Syndromic hyperinsulinism

Damien Lederer,
Dominique Roland

Congenital hyperinsulinism

- Most frequent cause of persistent hypoglycemia in infancy
- Severe hypoglycemia
- Inappropriate insulin secretion by pancreatic βcells
- Syndromic hyperinsulinism
- Non syndromic hyperinsulinism
  - Dominant
  - Recessive
  - Focal

Non syndromic hyperinsulinism

- Mutations in subunits of ATP-dependent potassium channe (K_{ATP})
  - ABCC8 (SUR1) (42%)
  - KCNJ11 (Kir6.2)
  - Dominant: variable response to diazoxide
  - Recessive: diazoxide unresponsive
  - Paternally inherited mutation and somatic loss of maternal allele in the 11p15 region
- Others
  - GLUD1
    - Glutamate dehydrogenase
    - Hyperammonemia, mild hypoglycemia, diazoxide responsive
  - GCK Glucokinase
    - Mild to severe HI
    - Activating: hyperinsulinism
    - LoF: diabete
  - HADH short chain l-3-hydroxyacyl CoA dehydrogenase
  - SLC16A1, HNF4A, HNF1A, UCP2, CACNA1D
  - *HK1 (familial dominant, diazoxyde responsive)*

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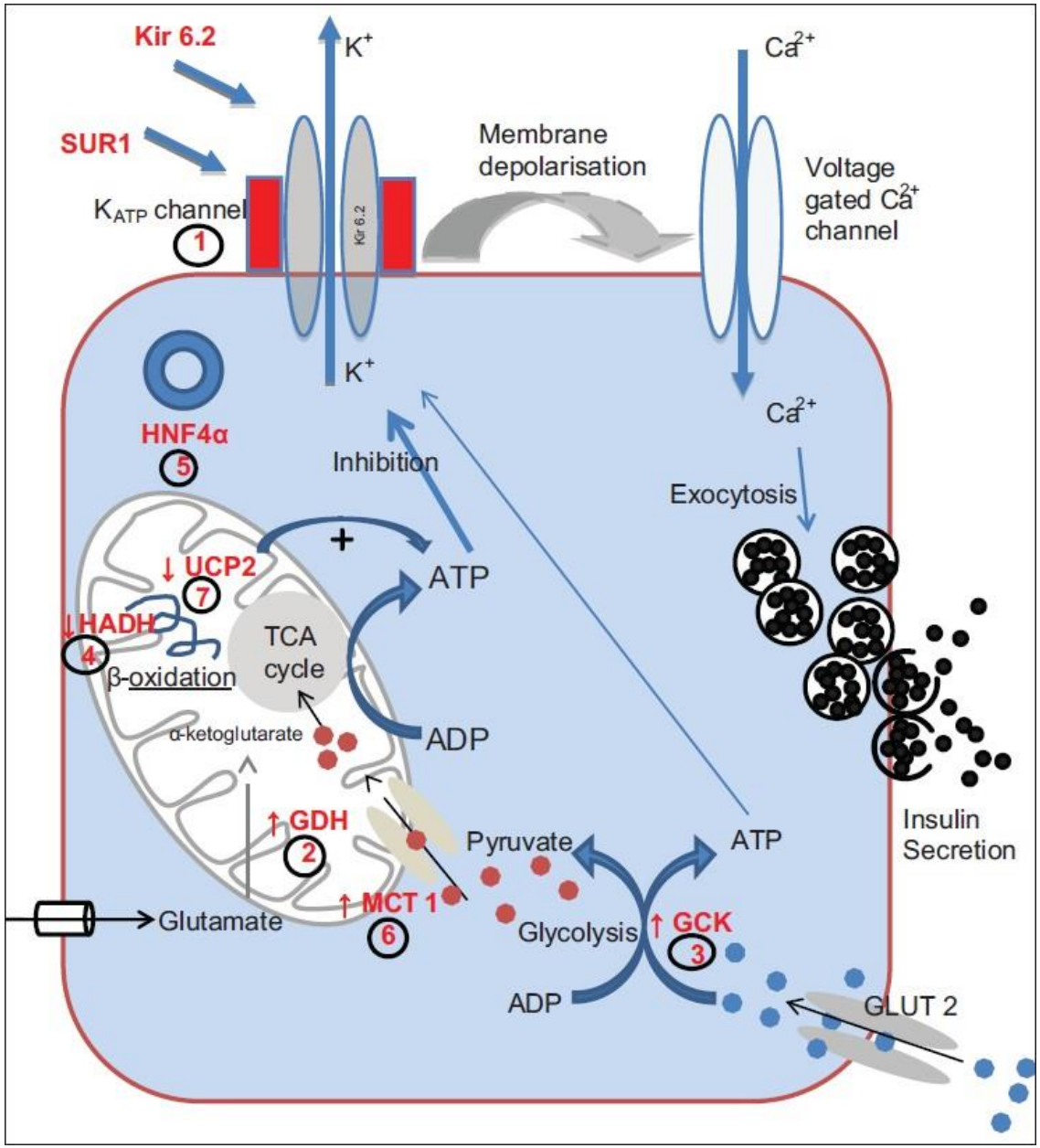
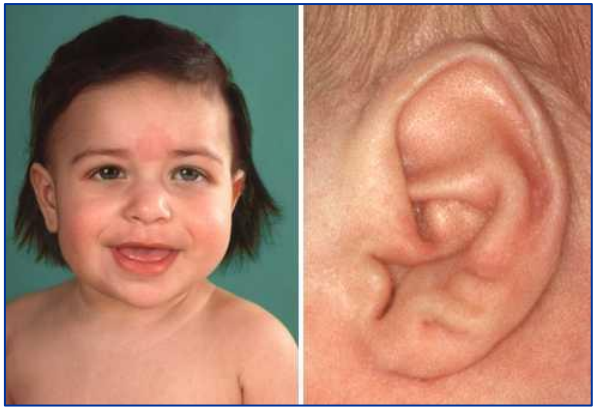
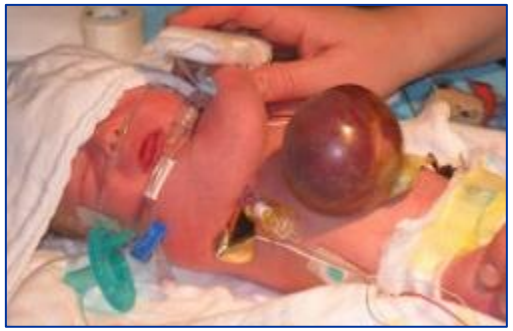

