Congenital hyperinsulinism

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Clinical diagnosis

- Wipple‘s triad
  - Glucopenic symptoms
    - Drowsiness
    - Fainting
    - Seizures
    - Hallucinations
    - Any kind of neurological symptoms
  - Glycemia <3,0 mmol/l (55mg/dl)
  - Resolution of all symptoms after normalization of glycemia

Source: Expert Opinion on Orphan Drugs (2014) 2(8): 779-795

JB

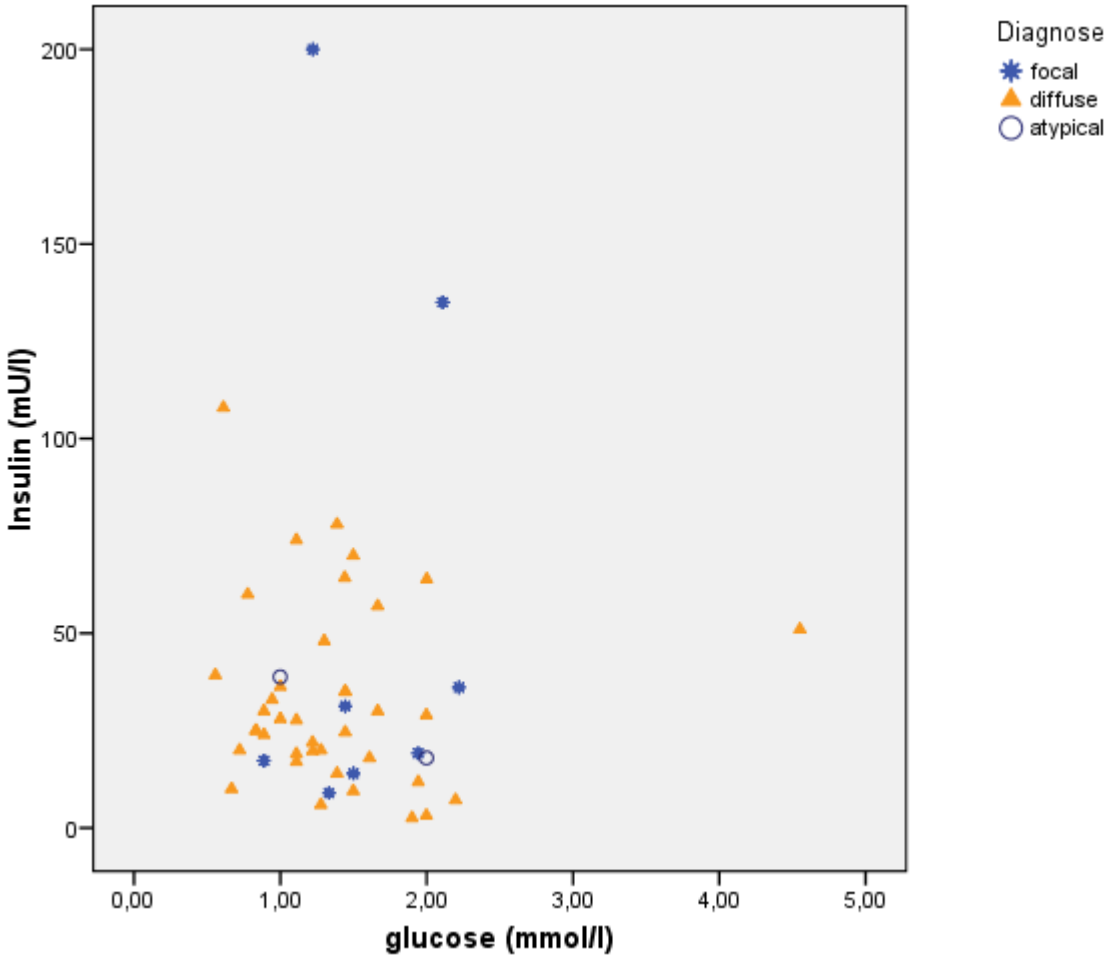
Biological diagnosis of HI

- Fasting and/or postpandrial hypoketotic hypoglycemia (<2,5 mmol/l)
- Inappropriate plasma insulin levels and c-peptide at time of hypoglycemia (in some cases, insulinemia can be seemingly null)
- Absent or low blood/urines ketone bodies and non-esterified fatty acids
- An increase in blood glucose <1,7 mmol/l within 30 min after administration of 1 mg glucagon
- Need of high glucose infusion rate to keep blood glucose >3,0 mmol/l (>8 mg/kg/min)

Source: Expert Opinion on Orphan Drugs (2014) 2(8): 779-795

JB

Insulin/ glucose at diagnosis



JB

Clinical diagnosis

- Syndromic CHI

  Overgrowth syndrome

Beckwith-Wiedemann	AD or S	11p15.5
Perlman	AR	?
Sotos	S	NSD1

  Developmental syndrome

Kabuki syndrome	AD or S	MLL2
CDG syndrome	AR	PMM2 / PMI
Costello	AD or S	HRAS
Turner	S	Monosomy X

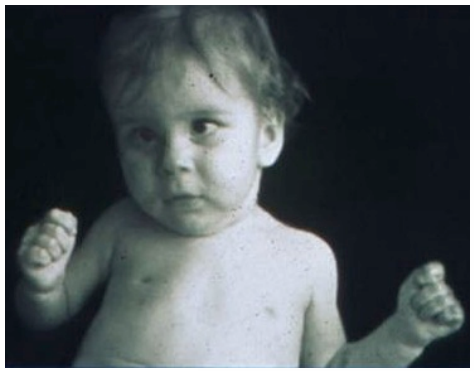
Source: Expert Opinion on Orphan Drugs (2014) 2(8): 779-795

JB

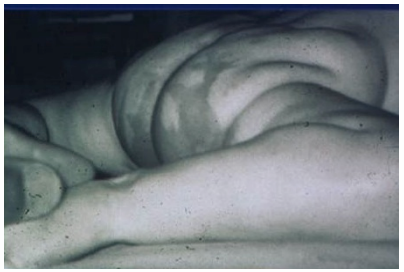
Clinical diagnosis

- Beckwith-Wiedemann syndrome
  - » Macrosomia, ear lobe creased, macroglossia, umbilical hernia, hemihypertrophia, heart defects…

- Congenital disorder of glycosylation (CDG) syndrome type Ia&b



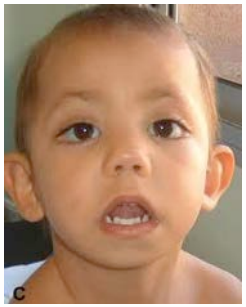
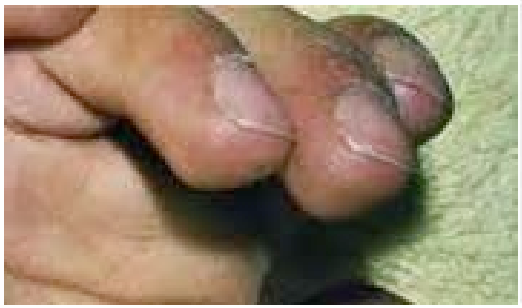
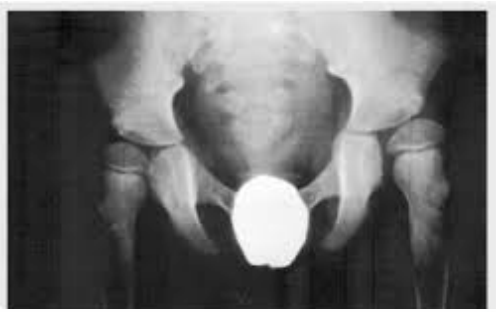
  - » strabism, progressive cerebellar atrophy, inverted nipple, abnormal fat distribution, lipoatrophy areas, abnormal coagulation factors…



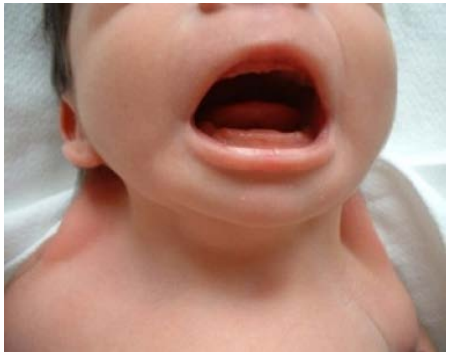
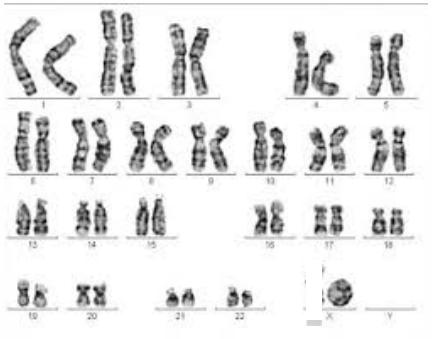
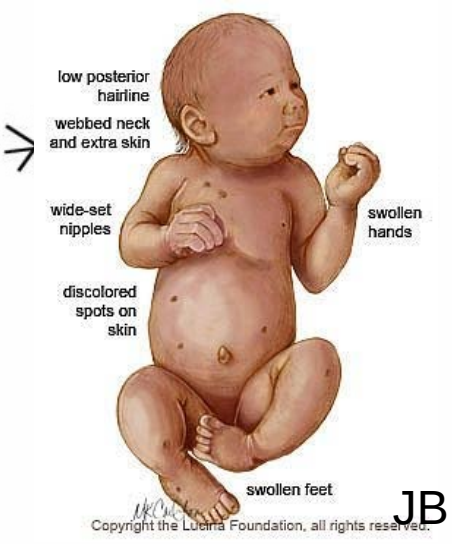
JB

Clinical diagnosis

- Kabuki make-up syndrome
  - elongated palpebral fissures with eversion of the lateral third of the lower eyelid, skeletal anomalies (costal, vertebral or hips), fetal fingertip pads, failure to thrive, congenital heart defects, hormones deficiencies…

- Turner syndrome
  - SGA, pterygium coli, heart, aortic, kidney malformation, growth delay…

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JB

Clinical diagnosis

- Transient CHI
  - Newborns from diabetic mothers
  - Small for gestational age babies (SGA)
  - Perinatal stress
    - Fetal distress
    - Asphyxia at birth

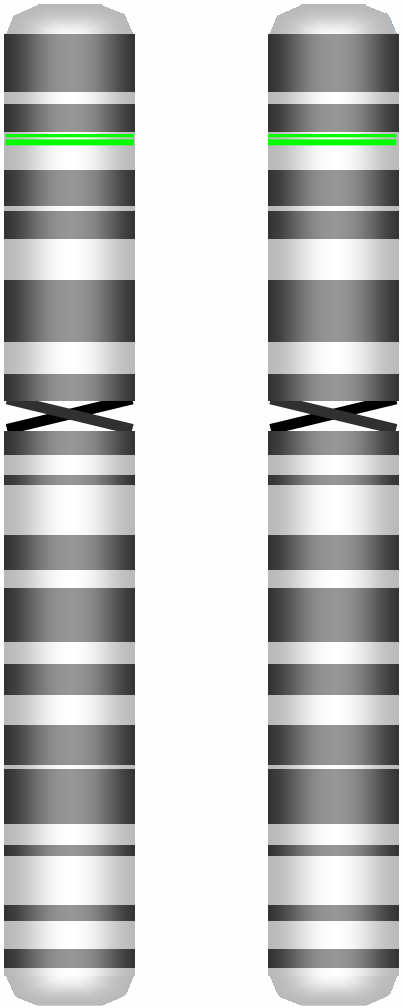
- Isolated CHI
  - Channelopathie: ABCC8, KCNJ11,
  - Metabolopathie: GLUD1, GCK, UCP2, HADH, SLC16A1
  - HNF1A, HNF4A

