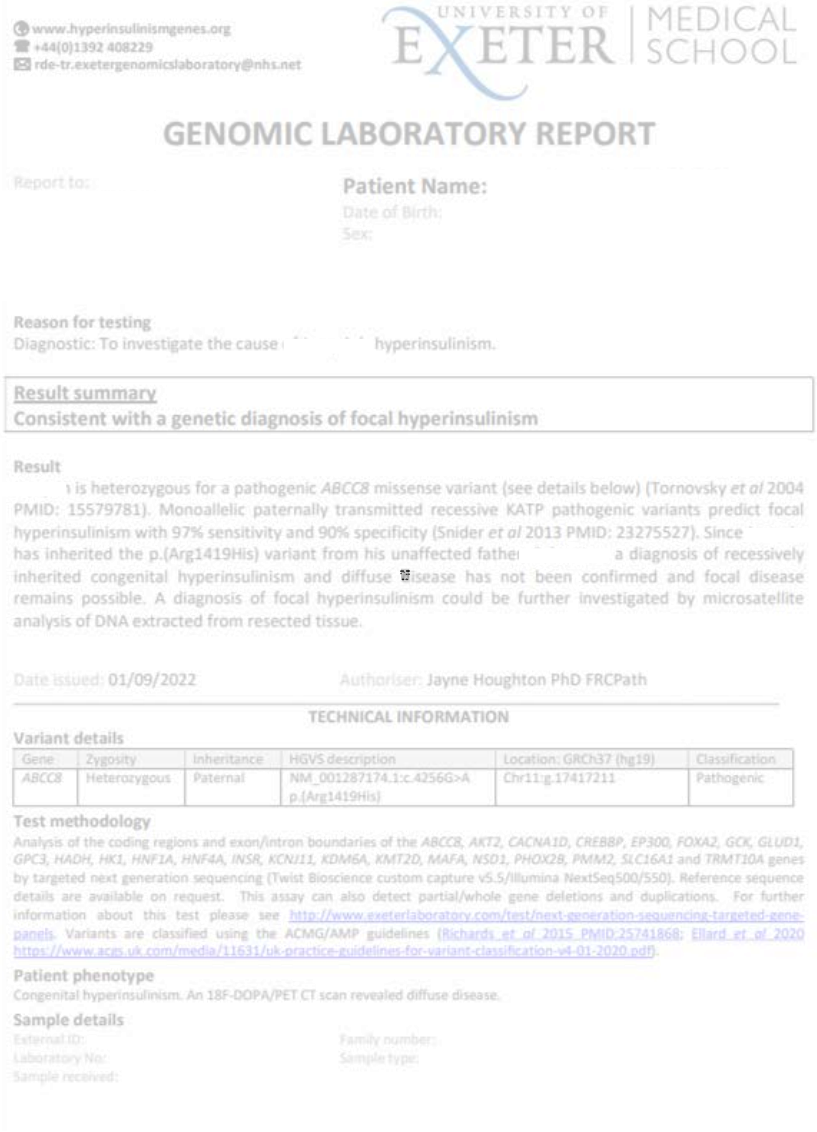

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Date issued: 01/09/2022 Authoriser: Jayne Houghton PhD FRCPath

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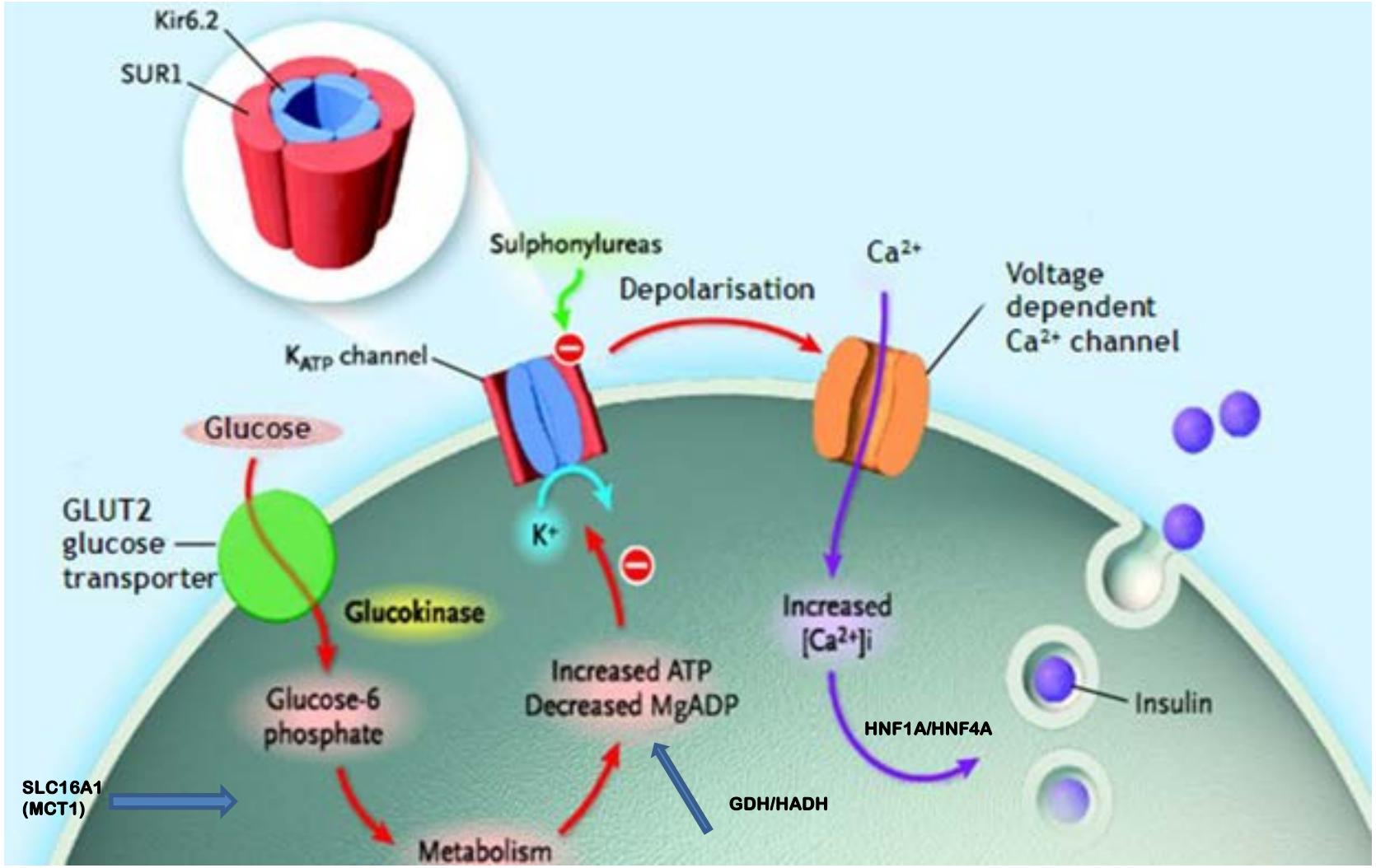
The Exeter laboratory test for 26 different genetic causes of hyperinsulinism