Kir 6.2
SUR1
K_{ATP} channel
1
K^+
Kir 6.2
K^+
Membrane depolarisation
Ca^{2+}
Voltage gated Ca^{2+} channel
Ca^{2+}
HNF4α
5
Inhibition
Exocytosis
↓ UCP2
7
↓HADH
4
β-oxidation
TCA cycle
ATP
ADP
α-ketoglutarate
↑ GDH
2
Pyruvate
ATP
Insulin Secretion
Glutamate
↑ MCT 1
6
Glycolysis
↑ GCK
3
ADP
GLUT 2

Syndromic hyperinsulinism

- Beckwith Wiedeman syndrome
- Sotos syndrome
- Perlman syndrome Kabuki syndrome
- CACNA1D (diazoxide responsive HI, aortic insuffisiceny, severe hypotonia, developmental delay, neuromuscular abnormalities, primary hyperaldosteronism)
- Congenital disorder of glycosilation
- Chromosomal rearrangement
  - 12q24
  - 5q11.2
  - 8q24
  - USH1C deletion (11p14-15)
  - 10p13-14 (HK1)

Becwith Wiedemann syndrome





- 1/13700
- Overgrowth
  - Prenatal
  - Postnatal
  - hemihyperplasia
- Abdominal wall defects
- Dysmorphic
  - Anterior ear lobe crease
  - Posterior helical pits
  - Cleft palate
- Other
  - Intra-abdominal visceromegaly
  - Renal abnormalities
- Tumor risk (Wilms, hepatoblastoma)
- Complex genetic

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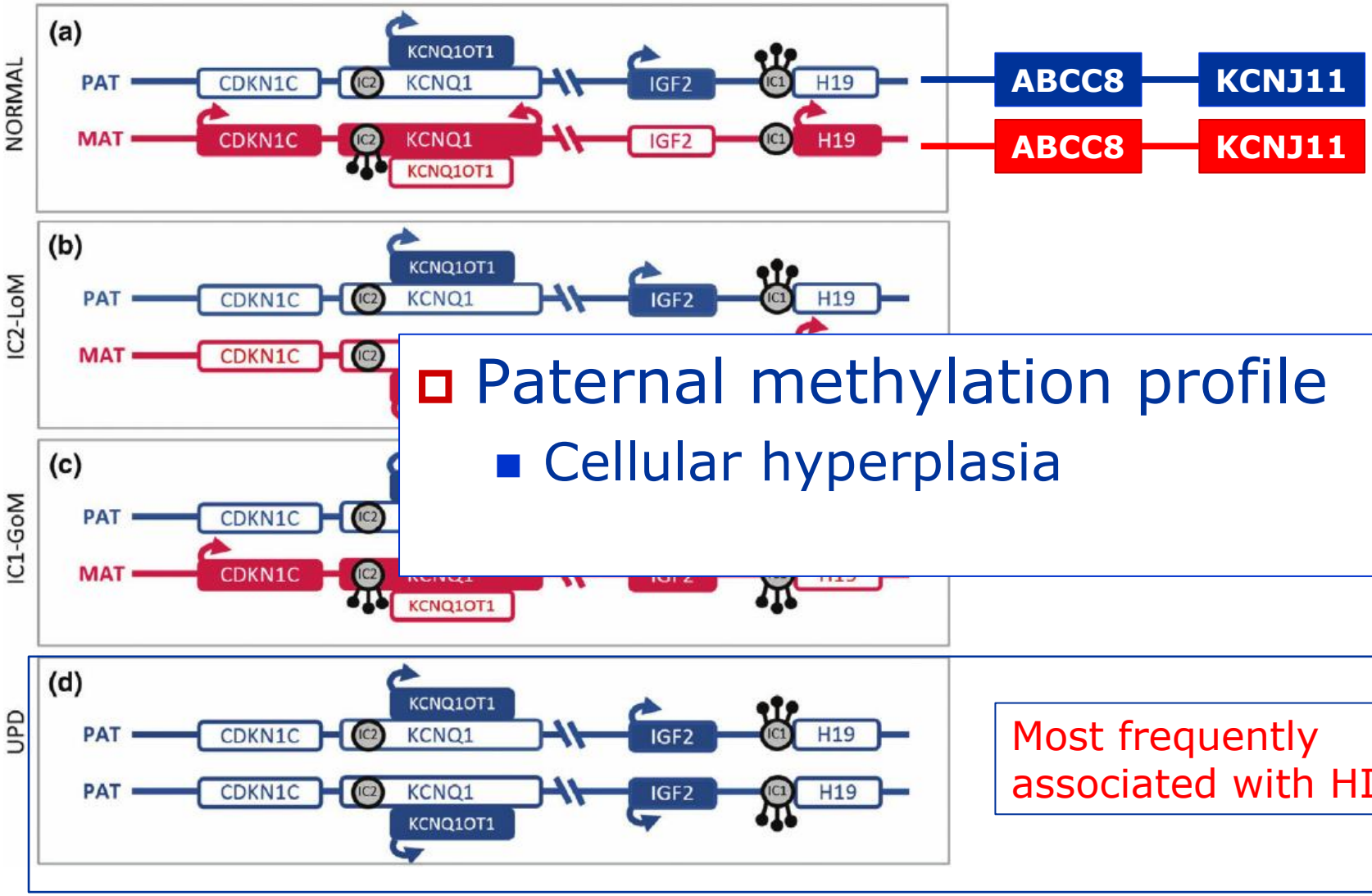
11p15 methylation