Source: Expert Opinion on Orphan Drugs (2014) 2(8): 779-795

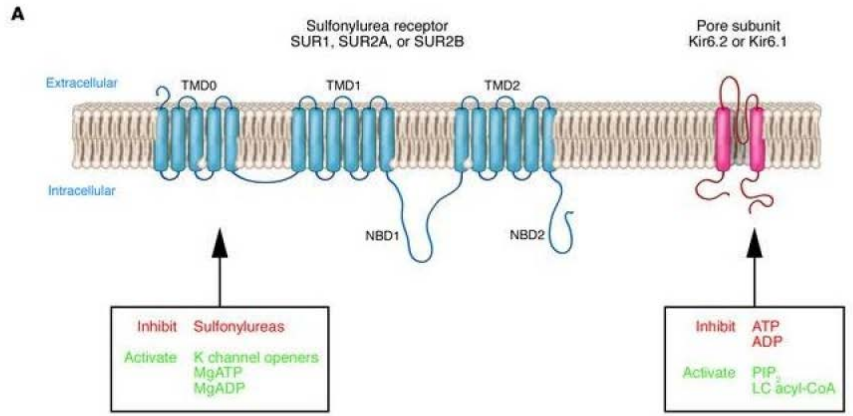
JB

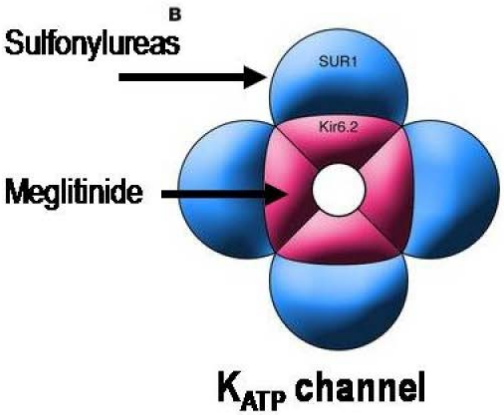
Genetics

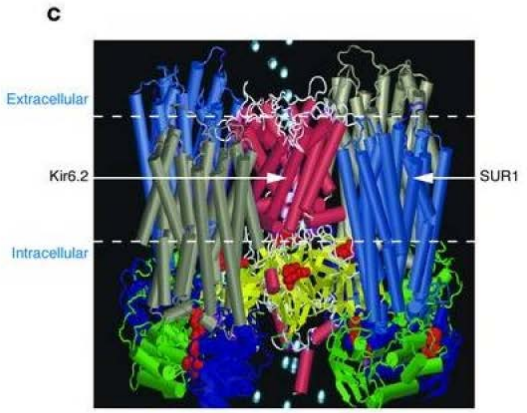
KCNJ11 (Kir6.2)
ABCC8 (SUR1)



Chromosome 11



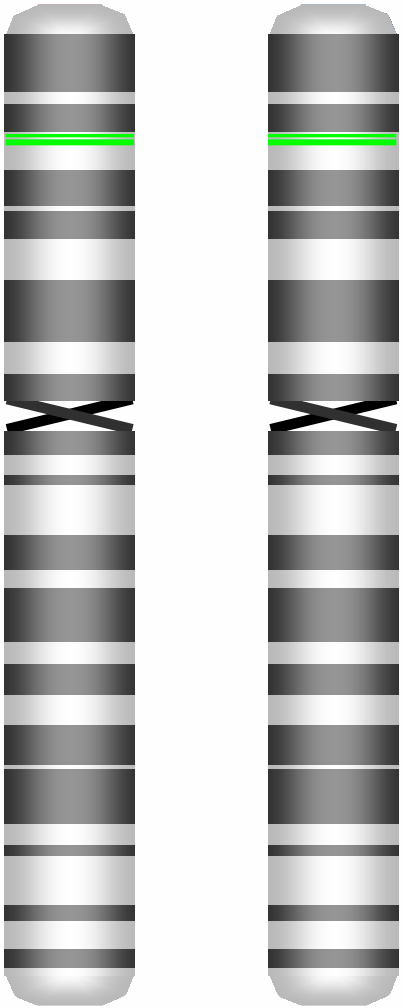




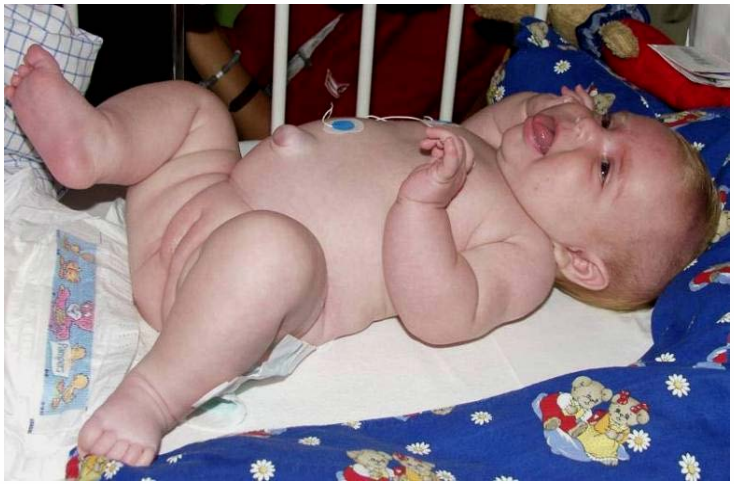
K

Genetics

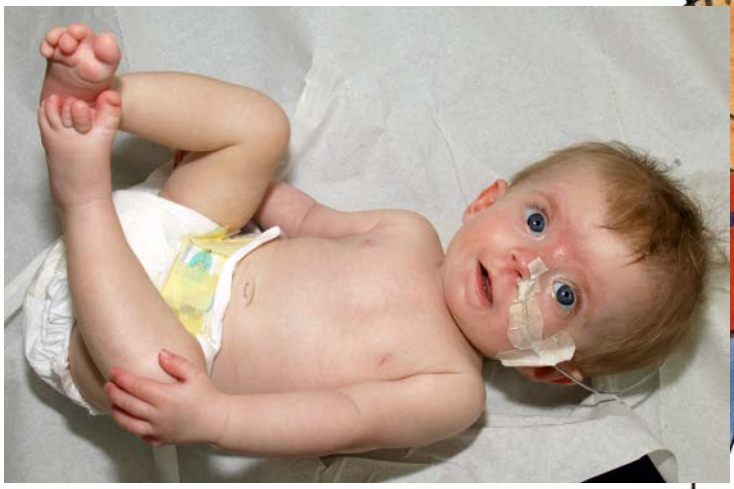
KCNJ11 (Kir6.2)
ABCC8 (SUR1)



Chromosome 11



Wiedemann-Beckwith-Syndrome



Silver-Russell-Syndrome

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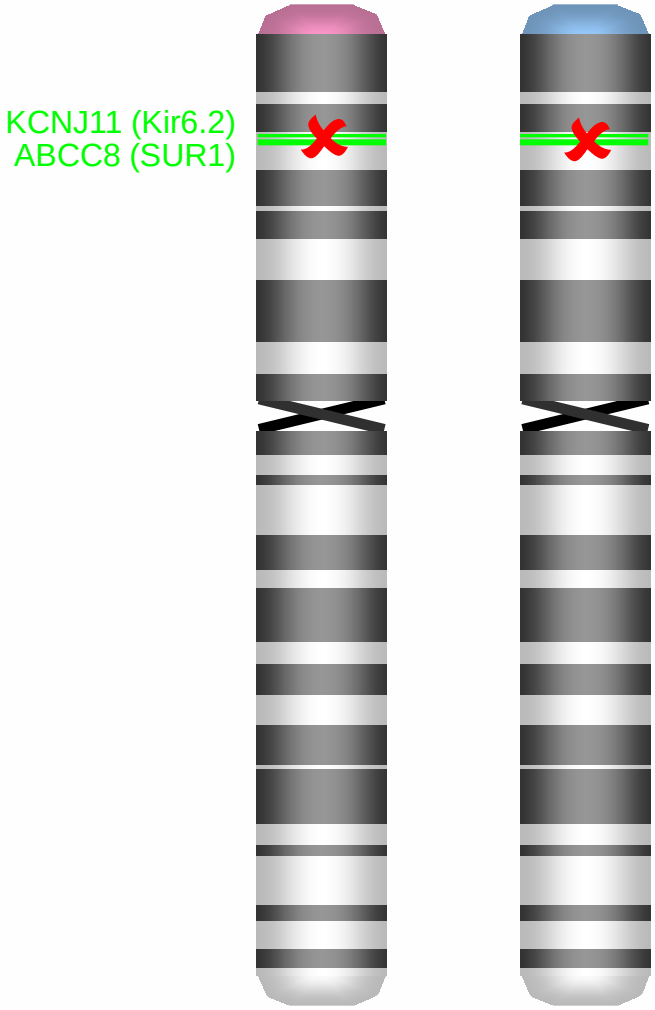
Genetics

Autosomal-recessive



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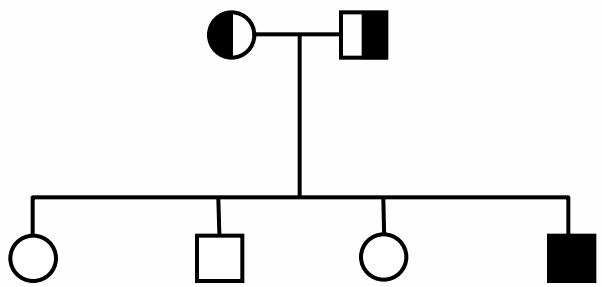