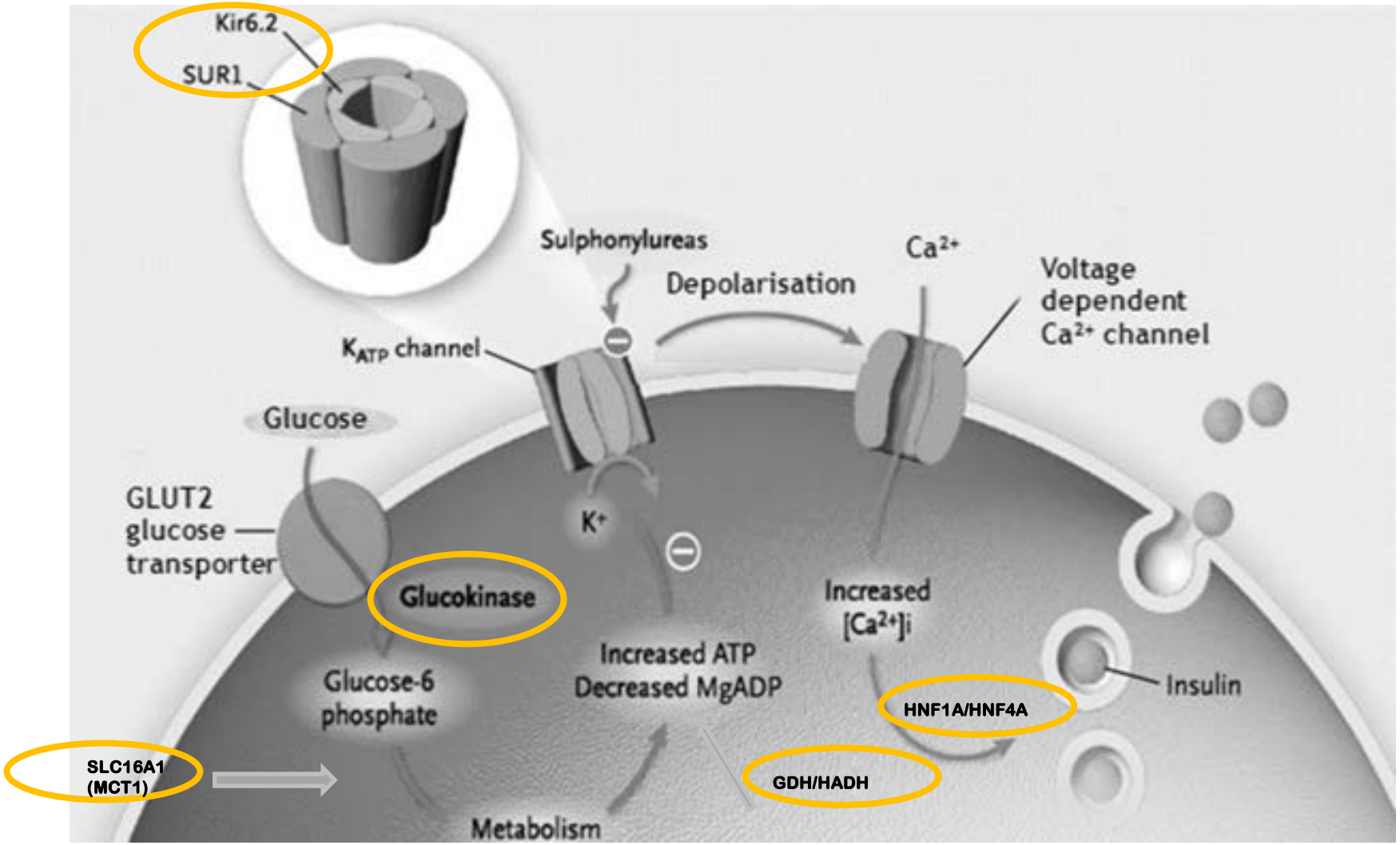
ABCC8, KCNJ11, GCK, GLUD1, HADH, SLC16A1, HNF4A, INSR, TRMT10A, HNF1A, CACNA1D, CREBBP, EP300, NSD1, HK1, PHOX2B, FOXA2, GPC3, PMM2, KDM6A, KMT2D, MAGEL2, Turner's Syndrome, Trisomy 13, 9p deletion syndrome

Variants in 8 genes encoding proteins important in beta-cell function cause isolated hyperinsulinism



Insulin secreting beta-cell in the pancreas

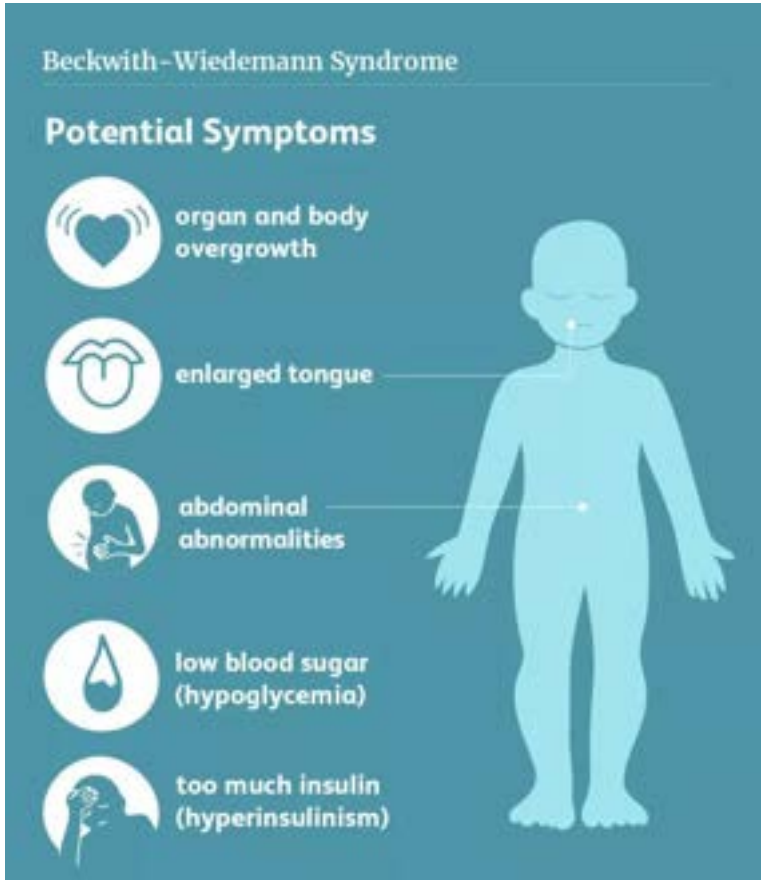
Variants in 8 different genes encoding proteins important in beta-cell function cause isolated hyperinsulinism

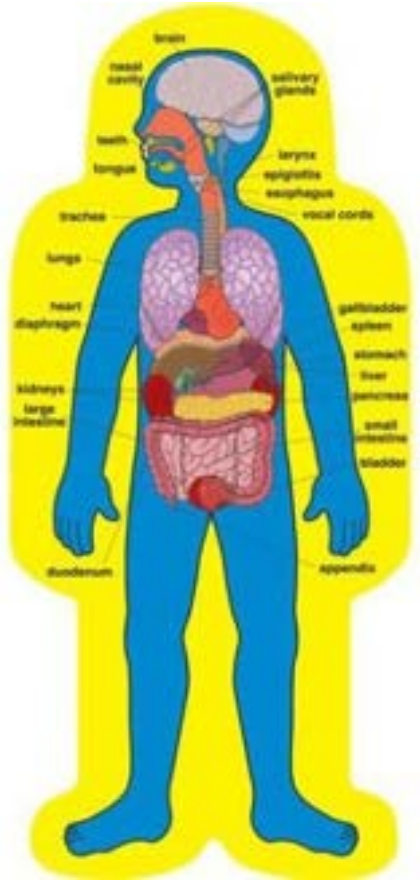


Insulin secreting beta-cell in the pancreas

Hyperinsulinism can be a rare feature of over 20 different syndromes

- Beckwith-Wiedemann syndrome
- Kabuki Syndrome (*KDM6A, KMT2D*)
- Fanconi renal tubular syndrome (*HNF4A*)
- ADK deficiency (*ADK*)
- Congenital disorders of glycosylation (*PMM2, MPI, ALG6, ALG3, PGM1*)
- Soto's syndrome (NSD1)
- Long QT-syndrome
- Perlman syndrome (*DIS3L2*)
- Costello syndrome (*HRAS*)
- Simpson-Golabi-Behmel (*GPC3*)
- FOXA2 syndrome
- Ondine syndrome (*PHOX2B*)
- Turner's syndrome
- Patau syndrome