- Paternal methylation profile
  - Cellular hyperplasia

Most frequently associated with HI

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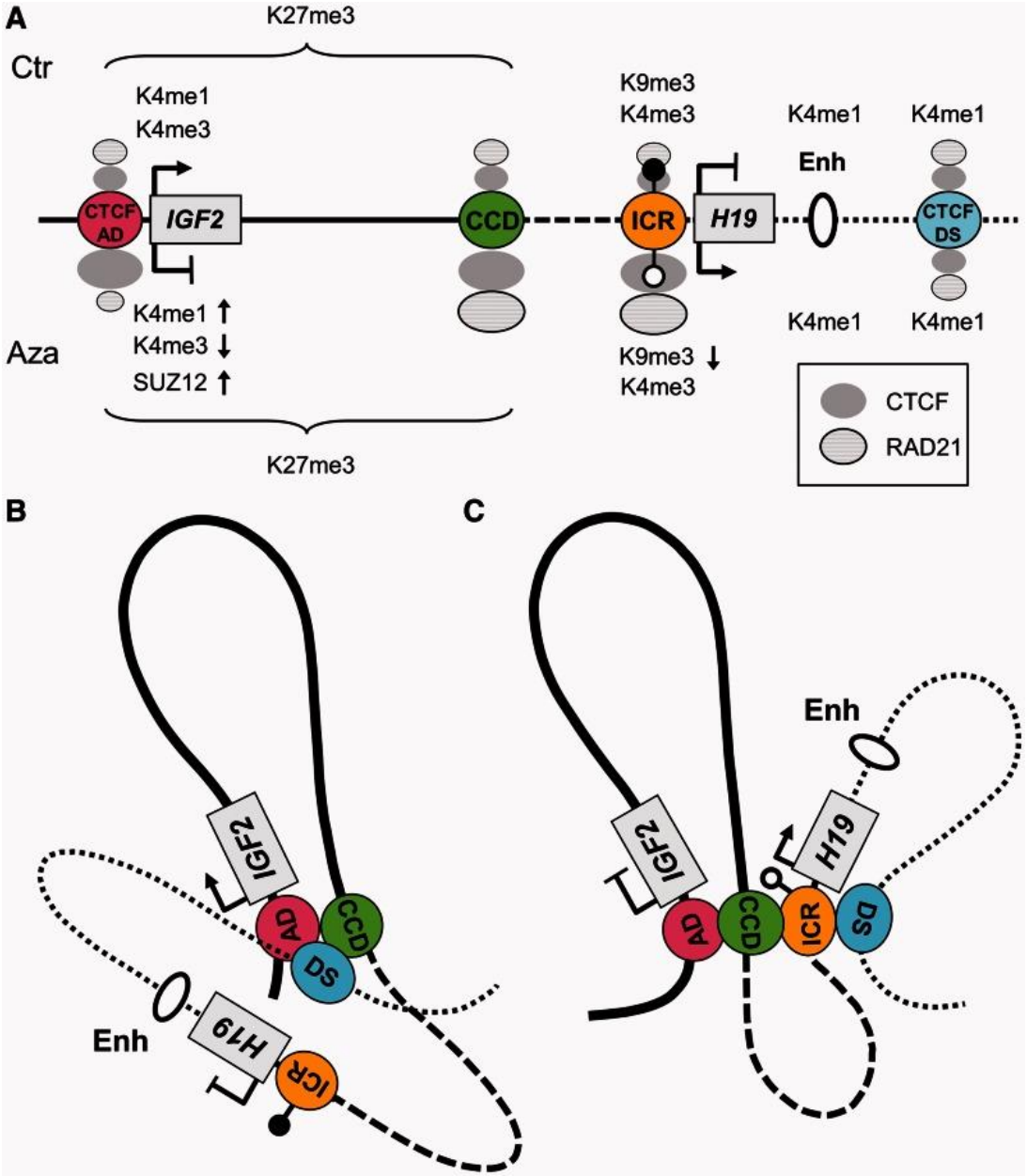
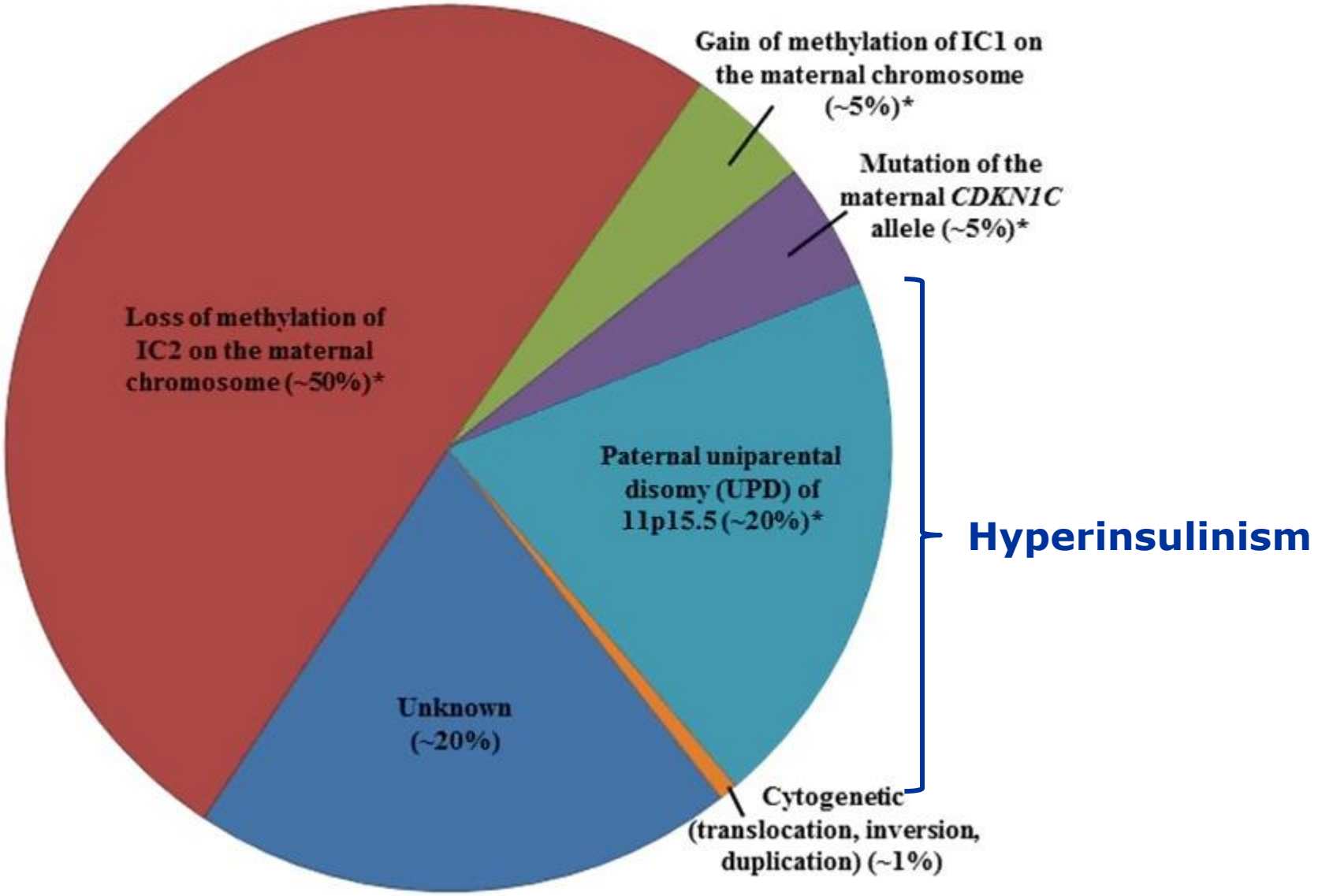
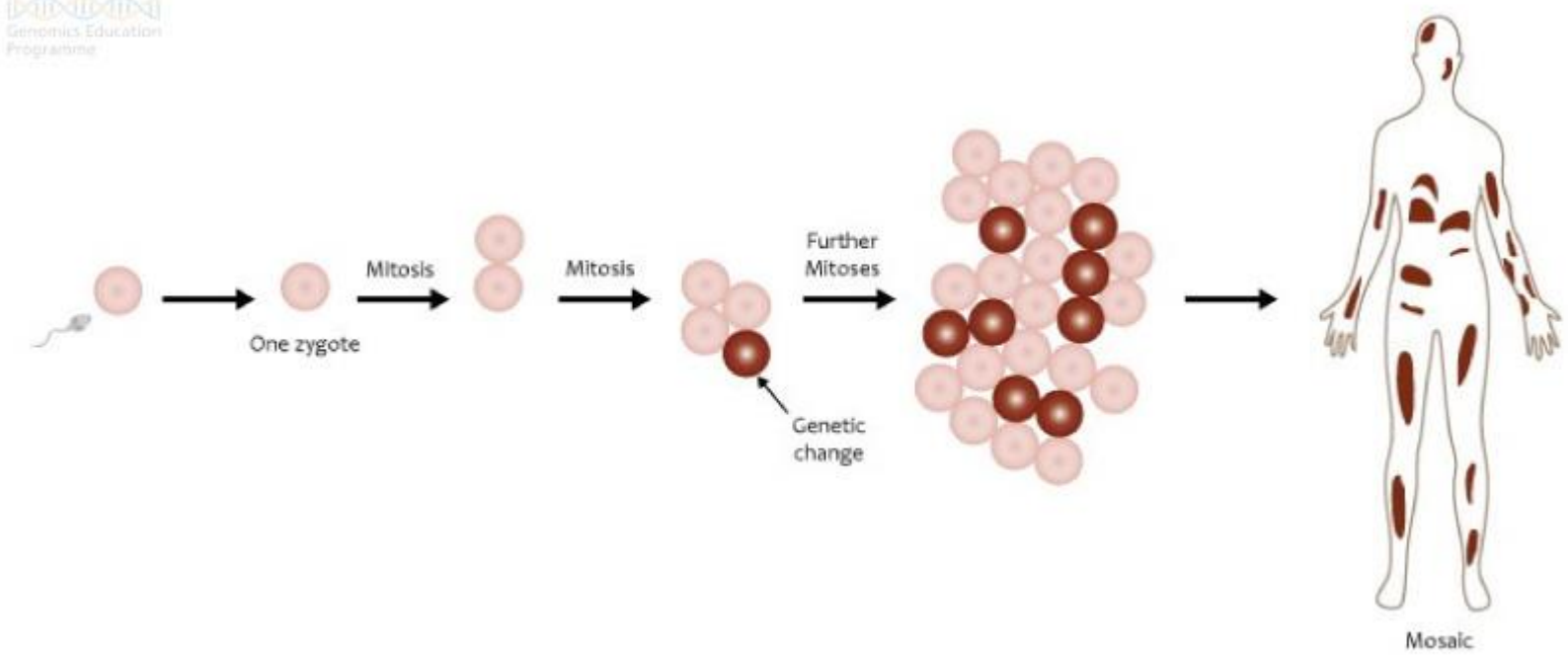

