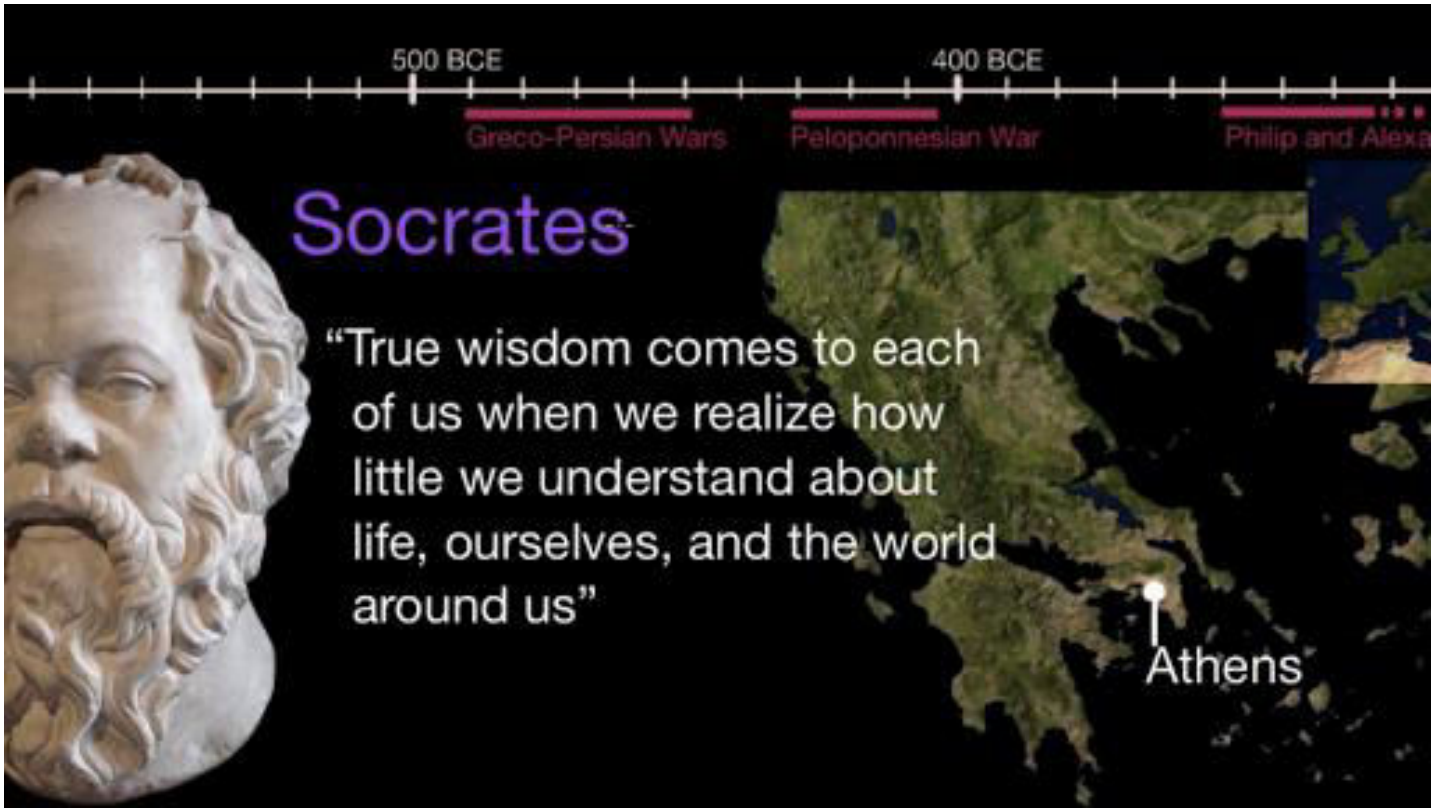
CHI: A continuous challenge



CHI family meeting,
Athens,
Sept. 25-26, 2018

Henrik Christesen, Professor, PhD, MD
International Hyperinsulinism Centre,
Hans Christian Andersen Children's Hospital,
Odense University Hospital, Denmark

CHI correlations: improve treatment!