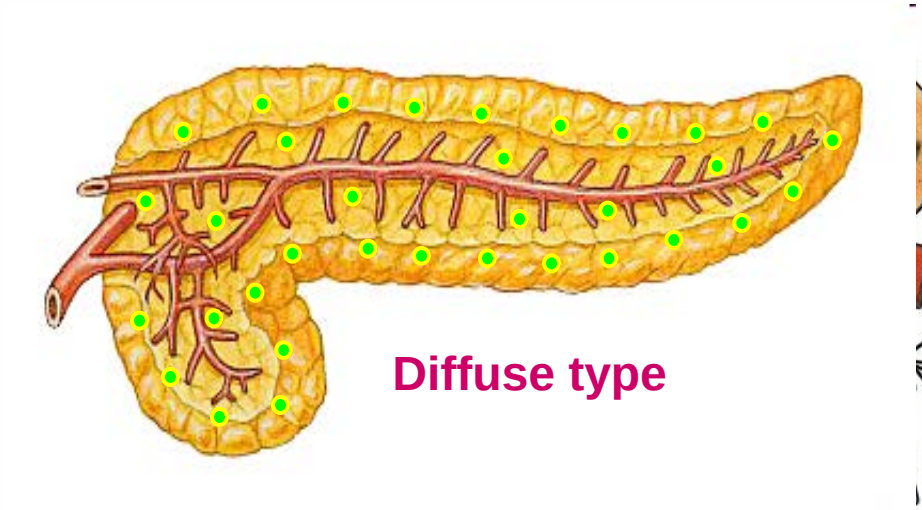

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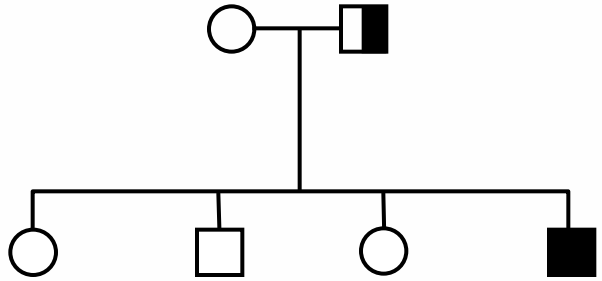
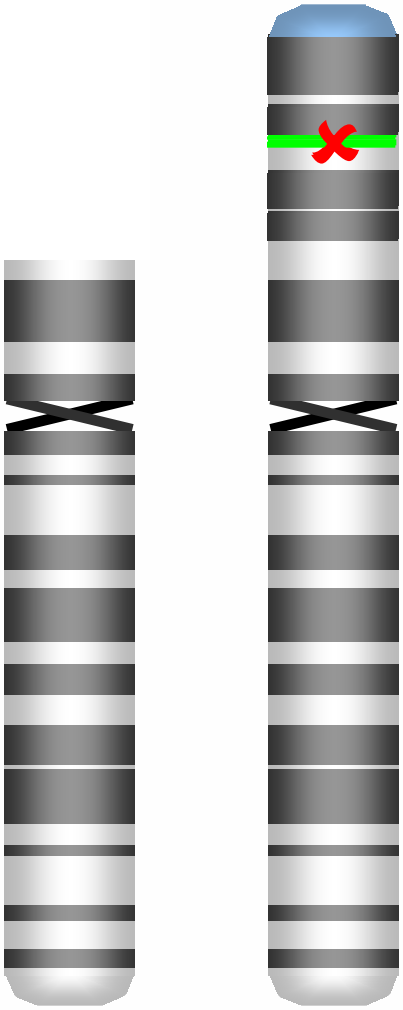
Genetics

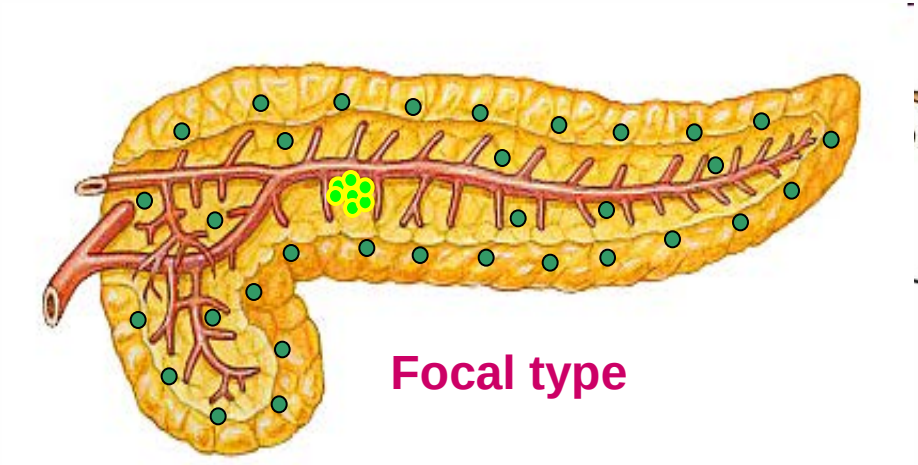
heterozygote, paternally inherited, recessive mutation



KCNJ11 (Kir6.2)
ABCC8 (SUR1)



Chromosome 11



„Second-Hit in islets by paternally inherited mutation: 1:270

K

PET-CT scan

PET-scanning and CT-scan in one single device.

For simultaneous registration and fusion of 2 signals

1. tracer (e.g. F18-L-DOPA) by PET and
2. anatomical image by CT.

K

PET-CT scan

L-DOPA is a

transmitter substance in the nervous system.

precursor of catecholamines (= noradrenaline and adrenaline)

Neuroendocrine cells

take up and decarboxylate amine precursors,

e.g. L-DOPA and 5-hydroxytryptophan

store biogenic amines (= dopamine and serotonin)

K

PET-CT scan

L-DOPA

Pancreatic cells contain markers of neuroendocrine cells,

such as tyrosine hydroxylase, dopamine,

neuronal and vesicular dopamine transporter,

monoamine oxidases A and B.

Pancreatic islets take up L-DOPA and convert it to dopamine through the **A**romatic **A**mino **a**cid **D**ecarboxylase

AAAD.

K

PET-CT scan

1. No moving of patients necessary
2. No transmission radiation
3. Quick scanning times (< 4 min.)
4. Software allows:
   Alignment of PET and CT datasets measurement of distances
5. Data acquisition up to 5* repeated
6. multiple time point imaging:

   from 20 to 60 min p.i.

K

PET-CT scan

1. Between 2004 and 2015, a [18F]F-DOPA-PET/CT was performed in 200 patients.
2. Analyses of 150 patients (67 girls, 83 boys) (median age: 0.53y; range: 0.09-30.35y.).
3. Mutation analysis of ABCC8 and KCNJ11 were carried out in the index patient and their parents.
4. Pancreatic surgery was done in focal form

K

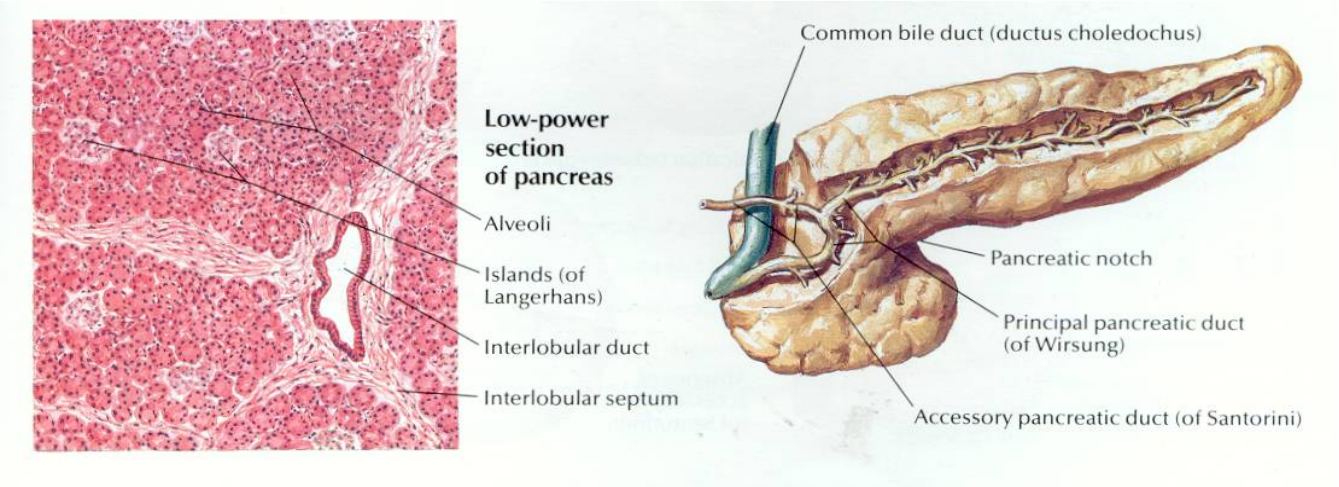
PET-CT scan

Pancreas

located behind the stomach between the spleen and duodenum

Islets of Langerhans

- α cells – glucagon
- β cells – insulin
- Δ cells – somatostatin/gastrin



Netter; Atlas of Human Anatomy

K

PET-CT scan

Focal form

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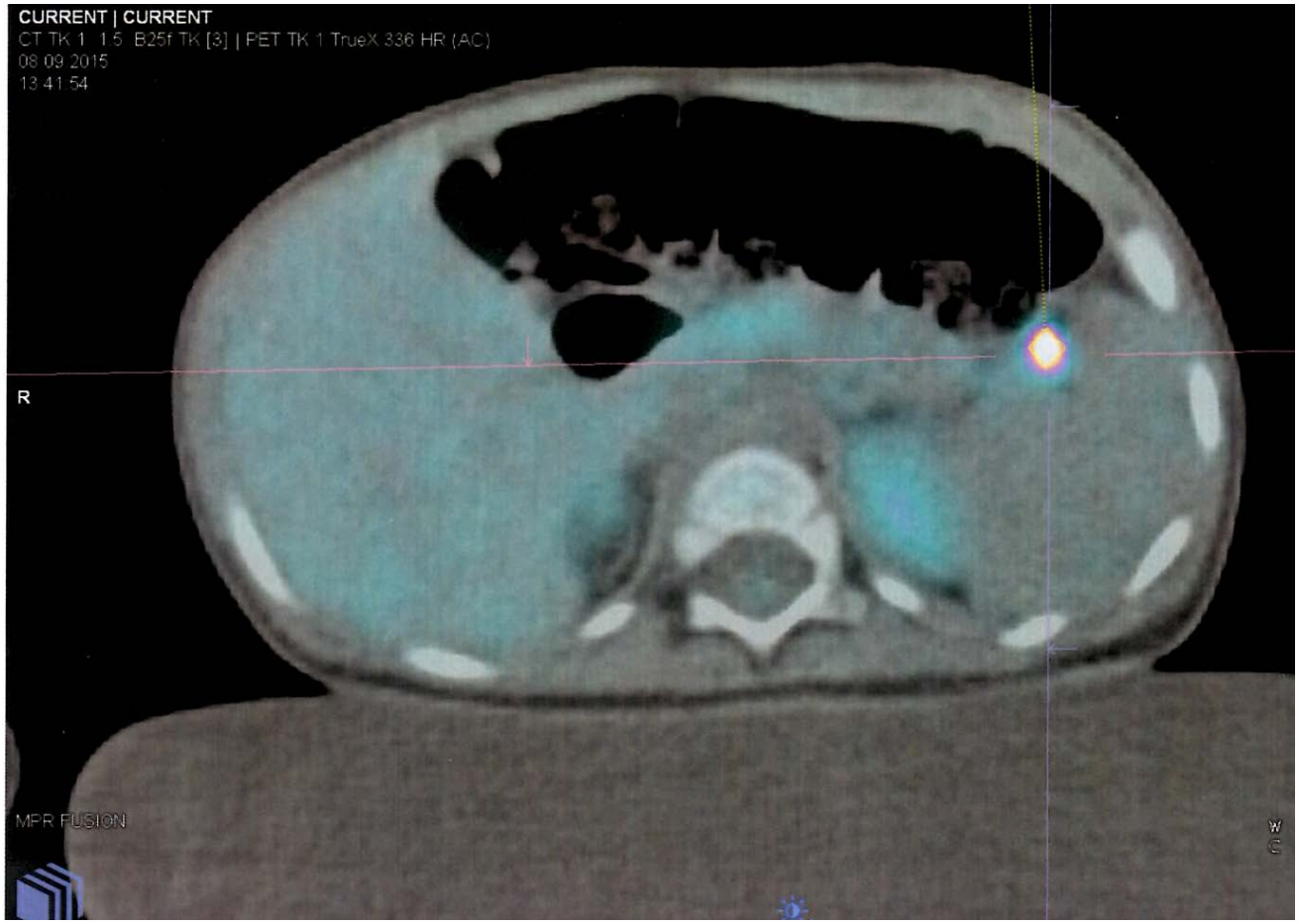
PET-CT scan