A
K27me3
Ctr
K4me1
K4me3
CTCF AD
IGF2
CCD
K9me3
K4me3
ICR
H19
K4me1
Enh
K4me1
CTCF DS
K4me1
K4me3
SUZ12
Aza
K9me3
K4me3
K4me1
K4me1
CTCF
RAD21
K27me3
B
C
IGF2
AD
CCD
DS
Enh
H19
ICR
Enh
IGF2
H19
AD
CCD
ICR
DS

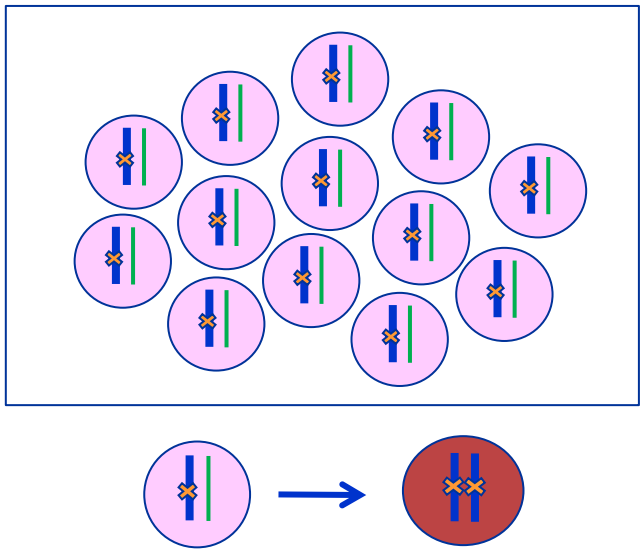

Gain of methylation of IC1 on the maternal chromosome (~5%)*
Mutation of the maternal CDKN1C allele (~5%)*
Loss of methylation of IC2 on the maternal chromosome (~50%)*
Paternal uniparental disomy (UPD) of 11p15.5 (~20%)*
Unknown (~20%)
Cytogenetic (translocation, inversion, duplication) (~1%)
Hyperinsulinism