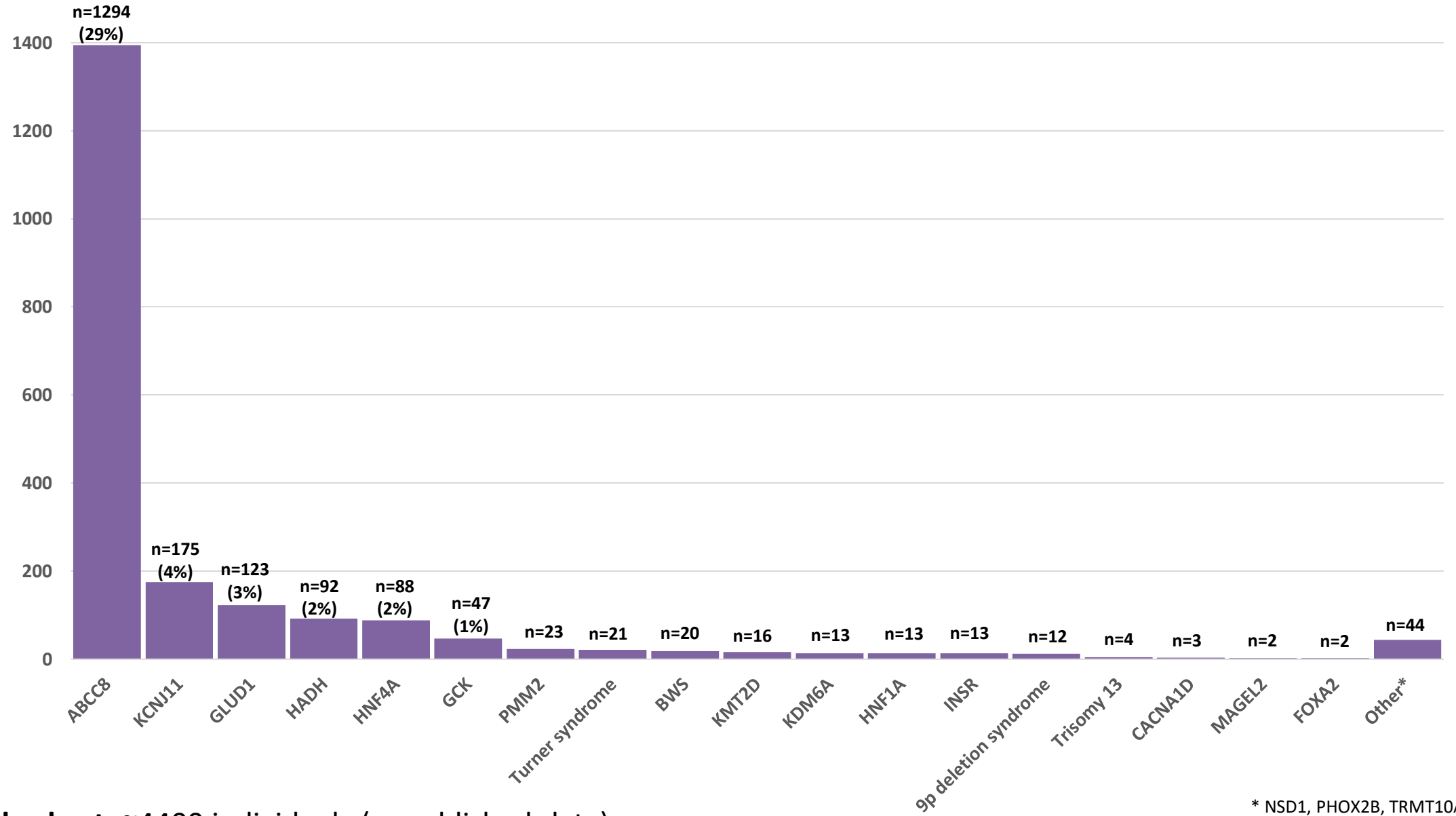
Protein (product of the gene) has an important role in multiple organs

Image credit: Verywellhealth.com / Brianna Gilmartin

International referral laboratory for genetic testing

4400 individuals referred from 82 countries

Screening 26 of known genes identifies the genetic cause of HI in 46% of individuals referred to Exeter



Total cohort: ~4400 individuals (unpublished data)

* NSD1, PHOX2B, TRMT10A, gwUPD, Chr20 deletion, CREBBP3, EP300, GPC3 etc

Reporting genetic variation

TECHNICAL INFORMATION

Variant details

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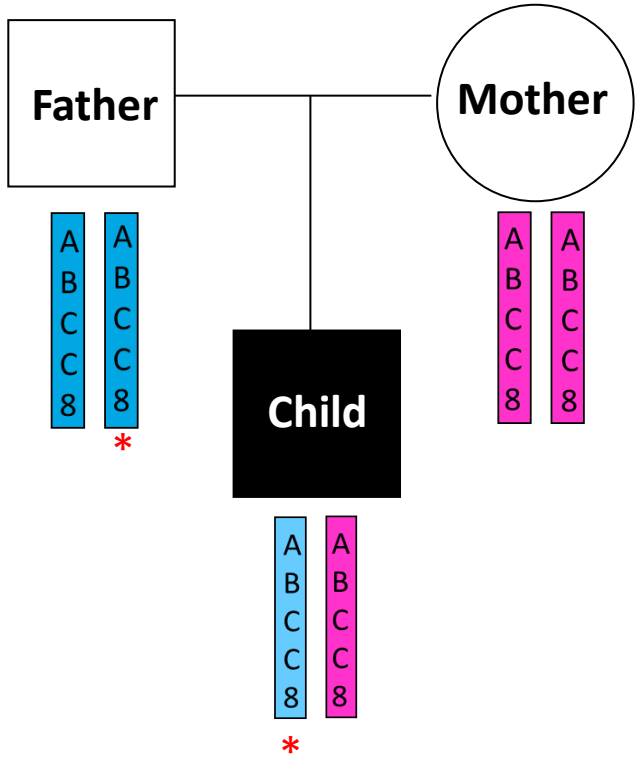
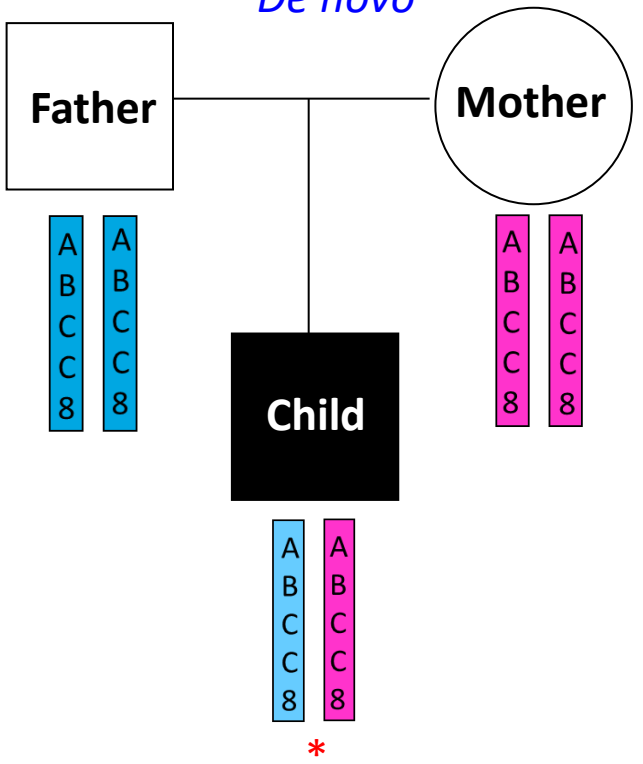
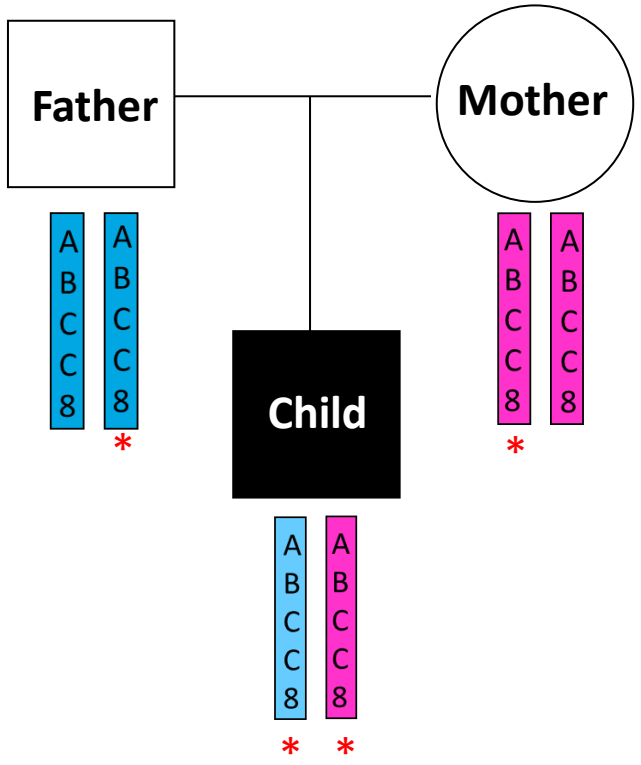
Heterozygous