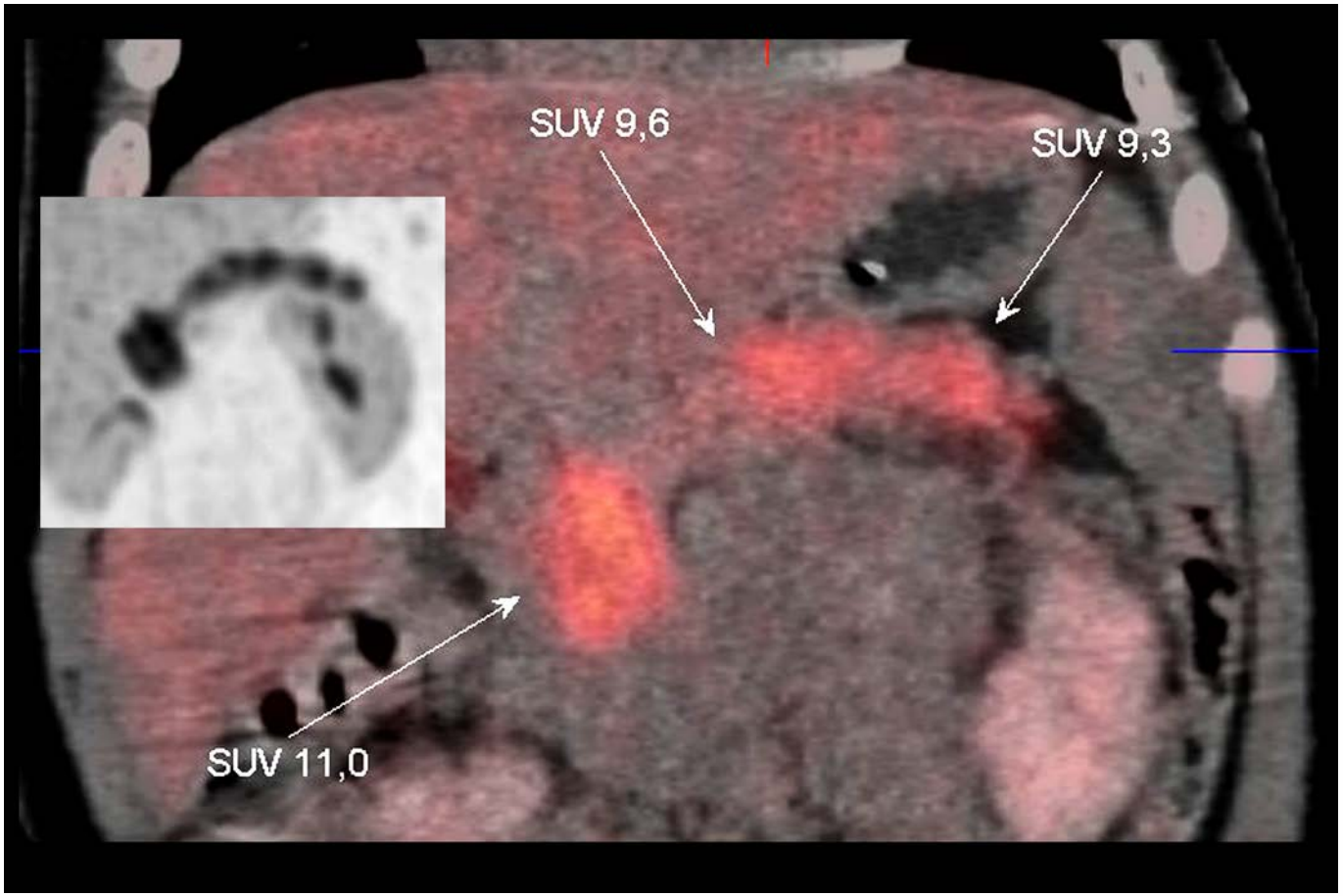
Focal form



K

PET-CT scan

Diffuse form



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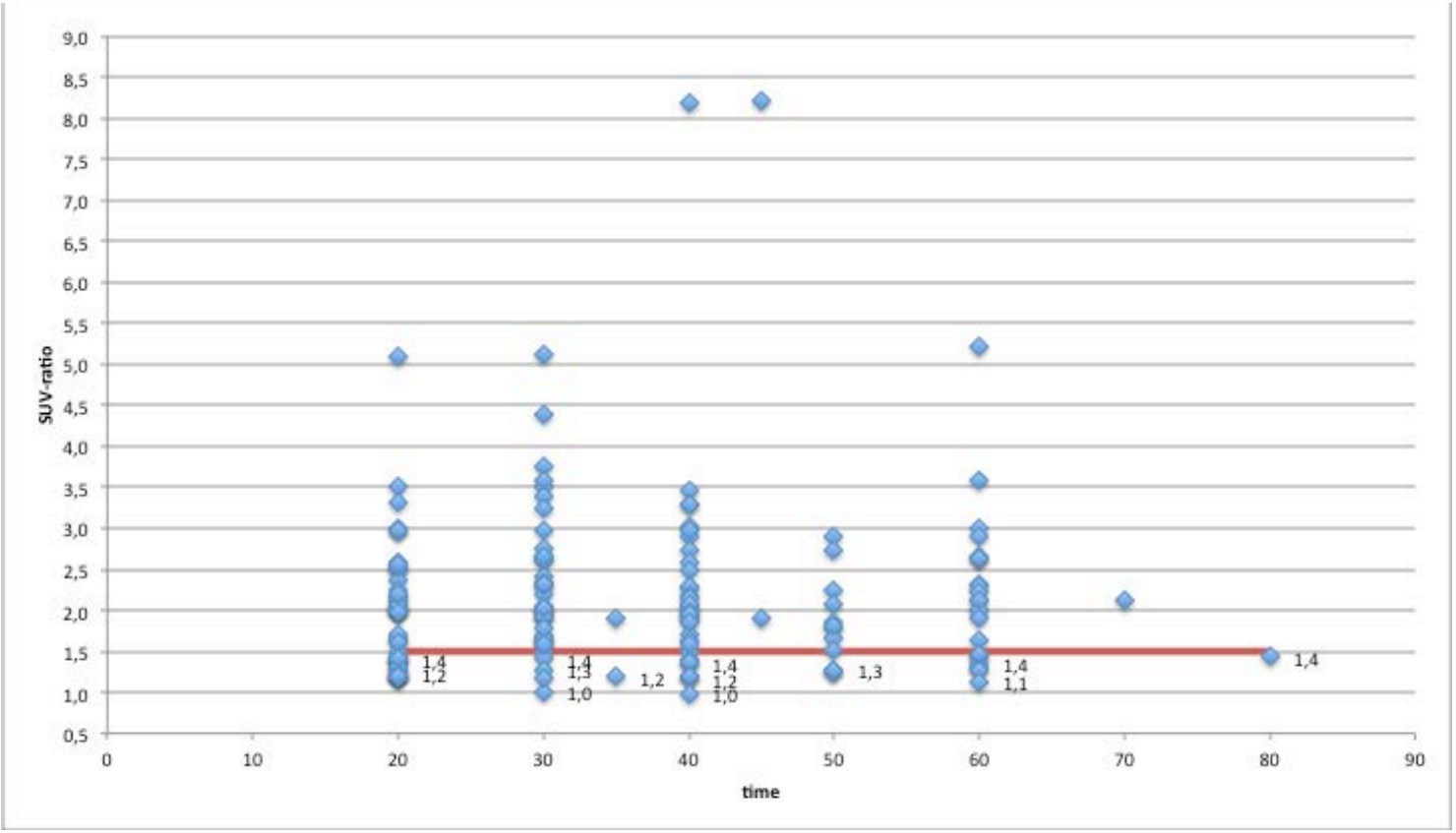
PET-CT scan

Focal form



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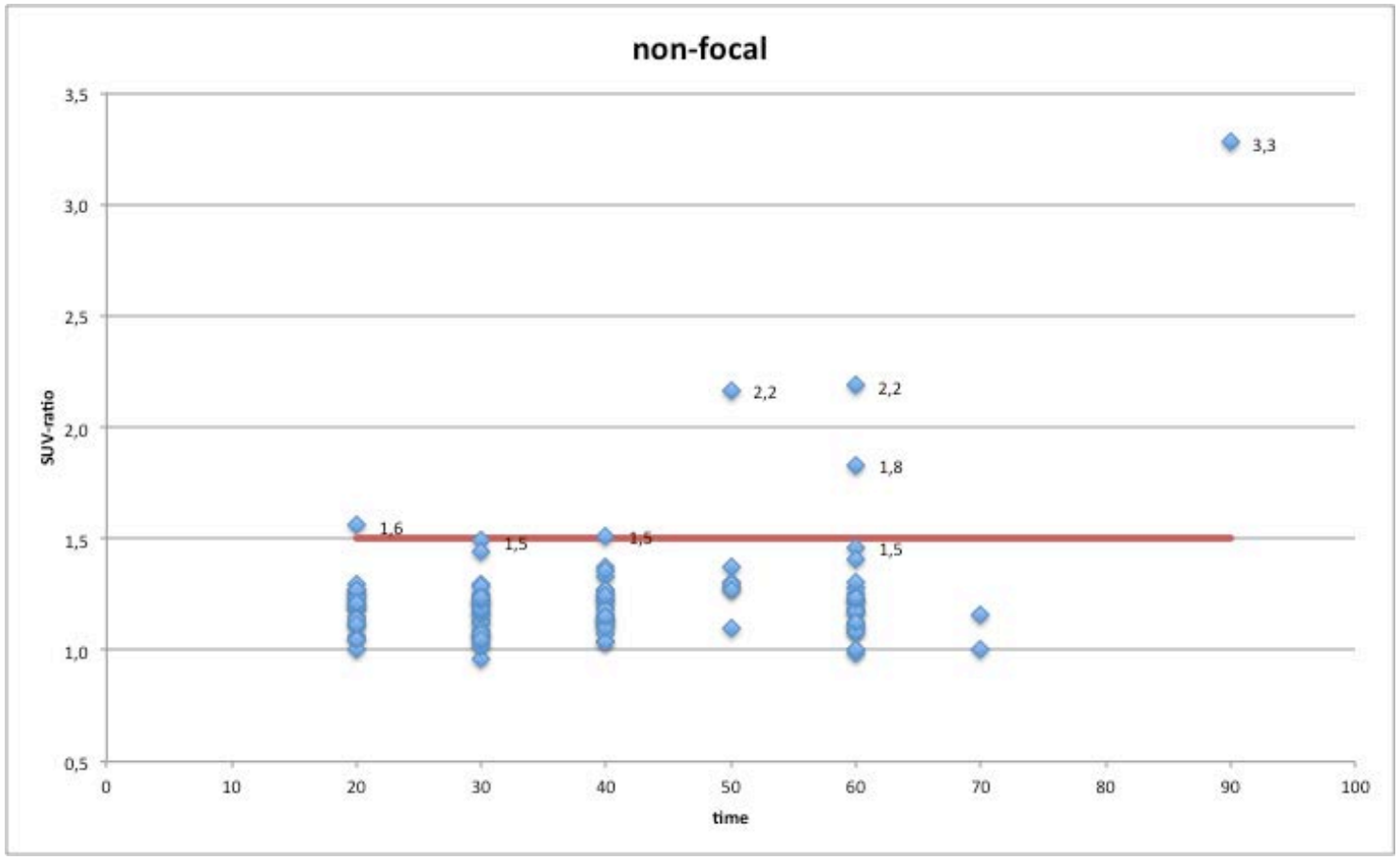
PET-CT scan