Mosaic mutation

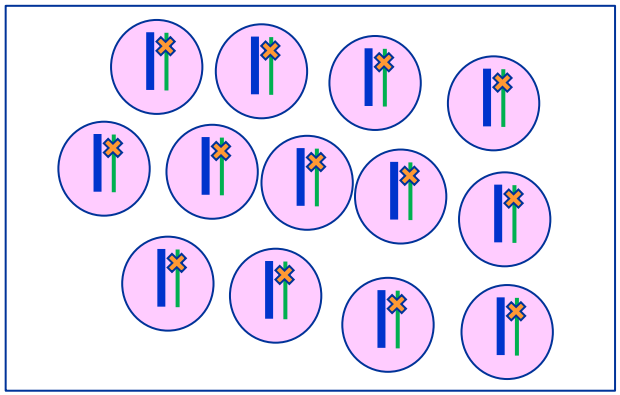


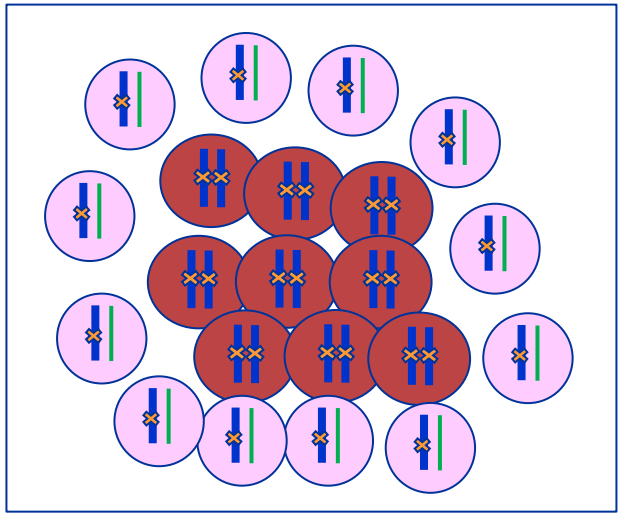
Focal hyperinsulinism

Paternal UPD

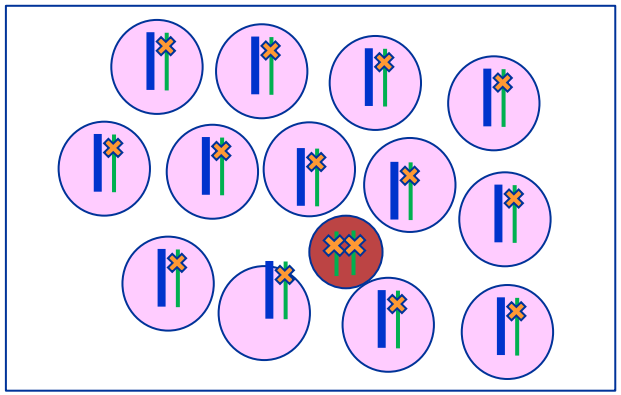


Maternal UPD





Focal Hyperinsulinism



No effect

Paternal allele | Maternal allele | ABCC8 mutation

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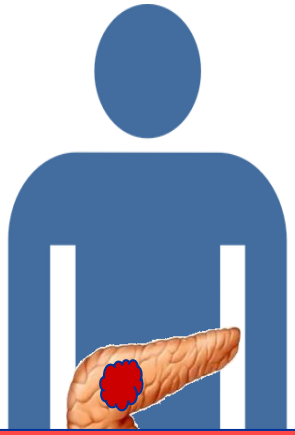
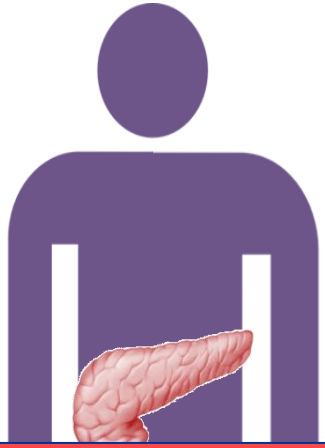
Mosaic Paternal UPD 11p15

Pancreas mosaïc



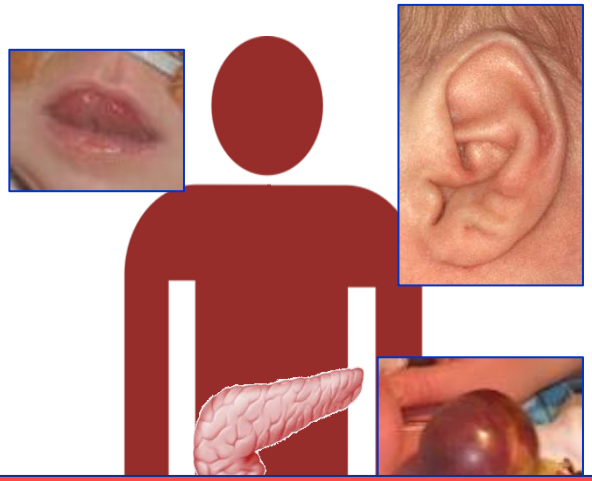
Focal HI

Late mosaïc



Hemihyperplasia
Diffuse HI

Early mosaïc



Beckwith Wiedemann

Paternally inherited mutation ABCC8/KCNJ11

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

Pınar Kocaay[a] Zeynep Şiklar[a] Sian Ellard[d] Aydın Yagmurlu[b]
Emine Çamtosun[a] Esra Erden[c] Merih Berberoglu[a] Sarah E. Flanagan[d]

Sotos syndrome

- Overgrowth syndrome
- Tall at birth
- Neonatal hypotonia

- Mild ID, seizure
- Dysmorphic
- Hyperlaxity, advanced bone age
- Malformation (heart, kidney)

- Few reports of hyperinsulinemic hypoglycemia of infancy
- NSD1 mutation/deletion
- Autosomal dominant

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Perlman syndrome

- Overgrowth syndrome
- Pre/post natal macrosomia
- Macroglossia
- Wilms tumor !!!
- Langerhans islet hyperplasia

- Malformation
  - Heart
  - Kidney
  - Vertebral
  - Digestive
  - …

- Genetic
  - **Rare**
  - Unknown
  - Recessive
  - DIS3L2 (RNA metabolism)

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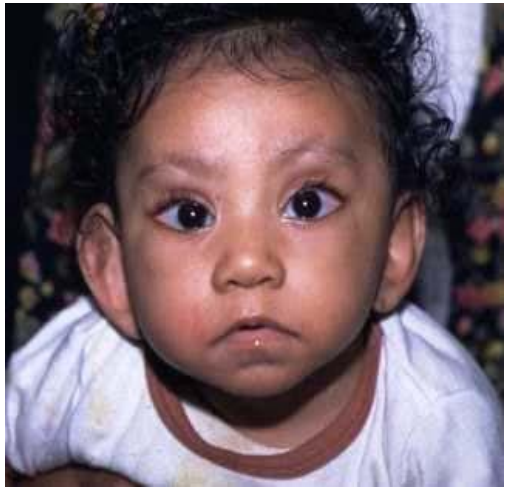
Kabuki syndrome

- Most frequent clinical features
  - long palpebral fissures
  - prominent ears
  - persistent finger pads
  - developmental delay



- Genes
  - KMT2D (90%
  - KDM6A (10%)

- Other frequent features
  - Small at birth
  - arched eyebrows
  - lateral sparse of eyebrows
  - long eyelashes
  - eversion of lower eyelid
  - broad nasal tip
  - short columella
  - joints hyperlaxity
  - feeding difficulties
  - hypotonia
  - congenital heart malformation
  - renal abnormalities
  - deafness
  - strabismus

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KDM6A clinical phenotype

- Endocrine features
  - Neonatal hypoglycemia
  - One patient with chronic hyperinsulinism
  - *KDM6A* tested first in a patient with chronic hyperinsulinism

    ⟶ ***KDM6A* mutation**
  - Another patient from Scotland with chronic hyperinsulinism and *KDM6A* mutation

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Kabuki syndrome

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Hypoglycemia in Kabuki Syndrome