Phenotype
- severity
- onset
- character
- duration

→ diabetes
- syndromic

Genotype
- *SUR1 (ABCC8)*
- Kir6.2 *(KCNJ11)*
- *GCK*
- *HK1*
- *GLUD1*
- *HADH*
- *INSR*
- *MCT promotor*
- *HNF4A*
- *UCP2*
- *HNF1A*
- *PGM1*
- *PMM2*

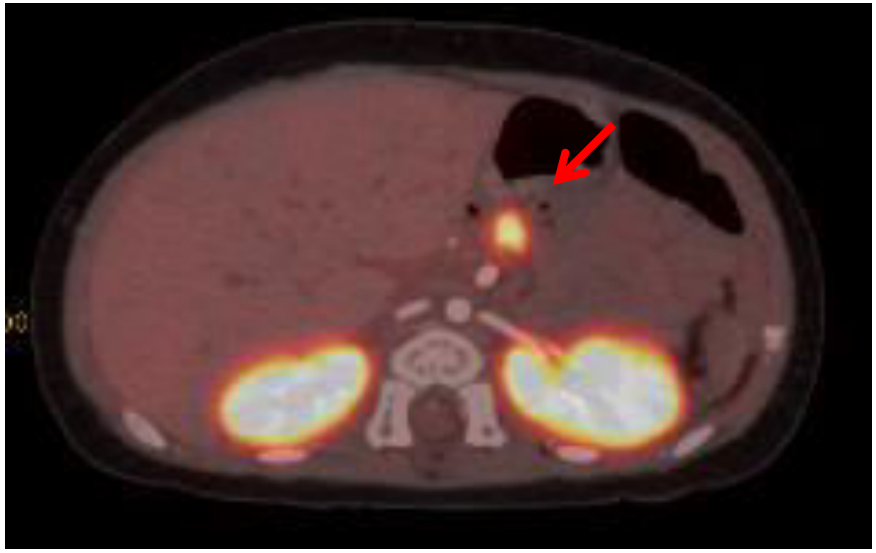
Histology
- Diffuse, focal, "atypical"