non-focal form



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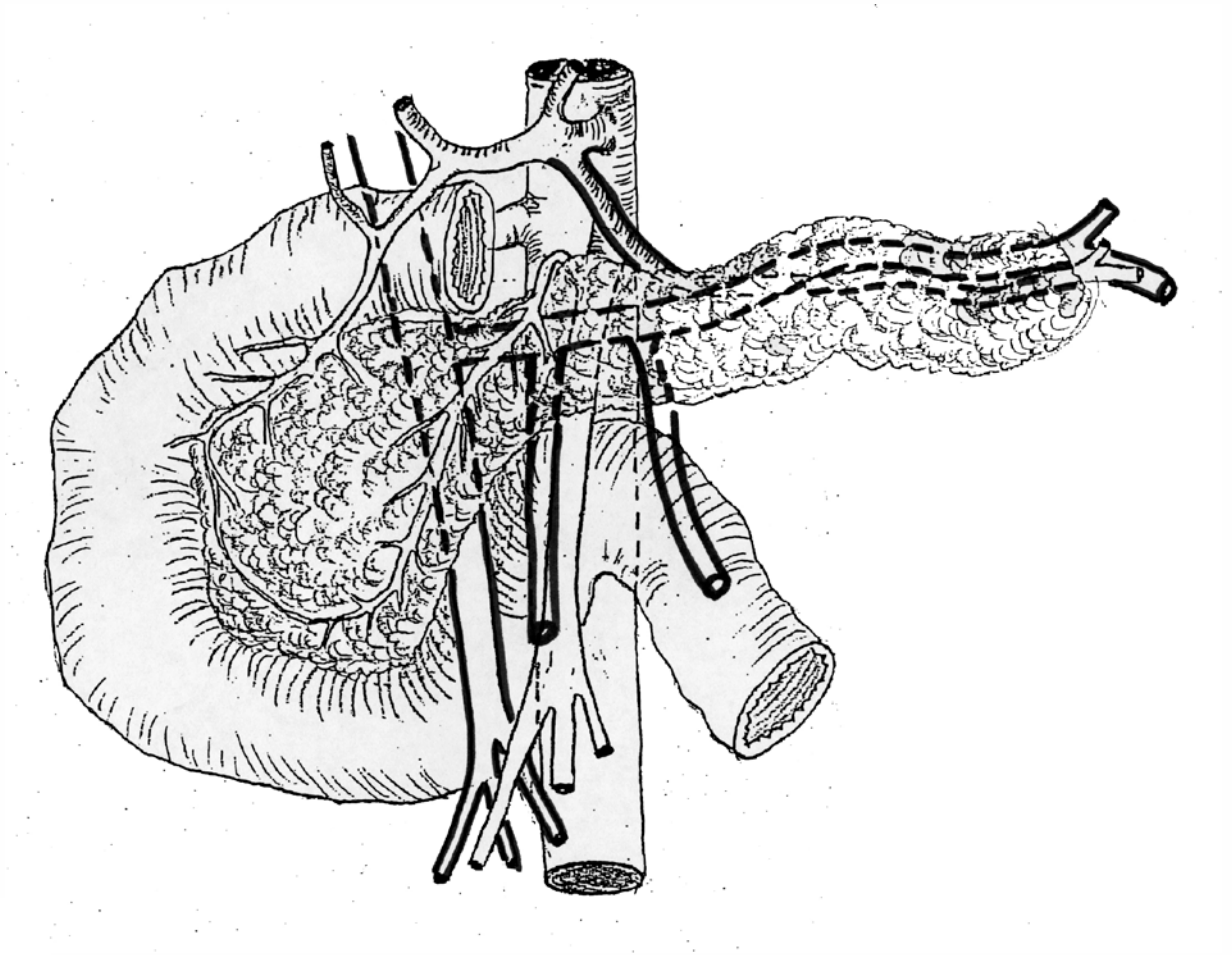
PET-CT scan