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[2]Developmental Endocrinology Research Group, Molecular Genetics Unit, Institute of Child Health, University College London, London, UK

TABLE II. Features of Hypoglycemia in KS

Features	Patient 1	Patient 2	Patient 3	Patient 4
Age of onset	Day 1	Day 1	Day 1	Day 1
Presenting symptoms	Seizure	Jitteriness	Poor feeding	Poor feeding
Investigations				
Blood glucose (mmol/L)	2.4	2.5	2.3	2.9
Insulin (mU/L)	22	3.9	42.3	<2
NEFA (mmol/L)	0.32	0.38	1.67	1.3
3-BOHB (mmol/L)	0.08	0.07	1.08	1.02
Cortisol (nmol/L)	454	317	610	221
Growth Hormone (μg/L)	—	10.8	5.2	2.9
Lactate (mmol/L)	—	2.2	1.6	1.2
Ammonia (mcg/dl)	—	40	35	37
Cause of hypoglycemia	Hyperinsulinism	Hyperinsulinism	Not known	Growth hormone deficiency
Treatment	Diazoxide + Chlorothiazide	Diazoxide + Chlorothiazide	Feeding regimen	Growth hormone
MLL2 mutation	Negative	Positive, c.6971dupC heterozygote	Positive, c.5845C> T heterozygote	Positive, c.2992C>G and c.12964C>T heterozygote

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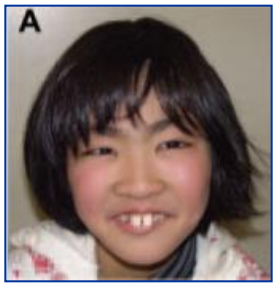
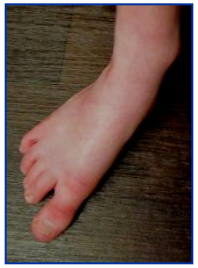
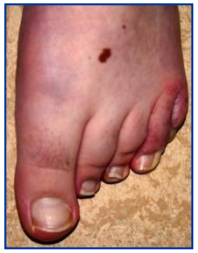
Lederer 2012