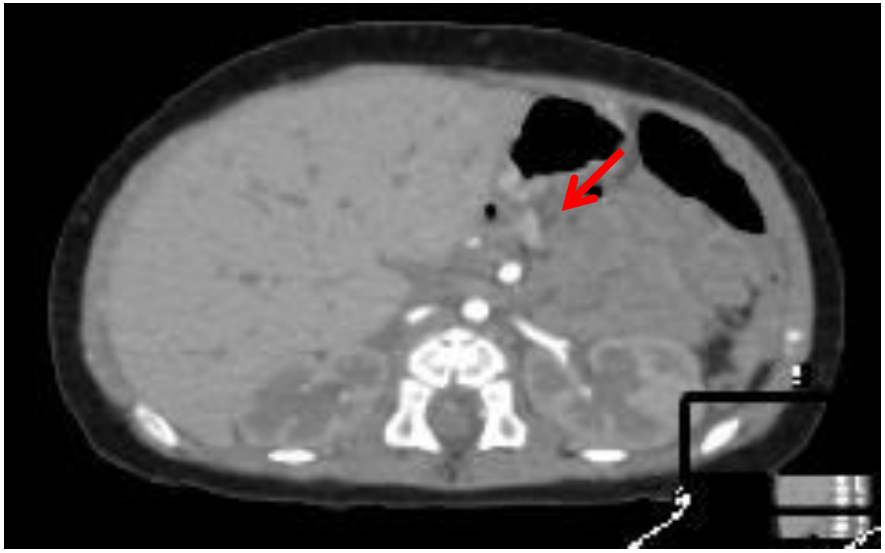
Focal: happy stories

Margarita, Ukraine,
2½ m

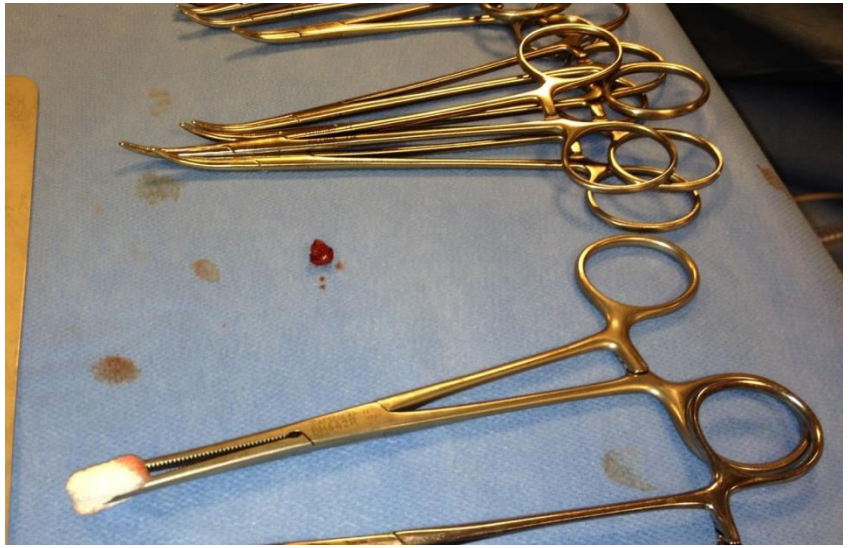
Paternal *ABCC8*
mutation

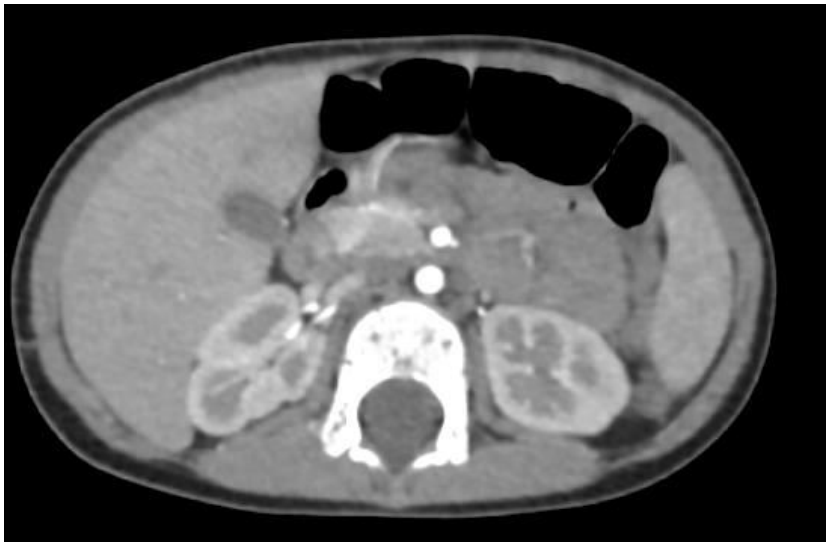
Margaritha, Ukraine





- Cured by enucleation of the focal lesion



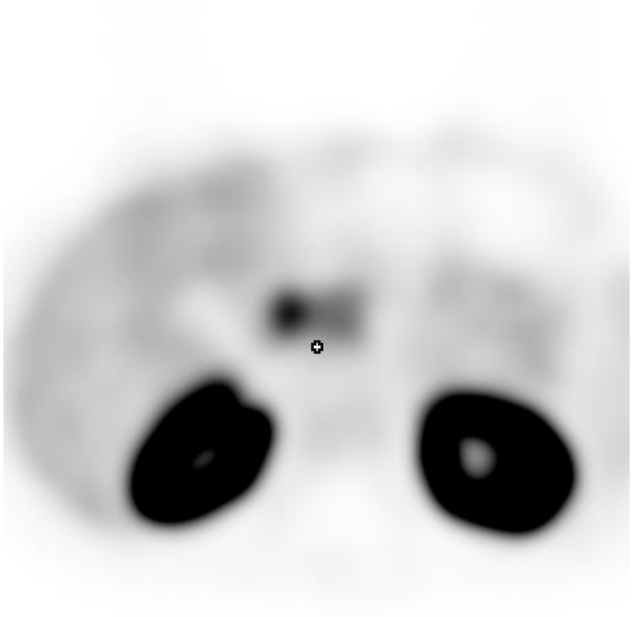


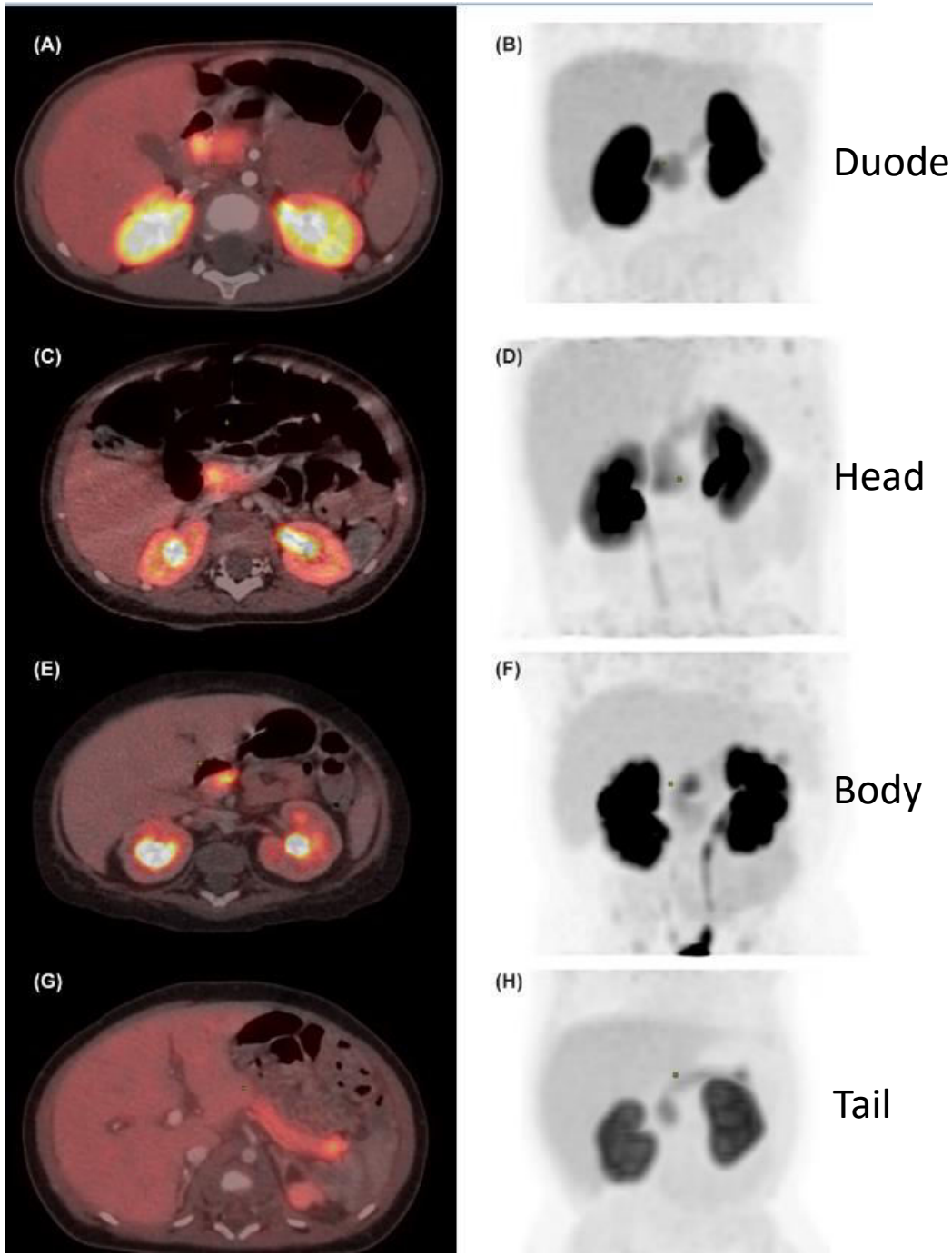
Arianna, Belarus

de novo mutation
ABCC8, p.Y1353X

DOPA PET/CT:
Focal, ectopic duodenal

Surgery: confirmed
duodenal, roux-en-y





By ^{18}F-DOPA PET/CT, all focal lesions correctly identified and localized

Visual
or
SUV max ratio 1.45

Bendix et al, Frontiers 2018

Intraoperative Ultrasound: A Tool to Support Tissue-Sparing Curative Pancreatic Resection in Focal Congenital Hyperinsulinism

Julie Bendix[1,2†], Mette G. Laursen[1,2†], Michael B. Mortensen[3,4], Maria Melikian[5], Evgenia Globa[6], Sönke Detlefsen[4,7], Lars Rasmussen[3,4], Henrik Petersen[8], Klaus Brusgaard[4,9] and Henrik T. Christesen[1,4]*

Frontiers in Endocrinology 2018

Tissue-sparing pancreatic resection (focal lesion enucleation, local resection of tail or uncinate process) was performed in 67%