Heterozygous
De novo



Homozygous



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c number (DNA change)	123	456	785	10,11,12	13,14,15	
	ATG	**CCC**	**CTG**	**GCC**	**TTC**	
p number (protein change)	Met	Pro	Leu	Ala	Phe	
	1	2	3	4	5	

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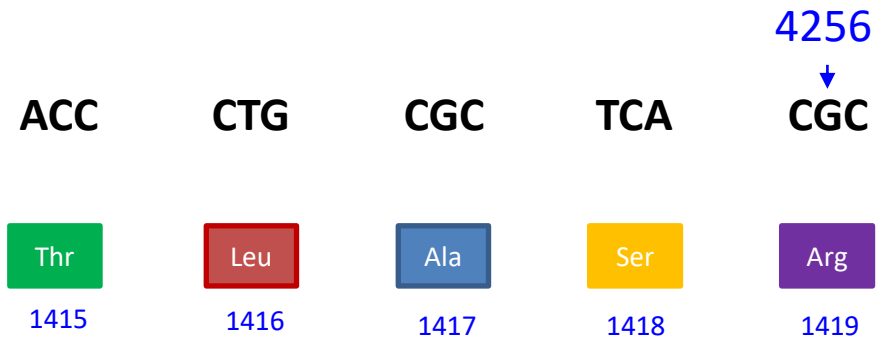
P number (protein change)



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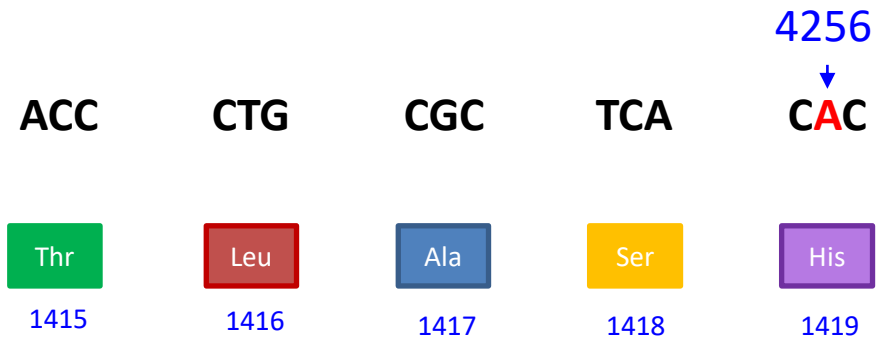
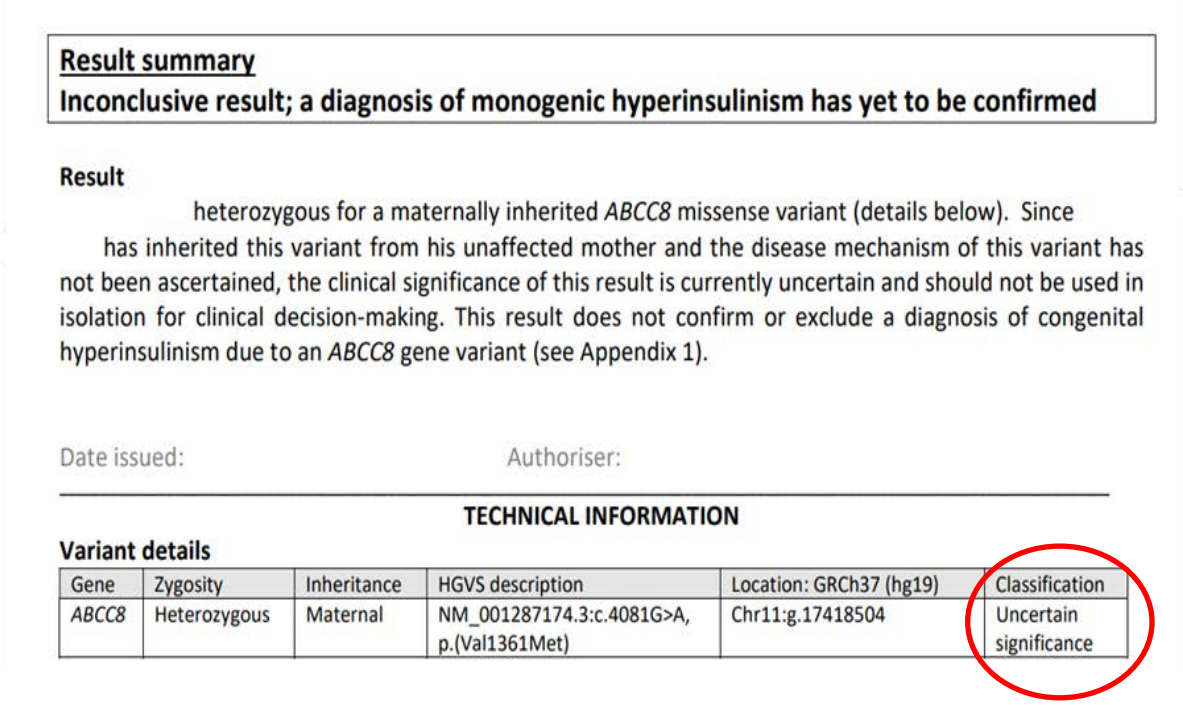


Sometimes the genetic testing can given an inconclusive result

A **variant of uncertain significance** (VUS) is a change in the DNA that has been identified through genetic testing but it is not known whether it is causing hyperinsulinism

Recommendation:

- If needed, work with clinician to obtain any needed family member samples for genetic testing
- Ask the screening laboratory to re-assess the variant on an annual basis



Result summary

Inconclusive result; a diagnosis of monogenic hyperinsulinism has yet to be confirmed

Result

heterozygous for a maternally inherited *ABCC8* missense variant (details below). Since has inherited this variant from his unaffected mother and the disease mechanism of this variant has not been ascertained, the clinical significance of this result is currently uncertain and should not be used in isolation for clinical decision-making. This result does not confirm or exclude a diagnosis of congenital hyperinsulinism due to an *ABCC8* gene variant (see Appendix 1).