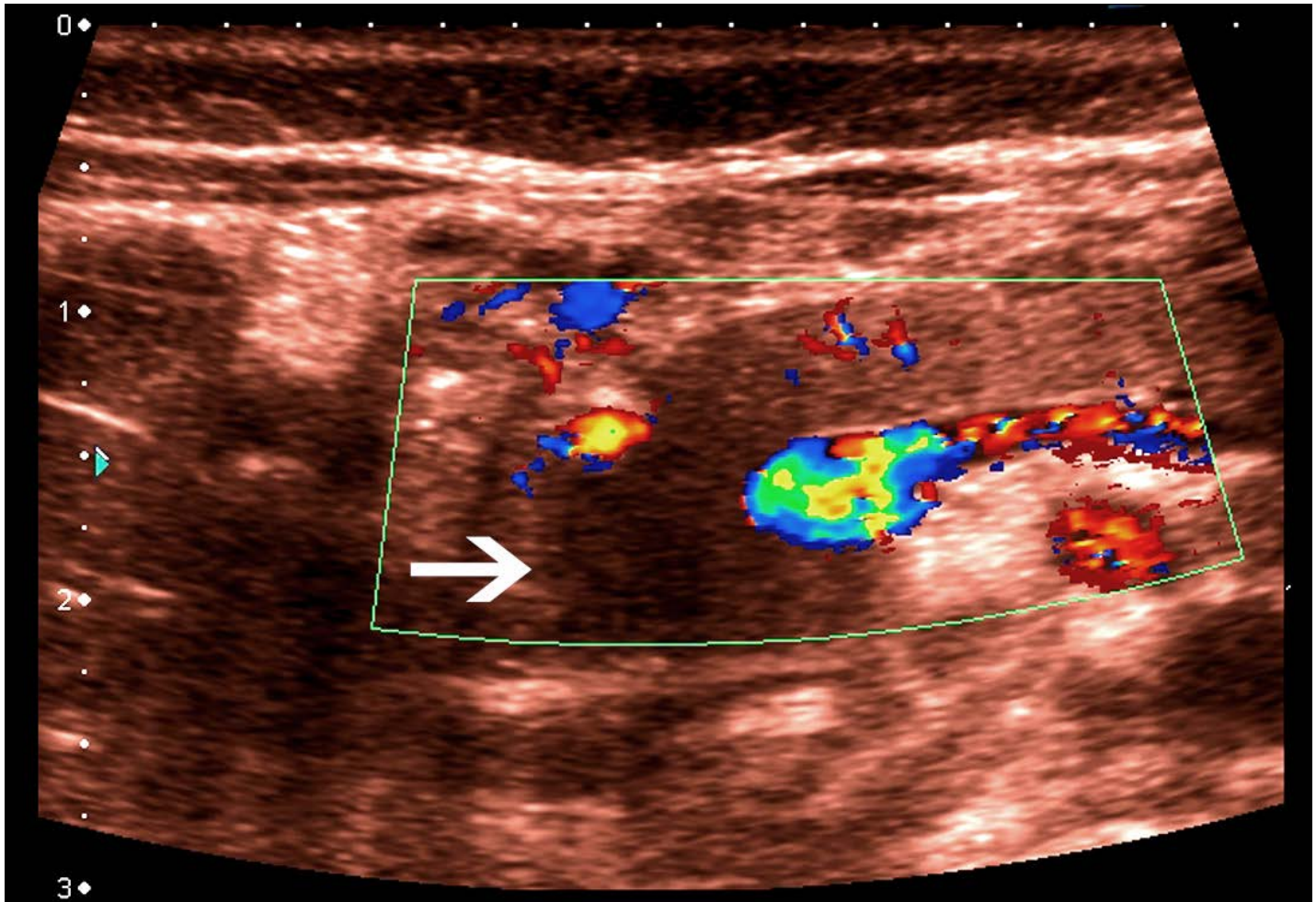
Localisation of important landmarks

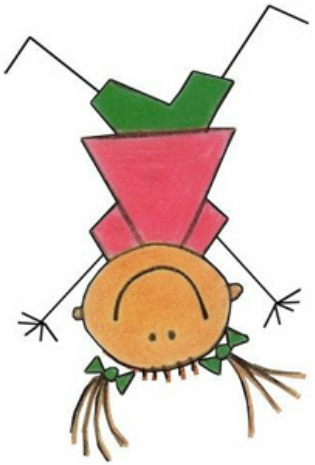


K

Intra operative diagnosis

Pre-operative ultra-sound

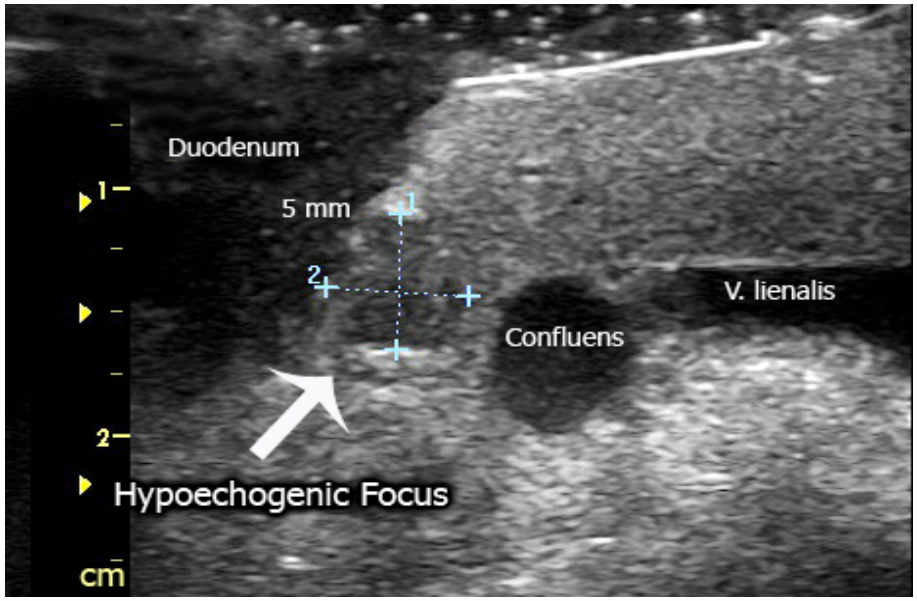


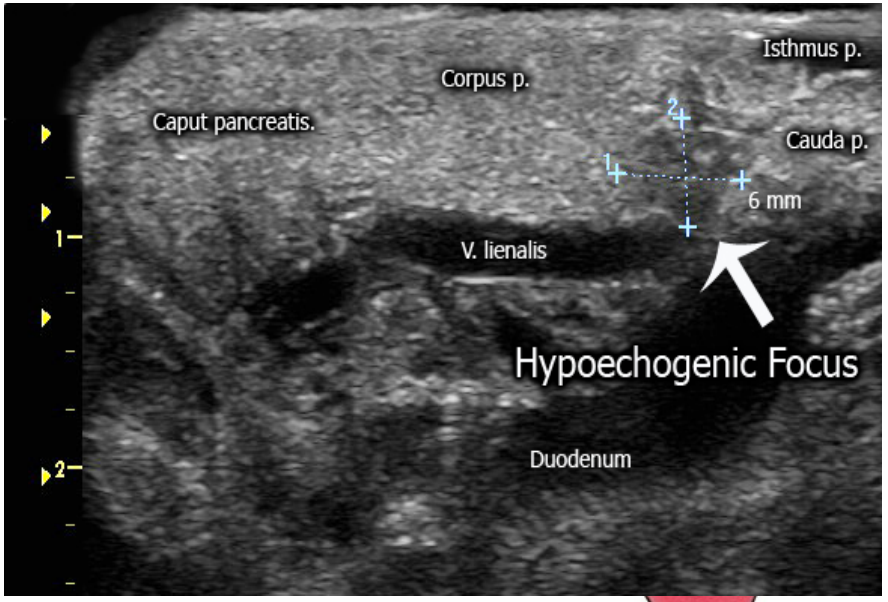


K

Intra operative diagnosis

Intra operative ultra-sound





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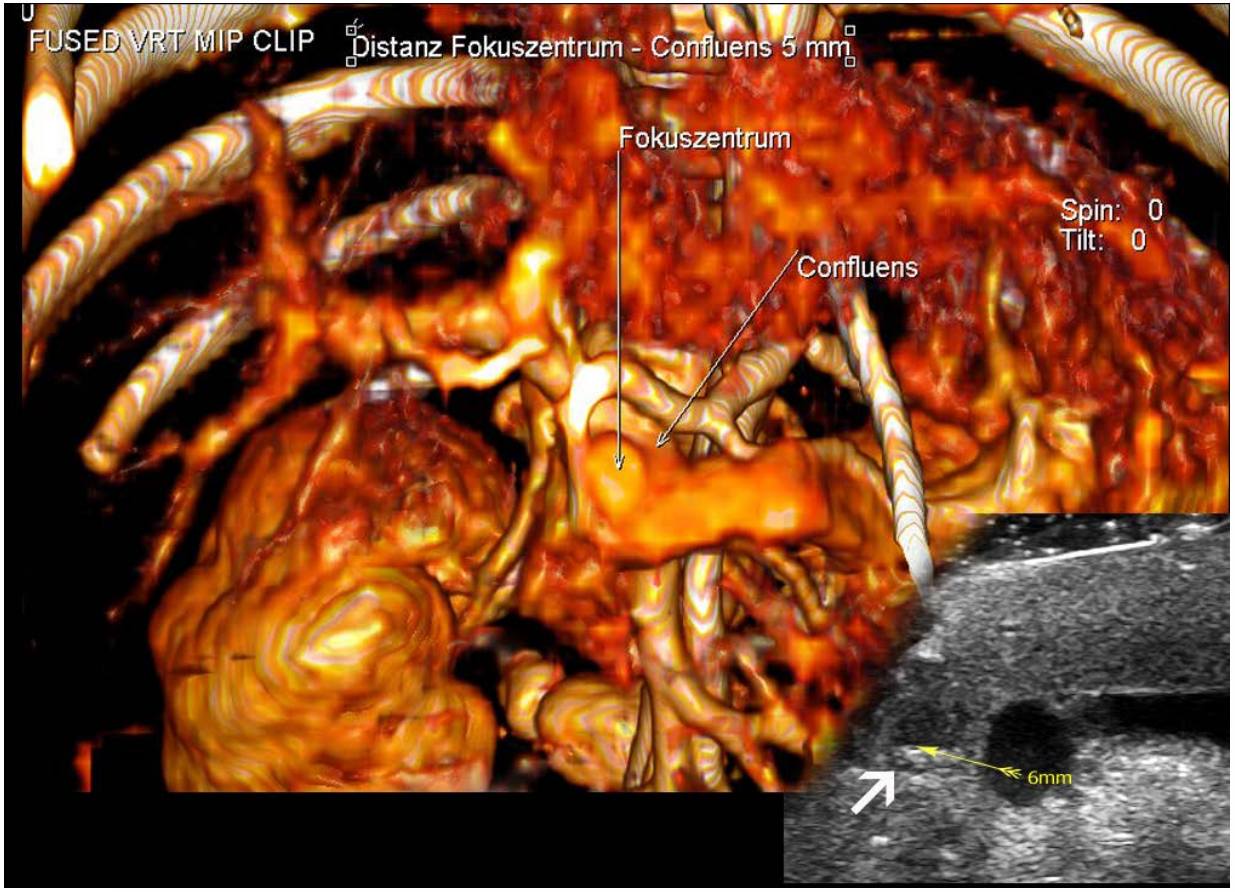
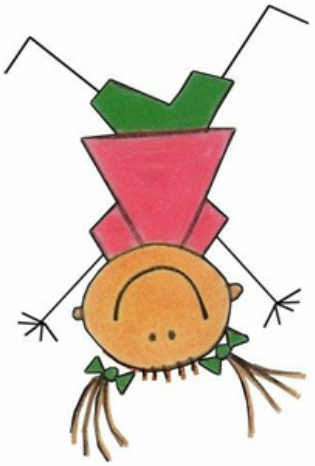
Intra operative diagnosis

Intra operative ultra-sound





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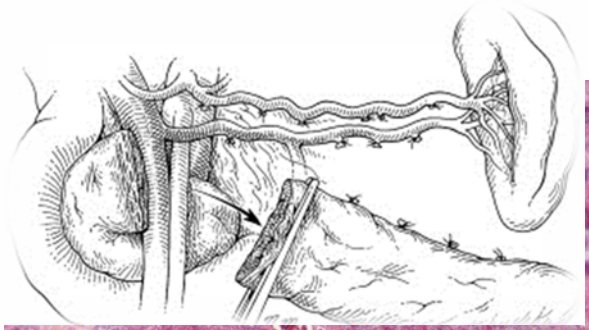
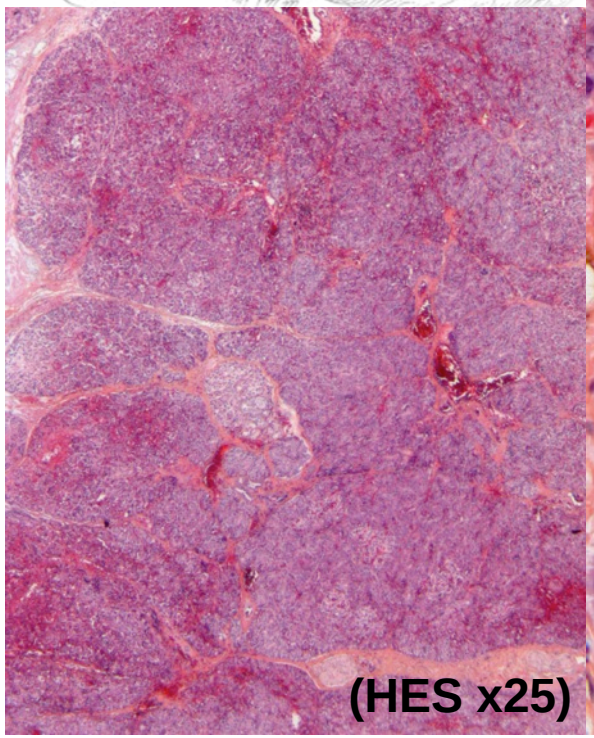
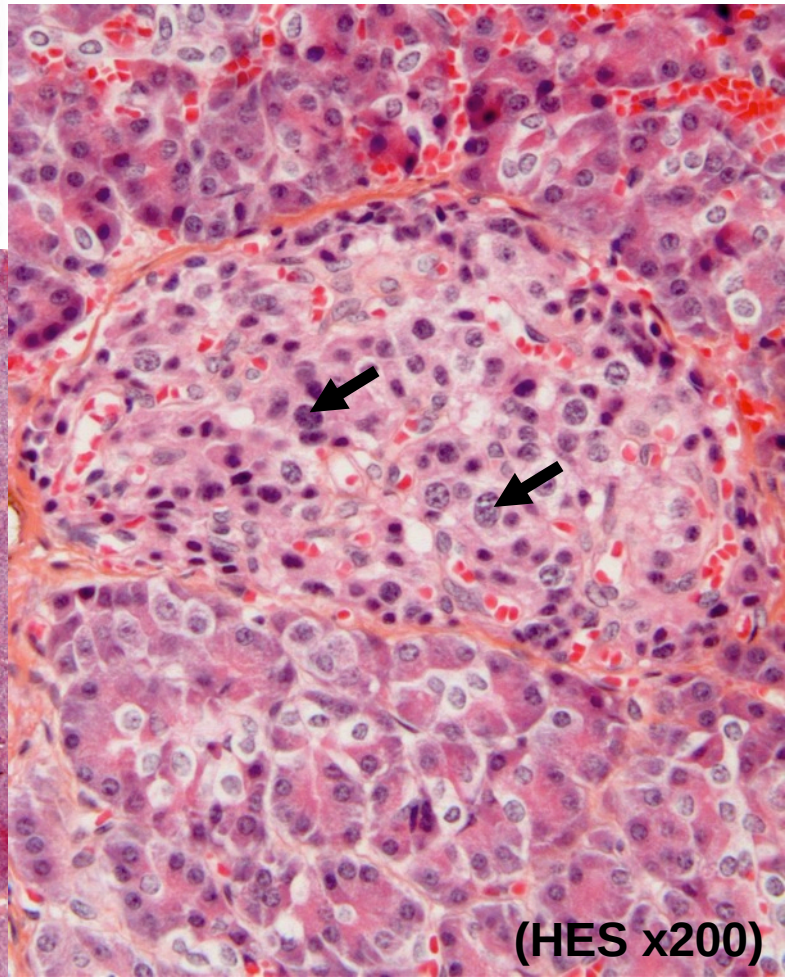
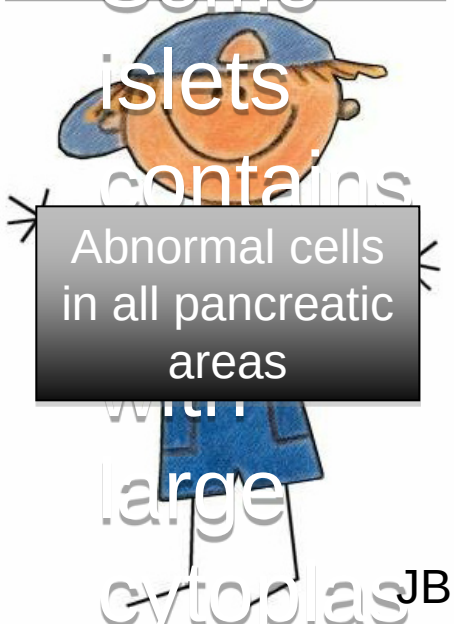
Pathology / CHI diffuse