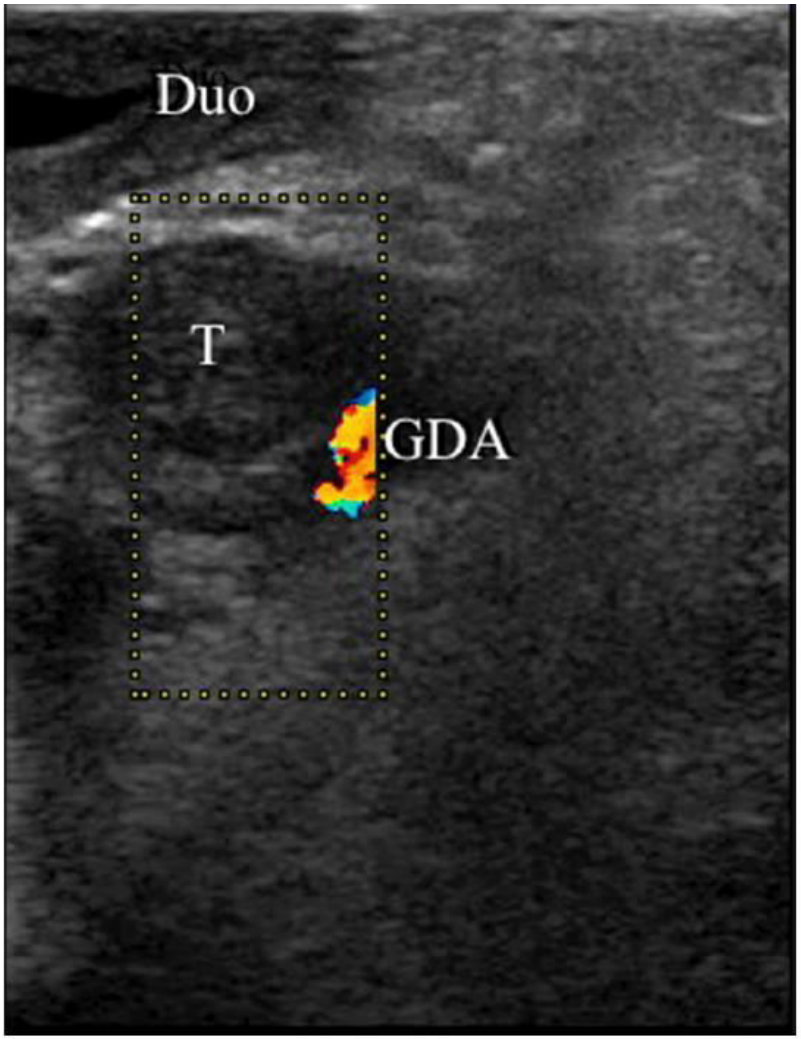


FIGURE 4 | Intraoperative ultrasound of a focal CHI lesion. A nine mm hypo-echoic focal CHI lesion ("T") is identified adjacent to the gastroduodenal

Progress in diffuse CHI

Original Paper

HORMONE
RESEARCH IN
PÆDIATRICS

Horm Res Paediatr
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Published online: December 14, 2017

A Multicenter Experience with Long-Acting Somatostatin Analogues in Patients with Congenital Hyperinsulinism

Ivo van der Steen[a] Mirjam E. van Albada[a] Klaus Mohnike[b]
Henrik Thybo Christesen[c] Susann Empting[b] Maria Salomon-Estebanez[d]
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Syndromic CHI challenges

- Beckwith Wiedemann Syndrome (BWS)
- Turner Syndrome
- Simpson-Golabi-Behmel Syndrome
- Pearlman Syndrome
- Soto Syndrome
- Kabuki Syndrome
- Costello Syndrome
- Timothy Syndrome
- Congenital Disorder of Glycosylation 1a+1b
- Undine Syndrome
- Usher Syndrome (Saudi Arabia)
- ……

Victoria, Sweden

- Sept. 2010
- Preterm, GA 30+, early severe hyperinsulinism
- No syndromal signs
- *ABCC8/KCNJ11* neg
- PET/CT: Diffus type
- pancreatectomy (approx. 70%, repeat resection 90%)

Unpublished

Victoria, Sweden

- Follow up:
- Makrosomia
- Hepatomegalia, small omphalocele
- Ultrasound/biopsy: Liver hemangioma
- Genetics: Beckwith Wiedemann syndrome (BWS)
  - Paternal uniparental disomy (pUPD) 11p15
- Liver tumor
- Adrenal tumor