Date issued: Authoriser:

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Variant details

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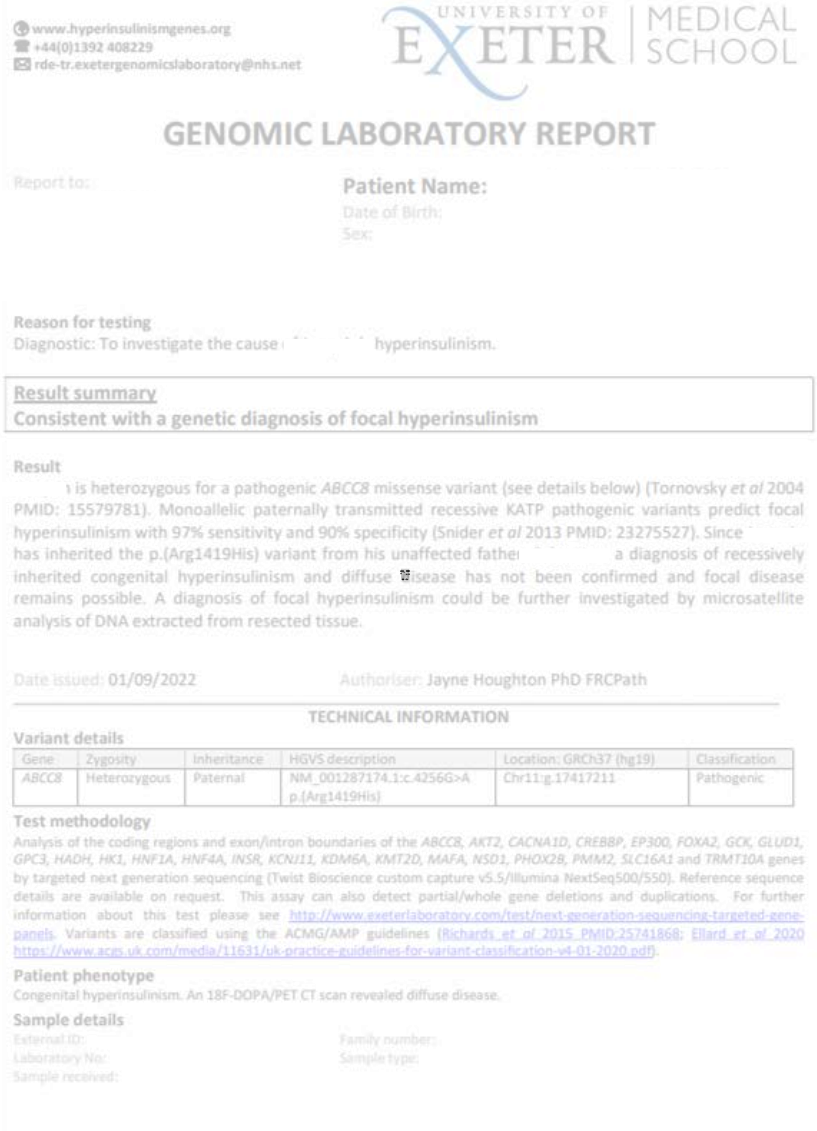

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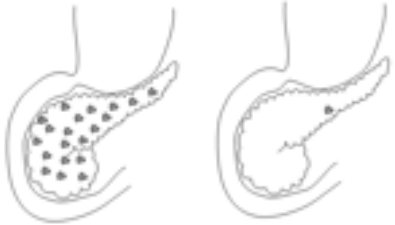
A genetic diagnosis can impact on medical management and treatment

Diffuse disease

Focal disease



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

Advise to restrict aerobic exercise (*SLC16A1* gene)

Dietary advice (mainly *GLUD1* gene)

Genetic report

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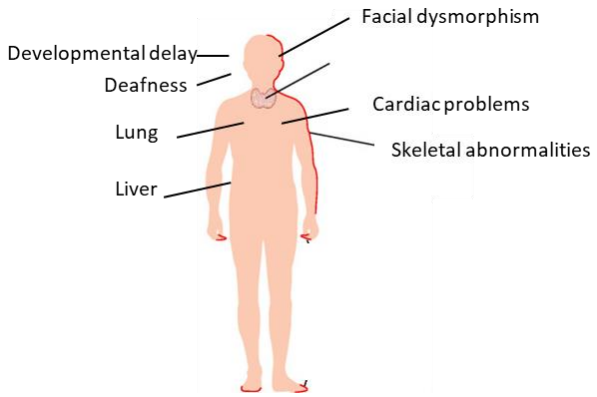
Recommended actions

18F-DOPA PET-CT scanning is recommended. If a focal lesion is identified and surgically resected, microsatellite analysis of DNA extracted from the lesion can be undertaken to confirm focal disease as the cause of 's hyperinsulinism.

A genetic diagnosis can allow for the monitoring of additional clinical features



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

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

Genetic report

Result summary

Genetic diagnosis of congenital hyperinsulinism, subtype HNF4A

Result

is heterozygous for a pathogenic *HNF4A* missense variant (see details below) (described as R303H by Pearson *et al* 2007 PMID: 17407387). Monoallelic pathogenic variants in *HNF4A* cause macrosomia and neonatal hyperinsulinaemic hypoglycaemia (Pearson *et al* 2007 PMID: 17407387) or maturity-onset diabetes of the young (MODY), subtype HNF4A in adolescence/adulthood (Pearson *et al* 2005 PMID: 15830177).

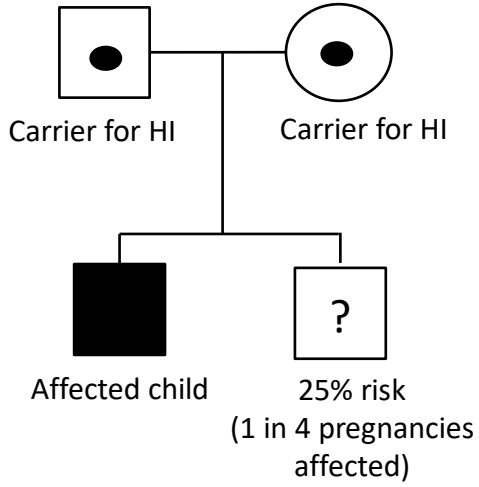
Implications of result

is genetically predisposed to diabetes (see appendix 1) and regular monitoring of her HbA1c level from the age of 10 years is recommended. Each of this patient's offspring will be at 50% risk of inheriting this variant and developing diabetes. There is also an increased risk of macrosomia and neonatal hypoglycaemia for a fetus that inherits this variant (see appendix 2 and Pearson *et al* 2007 PMID: 17407387).

Example of statement on patient report

A genetic diagnosis allows for accurate counselling of recurrence risk of hyperinsulinism within a family

Example 1



Genetic report

Result summary
Carrier of autosomal recessive congenital hyperinsulinism, subtype ABCC8

Result

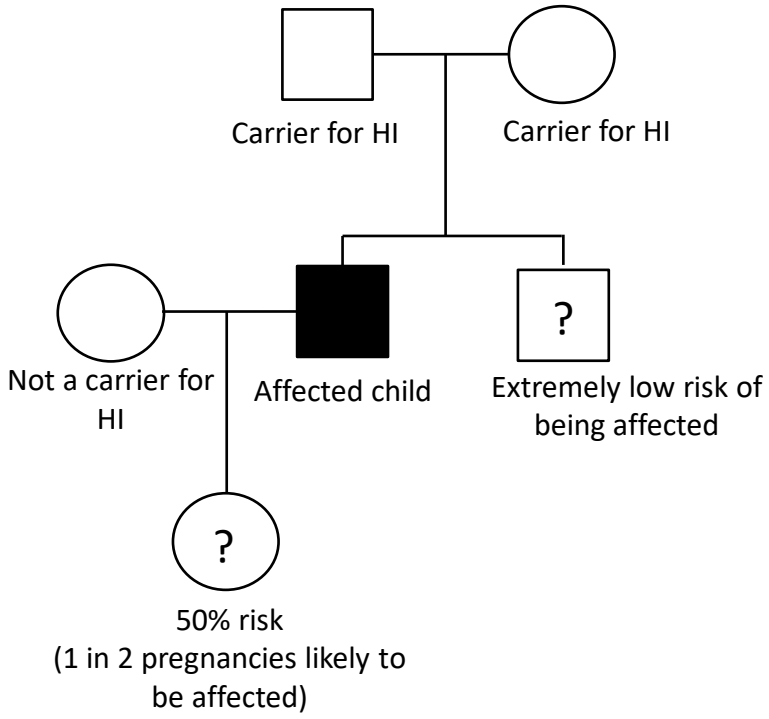
is heterozygous for a pathogenic *ABCC8* nonsense variant (details below) (De Franco *et al* 2020, PMID:3207066). Biallelic loss-of-function pathogenic variants in *ABCC8* cause congenital hyperinsulinism (MIM256450).

Implications of result

partner, . also heterozygous for the pathogenic ABCC8 variant. The risk that their next pregnancy will be affected by congenital hyperinsulinism is 1 in 4 (25%). Prenatal testing is possible for this couple and pre-implantation diagnosis may be an option.