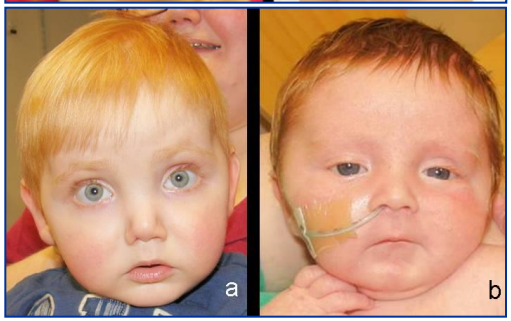


Miyake 2013a

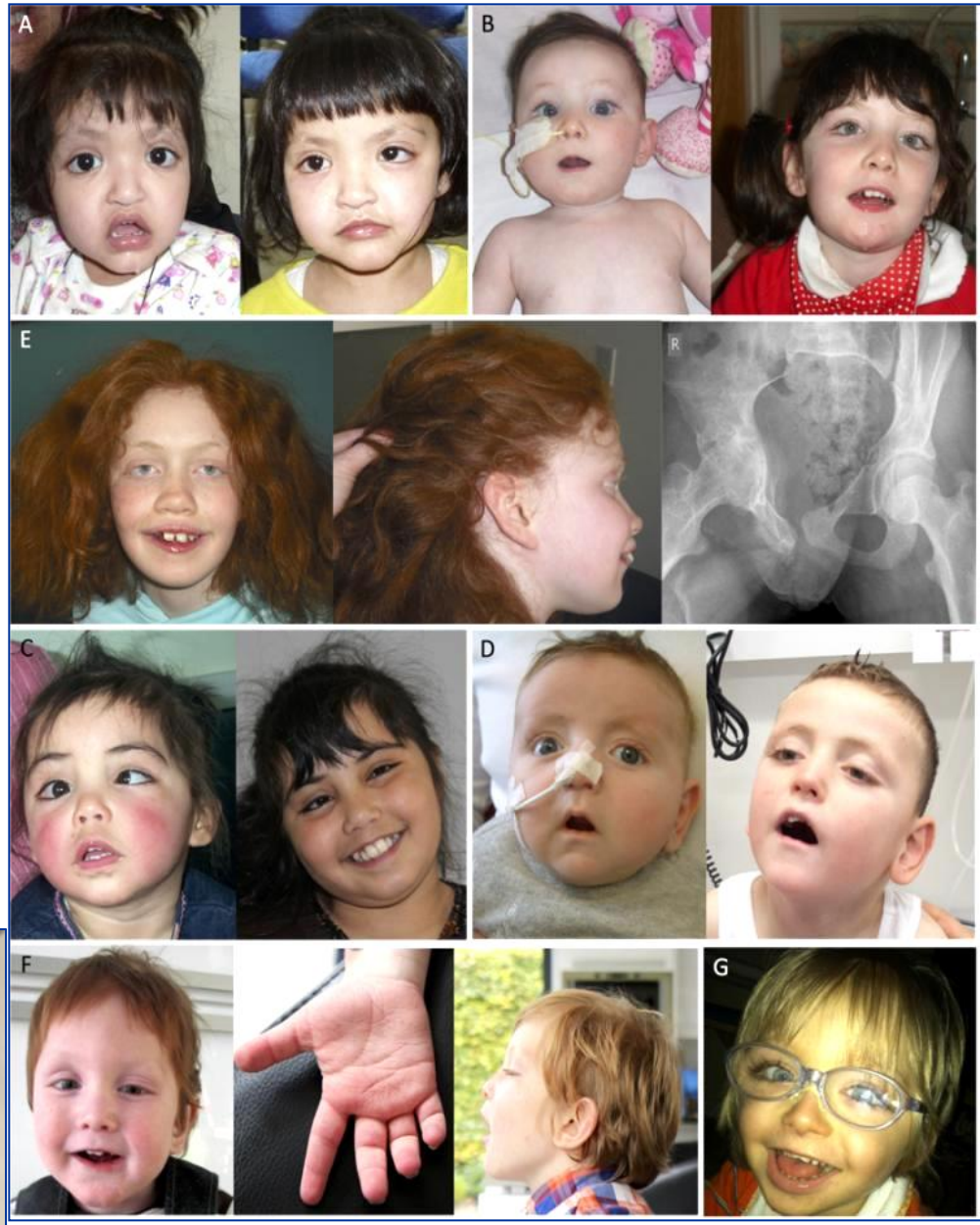
Miyake 2013b







Lederer 2014



Banka, Lederer 2014

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Other

- Chromosome disorder
  - Microarray CGH
  - 12q24
  - 5q11.2
  - 8q24
  - USH1C deletion (11p14-15) Hyperinsulinism-deafness-enteropathy-renal tubular dysfunction
  - 10p13-14 (HK1)
    - Poland Anomaly
    - Congenital hyperinsulinism
- CDG syndrome
- CACNA1D
  - Two cases
  - diazoxide responsive HI, aortic insufficiceny, severe hypotonia, developmental delay, neuromuscular abnormalities, primary hyperaldosteronism

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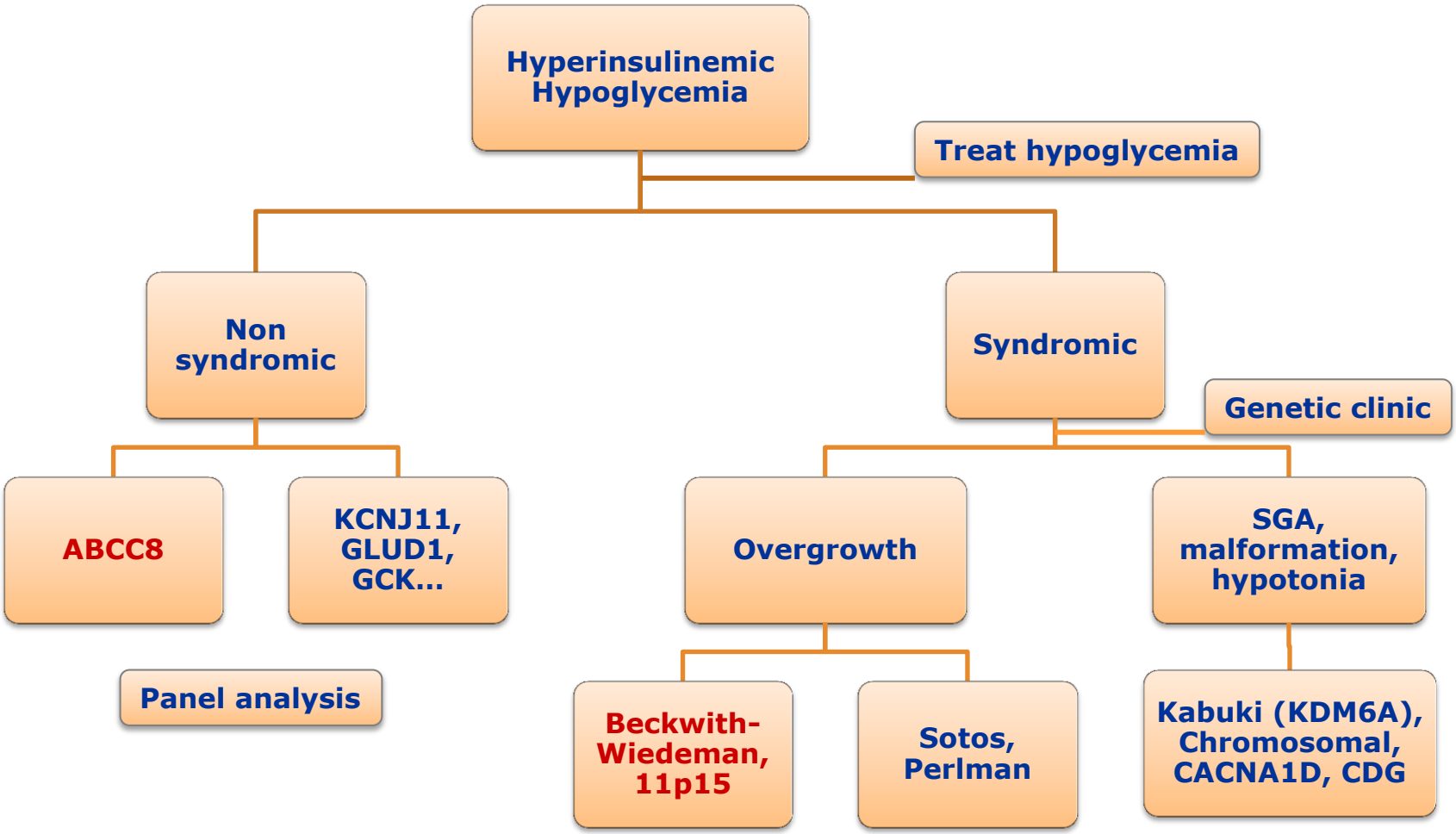
Conclusion



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Thank you for your attention!