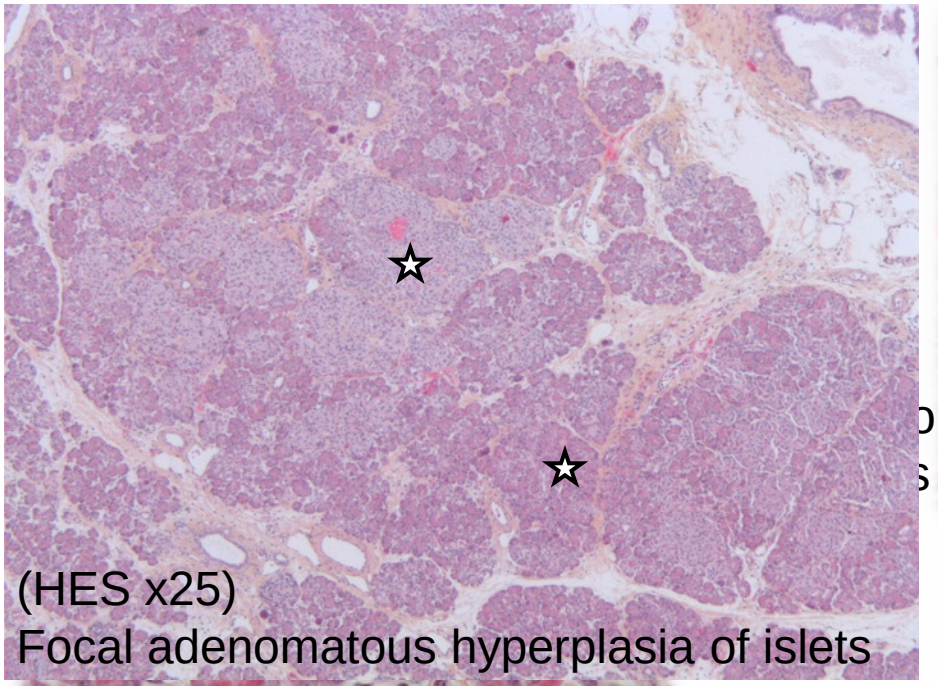
- Preserved islet pattern
- Some islets contains



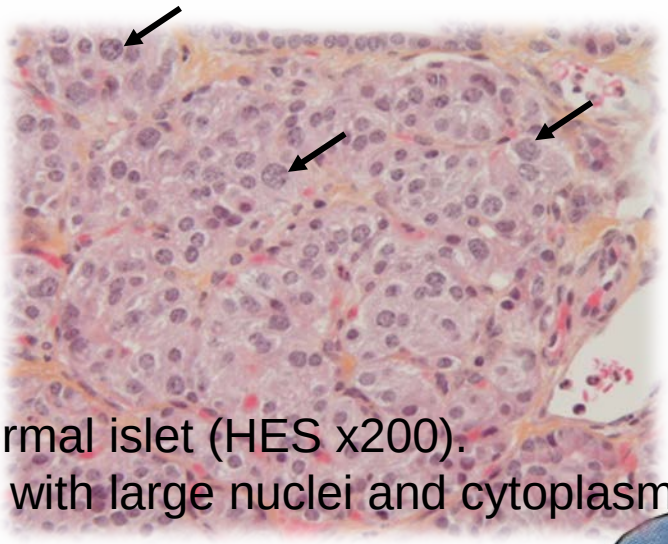
JB

Pathology / CHI focal

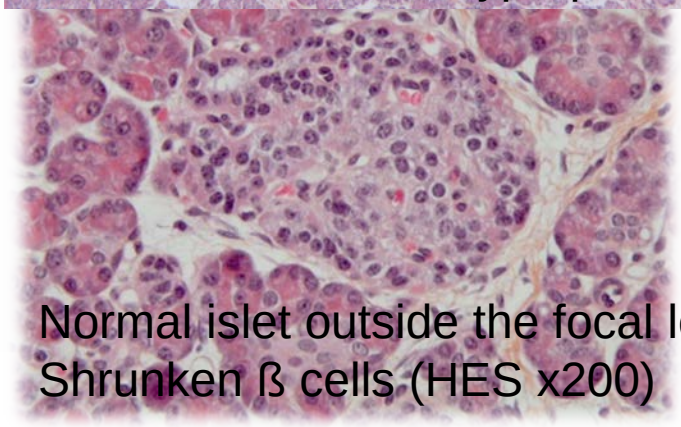
2.5-7.5 mmø



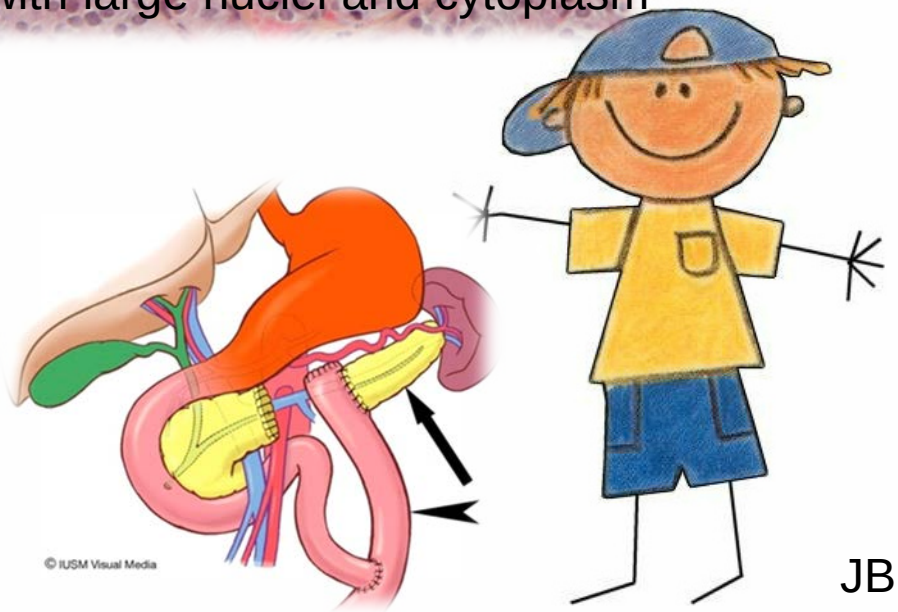
(HES x25)
Focal adenomatous hyperplasia of islets



ɔrmal islet (HES x200).
s with large nuclei and cytoplasm



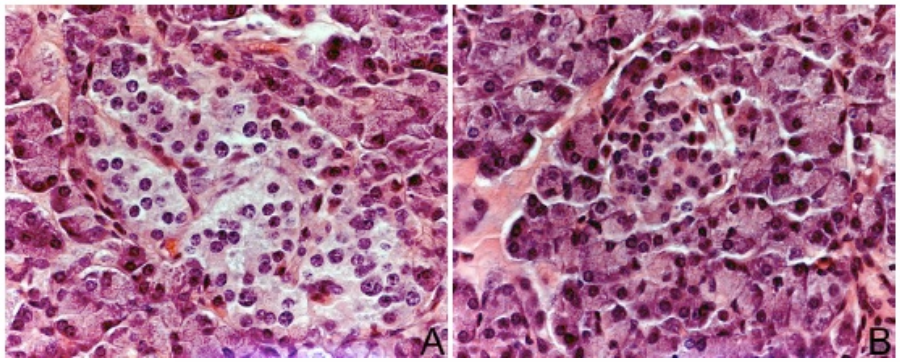
Normal islet outside the focal lesion.
Shrunken ß cells (HES x200)



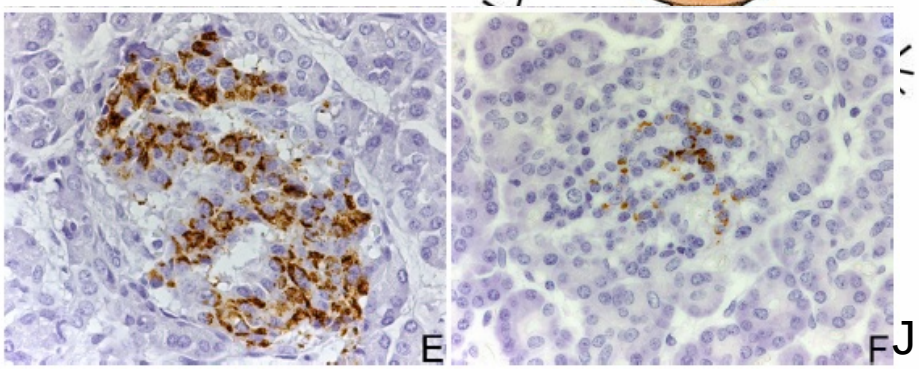
JB

Pathology / CHI atypical

- Mosaicism of the pancreatic islets (+/- 5% of severe CHI patients)
  - Described in two series 7/282 [Snider JCEM 2013] and 16/217 [Sempoux JCEM 2011]
- Pathology:
  - Normal pancreatic architecture
  - Large ß-cells & islets in several adjacent lobules
  - Outside of the lesion: ß-cells normal or at rest.