A genetic diagnosis allows for accurate counselling of recurrence risk within families

Example 2



Genetic report

Implications of result
Each of offspring would be at 50% risk of inheriting this variant and developing hyperinsulinism-hyperammonaemia syndrome.

A genetic diagnosis allows for accurate counselling of recurrence risk of Hyperinsulinism within a family

- Advise that families are referred to a clinical genetics team who will be able to offer advice based on the genetic findings within the family
- **Some** laboratories may offer pre-natal testing or preimplantation genetic testing when requested by a clinical geneticist. This is not possible for all families.

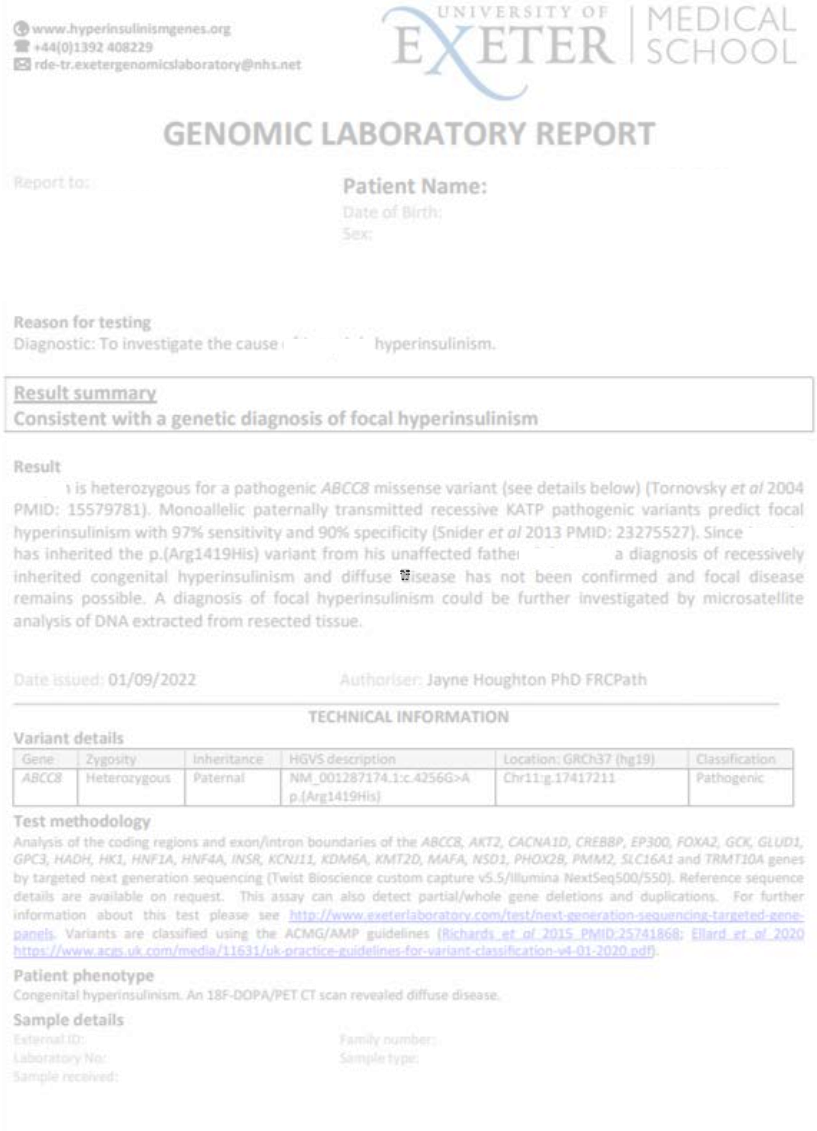
Genetic report

Implications of result

partner, , is also heterozygous for the pathogenic ABCC8 variant. The risk that their next pregnancy will be affected by congenital hyperinsulinism is 1 in 4 (25%). Prenatal testing is possible for this couple and pre-implantation diagnosis may be an option.

Aim of the presentation

- DNA and genetic variation
- Known genetic causes of congenital hyperinsulinism
- The importance of a genetic diagnosis
- Opportunities for families without a genetic diagnosis



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UNIVERSITY OF EXETER | MEDICAL SCHOOL

GENOMIC LABORATORY REPORT

Report to:

Patient Name:
Date of Birth:
Sex:

Reason for testing
Diagnostic: To investigate the cause hyperinsulinism.

Result summary
Consistent with a genetic diagnosis of focal hyperinsulinism

Result
is heterozygous for a pathogenic *ABCC8* missense variant (see details below) (Tornovsky *et al* 2004 PMID: 15579781). Monoallelic paternally transmitted recessive KATP pathogenic variants predict focal hyperinsulinism with 97% sensitivity and 90% specificity (Snider *et al* 2013 PMID: 23275527). Since has inherited the p.(Arg1419His) variant from his unaffected fathe a diagnosis of recessively inherited congenital hyperinsulinism and diffuse disease has not been confirmed and focal disease remains possible. A diagnosis of focal hyperinsulinism could be further investigated by microsatellite analysis of DNA extracted from resected tissue.

Date issued: 01/09/2022 Authoriser: Jayne Houghton PhD FRCPath

TECHNICAL INFORMATION

Variant details

Gene	Zygosity	Inheritance	HGVS description	Location: GRCh37 (hg19)	Classification
ABCC8	Heterozygous	Paternal	NM_001287174.1:c.4256G>A p.(Arg1419His)	Chr11:g.17417211	Pathogenic

Test methodology
Analysis of the coding regions and exon/intron boundaries of the *ABCC8, AKT2, CACNA1D, CREBBP, EP300, FOXA2, GCK, GLUD1, GPC3, HADH, HK1, HNF1A, HNF4A, INSR, KCNJ11, KDM6A, KMT2D, MAFA, NSD1, PHOX2B, PMM2, SLC16A1* and *TRMT10A* genes by targeted next generation sequencing (Twist Bioscience custom capture v5.5/Illumina NextSeq500/550). Reference sequence details are available on request. This assay can also detect partial/whole gene deletions and duplications. For further information about this test please see http://www.exeterlaboratory.com/test/next-generation-sequencing-targeted-gene-panels. Variants are classified using the ACMG/AMP guidelines (Richards *et al* 2015 PMID:25741868; Ellard *et al* 2020 https://www.acgs.uk.com/media/11631/uk-practice-guidelines-for-variant-classification-v4-01-2020.pdf).

Patient phenotype
Congenital hyperinsulinism. An 18F-DOPA/PET CT scan revealed diffuse disease.

Sample details
External ID:
Laboratory No:
Sample received:
Family number:
Sample type:

Removing barriers to genetic testing

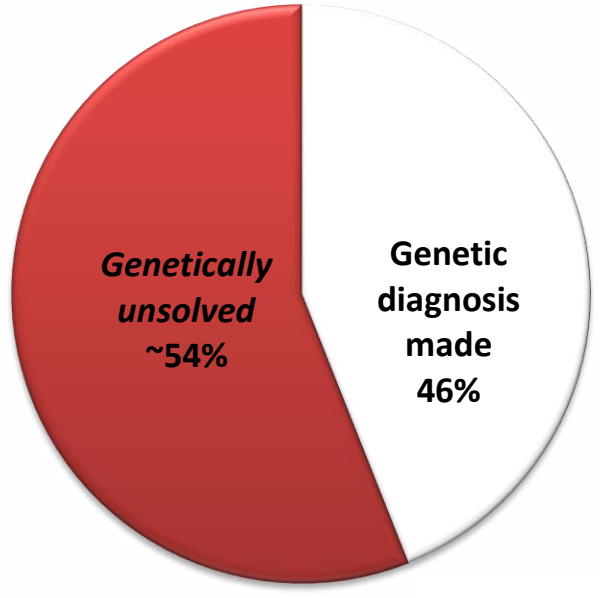
Since July 2018:

- 685 children tested
- 510 family members
- Referred from 59 countries across 5 continents
- Genetic diagnosis confirmed in 350 patients (51%)

Congenital Hyperinsulinism International

University of Exeter | Medical School

Individuals without a genetic diagnosis



Which genes have been tested?

Ask for a copy of your genetic report

Result summary
A genetic cause for congenital hyperinsulinism has not been identified

Result
Analysis of the known congenital hyperinsulinism genes listed below did not identify a pathogenic variant. Variants in these genes are found in ~50% of patients with congenital hyperinsulinism (James *et al* 2009 PMID: 19254908).

Interpretation
This result does not confirm a diagnosis of hyperinsulinism due to a variant in these genes but it does not exclude a monogenic aetiology since further genes remain to be identified. If this patient's hyperinsulinism persists for >6 months or is diazoxide-unresponsive please contact the laboratory as further testing is possible on a research basis.

Date issued: Authoriser:

TECHNICAL INFORMATION

Test methodology
Analysis of the coding regions and exon/intron boundaries of the *ABCC8, AKT2, CACNA1D, CREBBP, EP300, FOXA2, GCK, GLUD1, GPC3, HADH, HK1, HNF1A, HNF4A, INSR, KCNJ11, KDM6A, KMT2D, MAFA, NSD1, PHOX2B, PMM2, SLC16A1* and *TRMT10A* genes by targeted next generation sequencing (Twist Bioscience custom capture v5.5/Illumina NextSeq500/550). Reference sequence details are available on request. For further information about this test please see http://www.exeterlaboratory.com/test/next-generation-sequencing-targeted-gene-panels. Variants are classified using the ACMG/AMP guidelines (Richards *et al* 2015 PMID:25741868; Ellard *et al* 2020 https://www.acgs.uk.com/media/11631/uk-practice-guidelines-for-variant-classification-v4-01-2020.pdf).

New genetic causes of Hyperinsulinism are being discovered - Keep asking!

Polycystic Kidney Disease with Hyperinsulinemic Hypoglycemia Caused by a Promoter Mutation in Phosphomannomutase 2

ORIGINAL ARTICLE

Novel *FOXA2* mutation causes Hyperinsulinism, Hypopituitarism with Craniofacial and Endoderm-

Case Report

A Novel Homozygous Missense Mutation in the *YARS* Gene: Expanding the Phenotype

Article

Hyperinsulinemic Hypoglycemia Associated with a $Ca_V1.2$ Variant with Mixed Gain- and Loss-of-Function Effects

A *CACNA1D* mutation in a patient with persistent hyperinsulinaemic hypoglycaemia, heart defects, and severe hypotonia

SE Flanagan[1] | F Vairo[2] | MB Johnson[1] | R Caswell[1] | TW Laver[1] | H Lango Allen[1] | K Hussain[3] | S Ellard[1]

Baby E

Referred to Exeter for genetic testing in 2011.

Screening of genes known to cause HI at that time did not identify a disease-causing variant.

Patient retested in 2020

Pathogenic variant in CACNA1D identified

Finding out about opportunities research

National initiatives

Result summary

A genetic cause for congenital hyperinsulinism has not been identified

Result

Analysis of the known congenital hyperinsulinism genes listed below did not identify a pathogenic variant. Variants in these genes are found in ~50% of patients with congenital hyperinsulinism (James *et al* 2009 PMID: 19254908).

Interpretation

This result does not confirm a diagnosis of hyperinsulinism due to a variant in these genes but it does not exclude a monogenic aetiology since further genes remain to be identified. If this patient's hyperinsulinism persists for >6 months or is diazoxide-unresponsive please contact the laboratory as further testing is possible on a research basis.

Research Teams

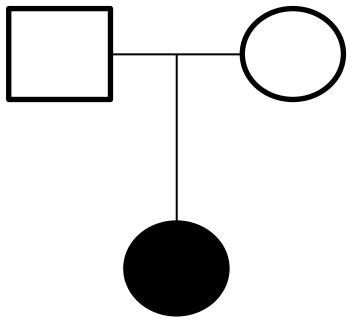
Family conferences

Searching for the cause of HI in Baby T

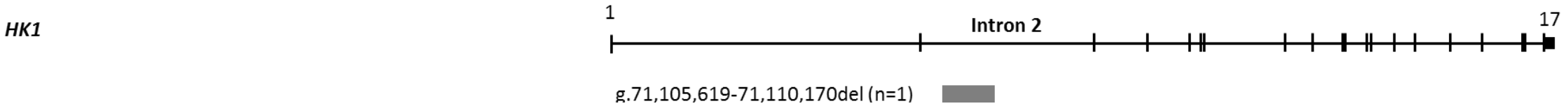
Baby T.

- HI at birth (glucose 1.2 mmol/L, insulin 77pmol/L)
- Near total pancreatectomy aged 23 months
- No disease-causing variants identified
- Ongoing HI (6.5mg.kg.day) at 14 years

Whole genome sequencing



Genome sequencing identified a *de novo* deletion affecting the *HK1* gene



Wakeling et al 2021, Medrxivs

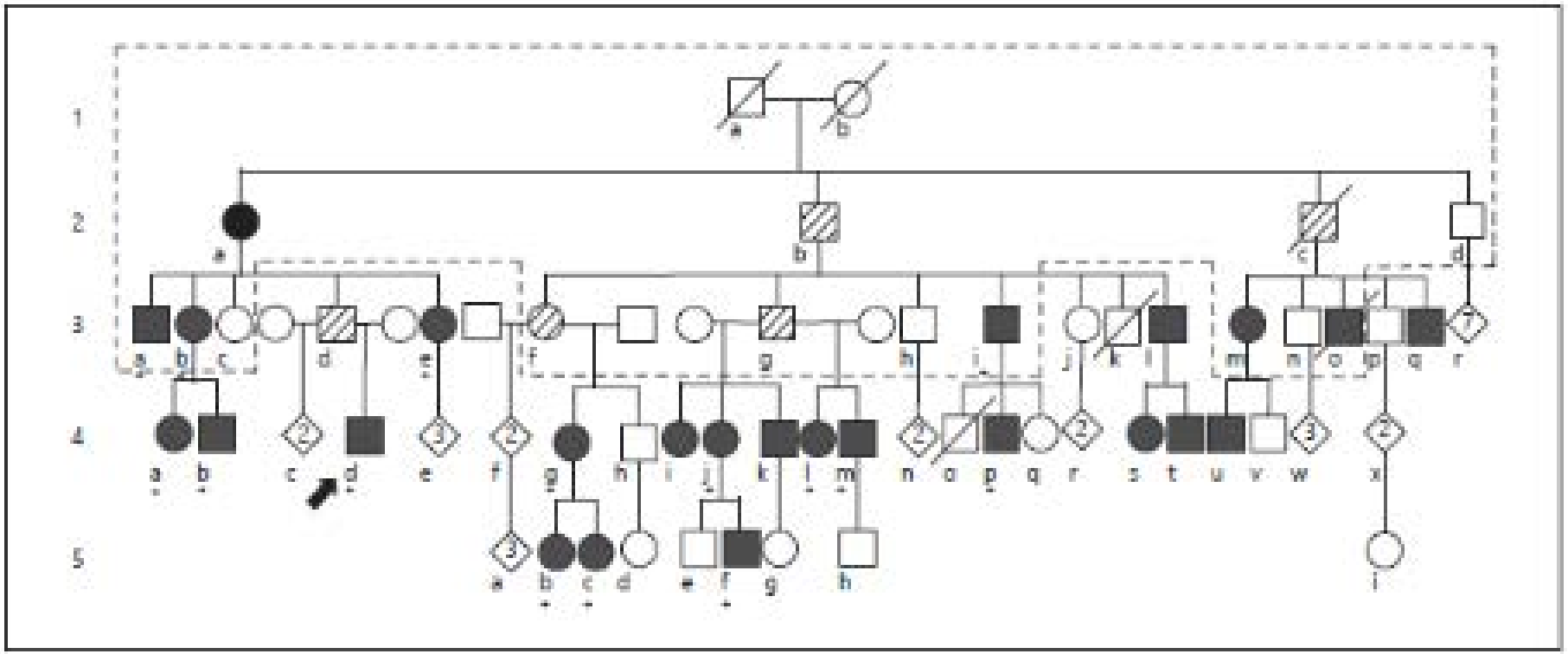
Previous study had highlighted *HK1* as the cause of HI in a large family