Islet inside the lesion And outside



ProInsulin staining in and outside the lesion

JB

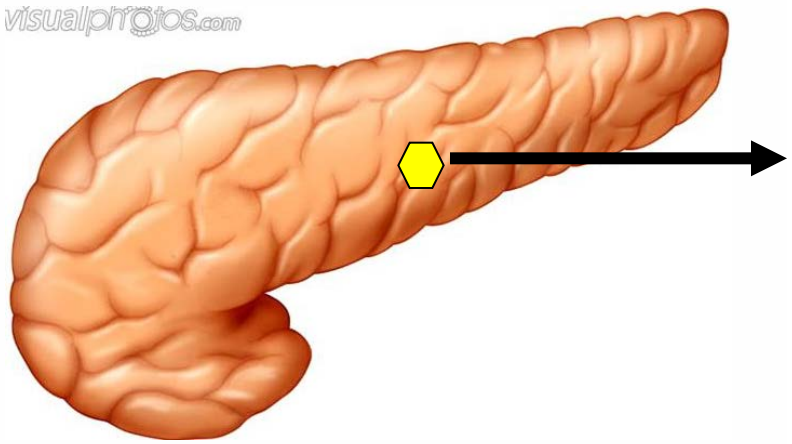
Pathology / CHI atypical

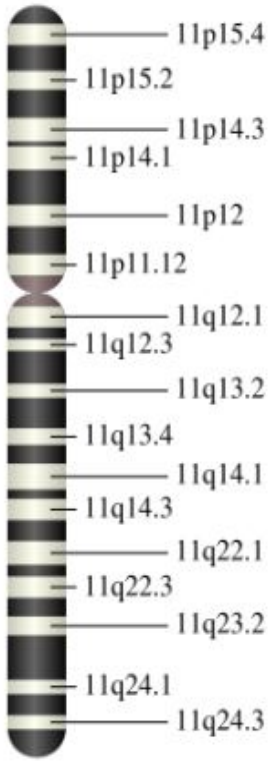
- Distinct clinical course compared to DZX-unresponsive K_{ATP} CHI
  - Normal birth weight
  - Late median age at presentation (150-165 days)
  - Can be cured by partial pancreatecomy
  - Increased incretin secretion after oral glucose load in some pts? [Shy J Pediatr 2013]
  - Undue expression of HK1 in the lesion (5 pts) [Henquin Diabetes 2013]
- Cause:
  - Somatic GCK mutation (1 pt/6 [Henquin Diabetes 2013])
  - Unknown

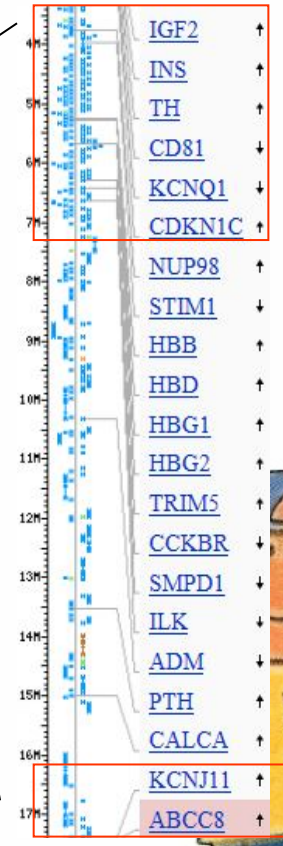
JB

Post-operative diagnosis

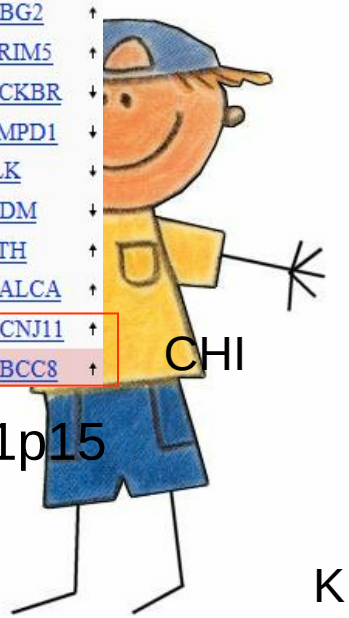
Focal islet-cell hyperplasia







BWS



CHI

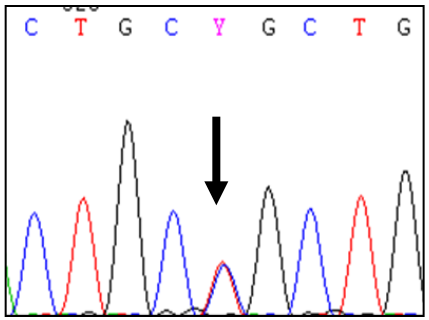
What are the genetic events?

Chromosome 11 → 11p15

K

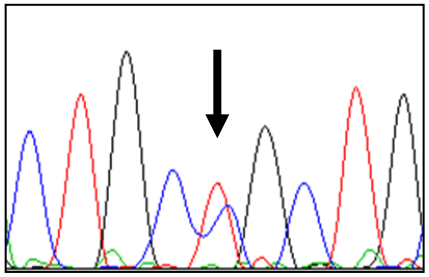
Post-operative diagnosis

Patient no 6:
Age at surgery: 6 months
ABCC8 mutation:
c.4241C>T, p.P1414L



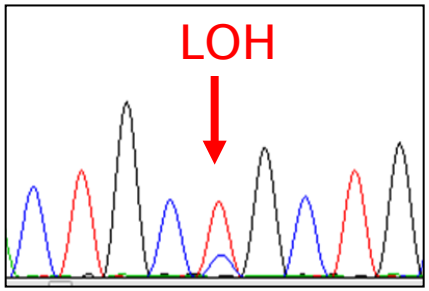
gDNA
normal pancreatic tissue

Bi-allelic expression of both parental alleles



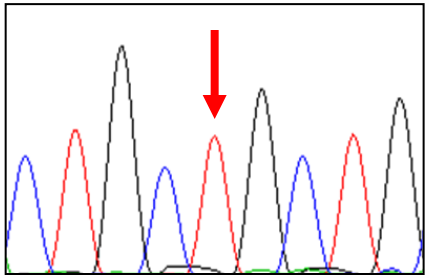
cDNA
normal pancreatic tissue

Loss of heterozygosity



gDNA
focal lesion

Monoallelic expression of paternal mutant allele



cDNA
focal lesion

Post-operative diagnosis

Summary: pUPD and expression of focal CHI

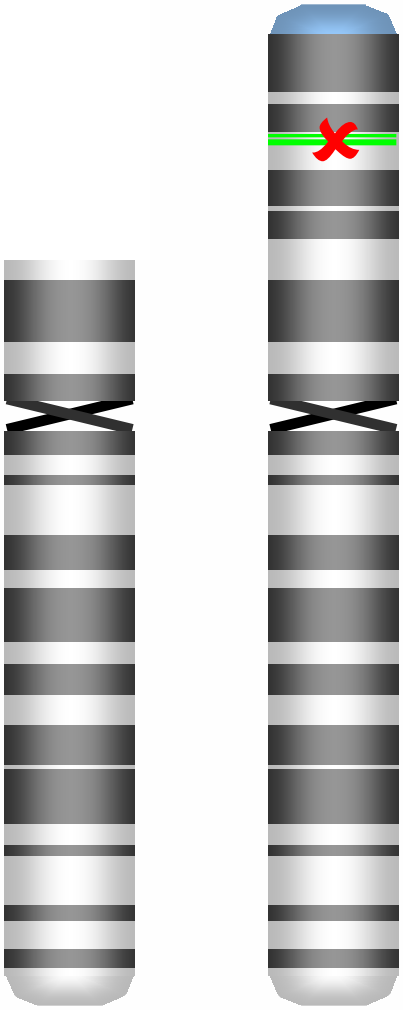
Patient. No.	Exon	Mutation		Observed freq.* [Ref.]	Age at surgery (months)	mRNA expression	LOH	Paternal UPD11p15
		Nucleotide	Protein					
ABCC8								
1	1	c.50T>C	p.V17A	2* [11]	10	monoallelic mutant	++	++
2	10	c.1530G>T	p.K510N	1 [11]	10	monoallelic mutant	++	++
3	12	c.1792C>T	p.(R598*)	Multiple [CM050968]	7	no (NMD)	++	++
4	22	c.2560-?_2697+?	p.(D854_W899del46)	2 [CG107114]	8	monoallelic r.2560_2697del	ROH	n.d.
5	34	c.4162_4164delTTC	p.F1388del	Multiple [CD962164]	9	monoallelic mutant	++	++
6	35	c.4241C>T	p.P1414L	Multiple [CM068331]	6	monoallelic mutant	++	++
7	35	c.4259C>T	p.S1420L	1 [Barthlen et al, submitted]	2	monallelic mutant	+	+
KCNJ11								
8	1	c.286G>A	p.A96T	1* [11]	2	mutant/wt 75%/25%	+	+
9	1	c.612C>A	p.D204E	2 [CM083531]	2	monoallelic mutant	++	++
10	1	c.844G>A	p.E282K	3 [CM071810]	17	monoallelic mutant	++	++
11	1	c.901C>G	p.R301G	Multiple [CM088147]	6	monoallelic mutant	(+)	+

Questions?

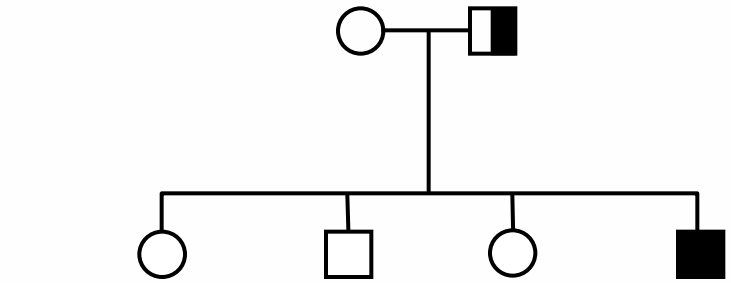
Genetics

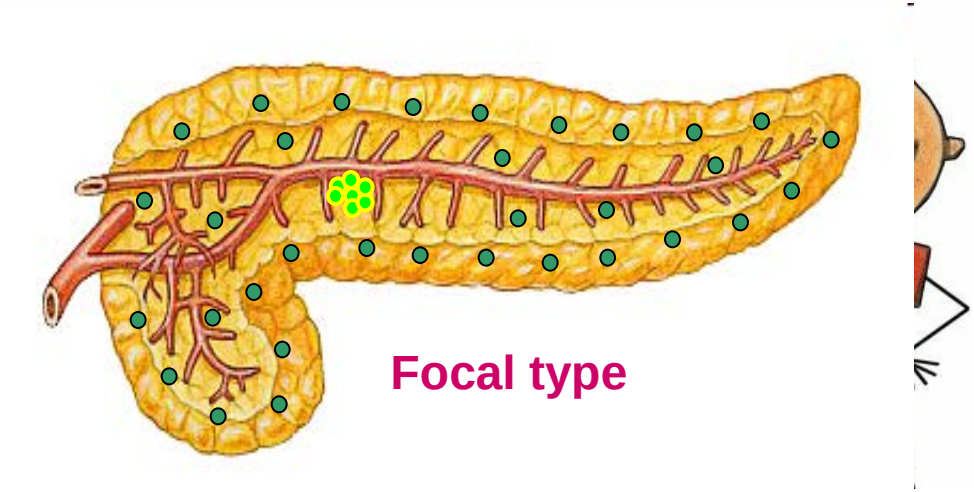
heterozygote, paternally inherited, recessive mutation

KCNJ11 (Kir6.2)
ABCC8 (SUR1)



Chromosome 11





„Second-Hit in islets by paternally inherited mutation: 1:270