HORMONE RESEARCH IN PÆDIATRICS

Original Paper

Dominant Form of Congenital Hyperinsulinism Maps to HK1 Region on 10q

Sara E. Pinney[a, b] Karthik Ganapathy[a] Jonathan Bradfield[c] David Stokes[d]
Ariella Sasson[a] Katarzyna Macklewicz[c] Kara Boodhansingh[a] Nkecha Hughes[d]
Susan Becker[a] Stephanie Givler[a] Courtney Macmullen[a] Dimitrios Monos[b, c]
Arupa Ganguly[a] Hakon Hakonarson[b, c] Charles A. Stanley[a, b]



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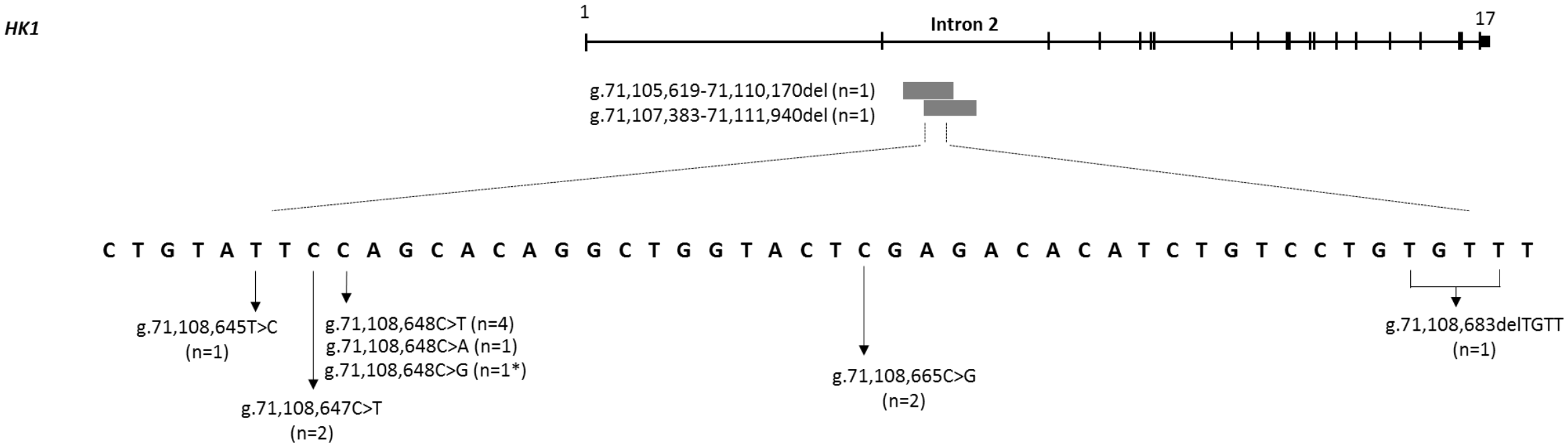
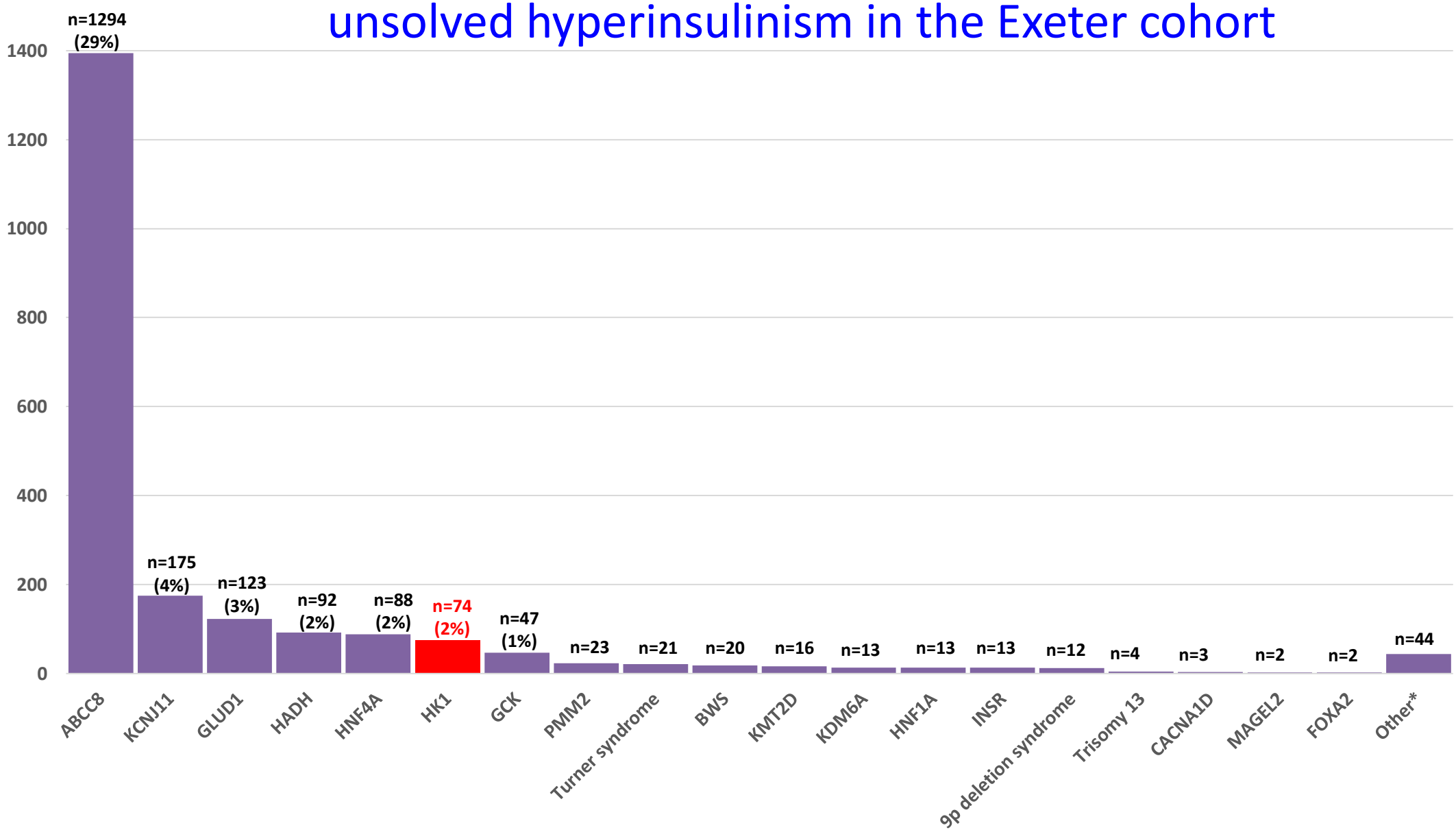


Wakeling et al 2021, Medrxivs

Variants identified in 17 individuals with isolated hyperinsulinism

HK1 screening in over 2000 children with unsolved hyperinsulinism in the Exeter cohort



Summary

- Congenital hyperinsulinism can be caused by changes in over 30 different genes
- Understanding the genetic cause of hyperinsulinism can impact on medical management
- If you do not have a genetic diagnosis – keep asking whether more testing would be useful
- Ask for a copy of your report

The Exeter Hyperinsulinism Genes Team

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Geneticist

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Clinical Scientist

Dr Rachel Van Heugten
Clinical Scientist

Tom Hewat
PhD student

Dr Kash Patel
Clinician Scientist

Dr Matthew Wakeling
Bioinformatician

Dr Jessica Hopkinson
Functional Biologist

Eleanor Self
Research Assistant

Jasmin Hopkins
PhD student

Thank you!

Congenital Hyperinsulinism International

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