Unpublished

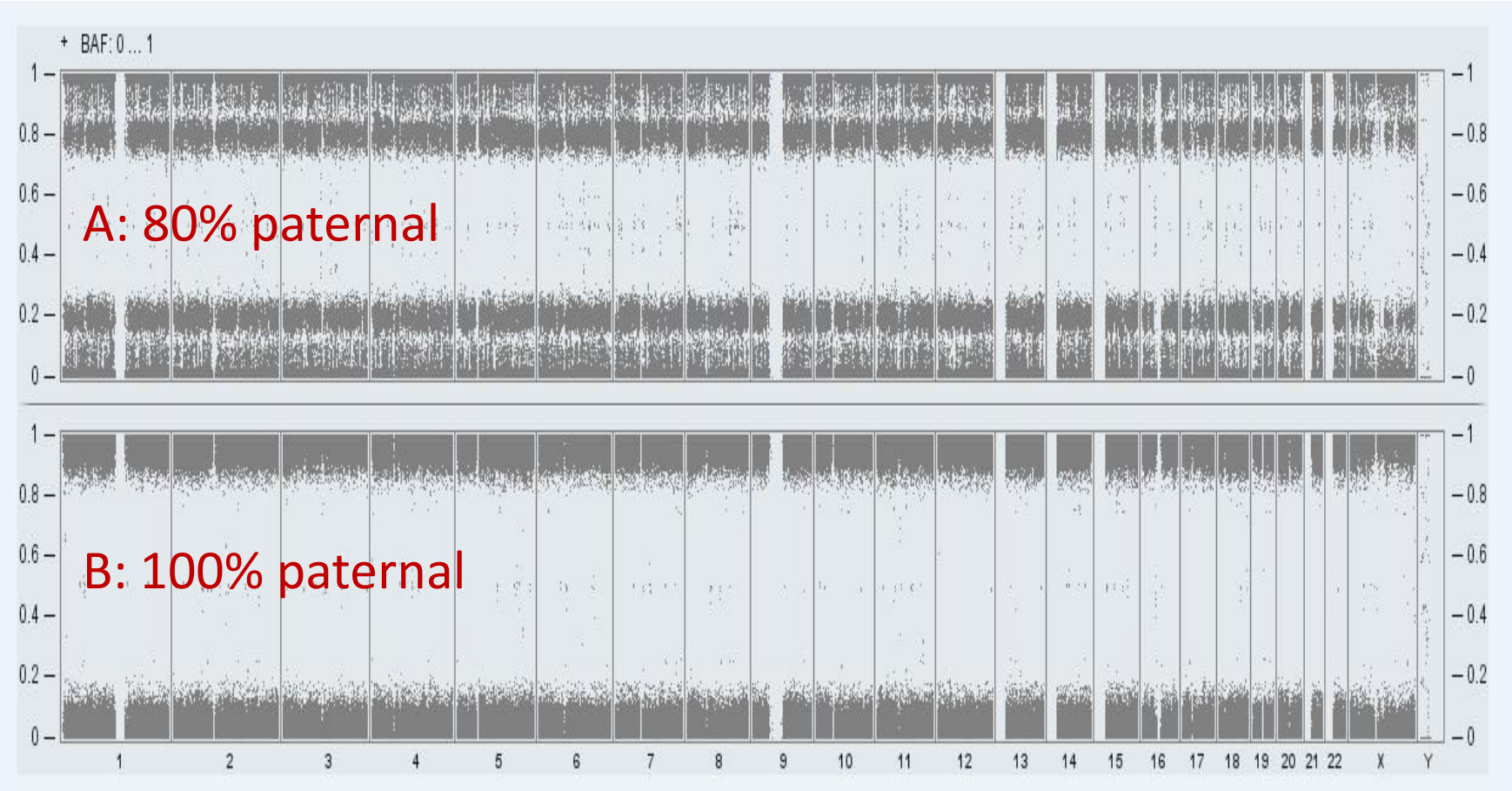
Victoria, Sweden

1. pUPD 11p15
2. pUPD 11
3. Whole genomic pUPD (WG-pUPD)
   - Blood, saliva: 33%
   - Pancreas, liver and adrenal tumors: >90%

- No additional somatic CHI gene mutations in pancreatic tissue

Unpublished

GW-pUPD: liver (A), liver tumor (B)



Unpublished

Victoria, Sweden

Mosaic WG-pUPD: Clinical features

- pUPD11: BWS with tumors
- pUPD6: Transient DM; low BW, conjungated hyperbilirubinemia
- pUPD15: Angelmann syndrome (CNS, behavior)
- pUPD14: Thoracic outlet obstruction syndrome
- pUPD20: Pseudohypoparathyroidism

MULTISYNDROMIC CHI

Unpublished

No mutations by CHI NGS panel

- Syndromic?
- Germline mutations in novel genes?

-> Trio whole exome sequencing (WES)

blood

Novel germline gene mutation

- Swedish boy. Non-syndromic CHI, onset 4 mo. Old. Responded to diazoxide
- WES: Compound heterozygous gene ”Z” mutations
- Gene ”Z” expressed in beta cells
- SIFT, PolyPhen-2, PANTHER, SNPs&GO, and nsSNPAnalyzer all predicted both variants to be deleterious

Submitted

Novel germline gene mutation

- Gene knock out (CRISPR/Cas9, RIN-m cell line)

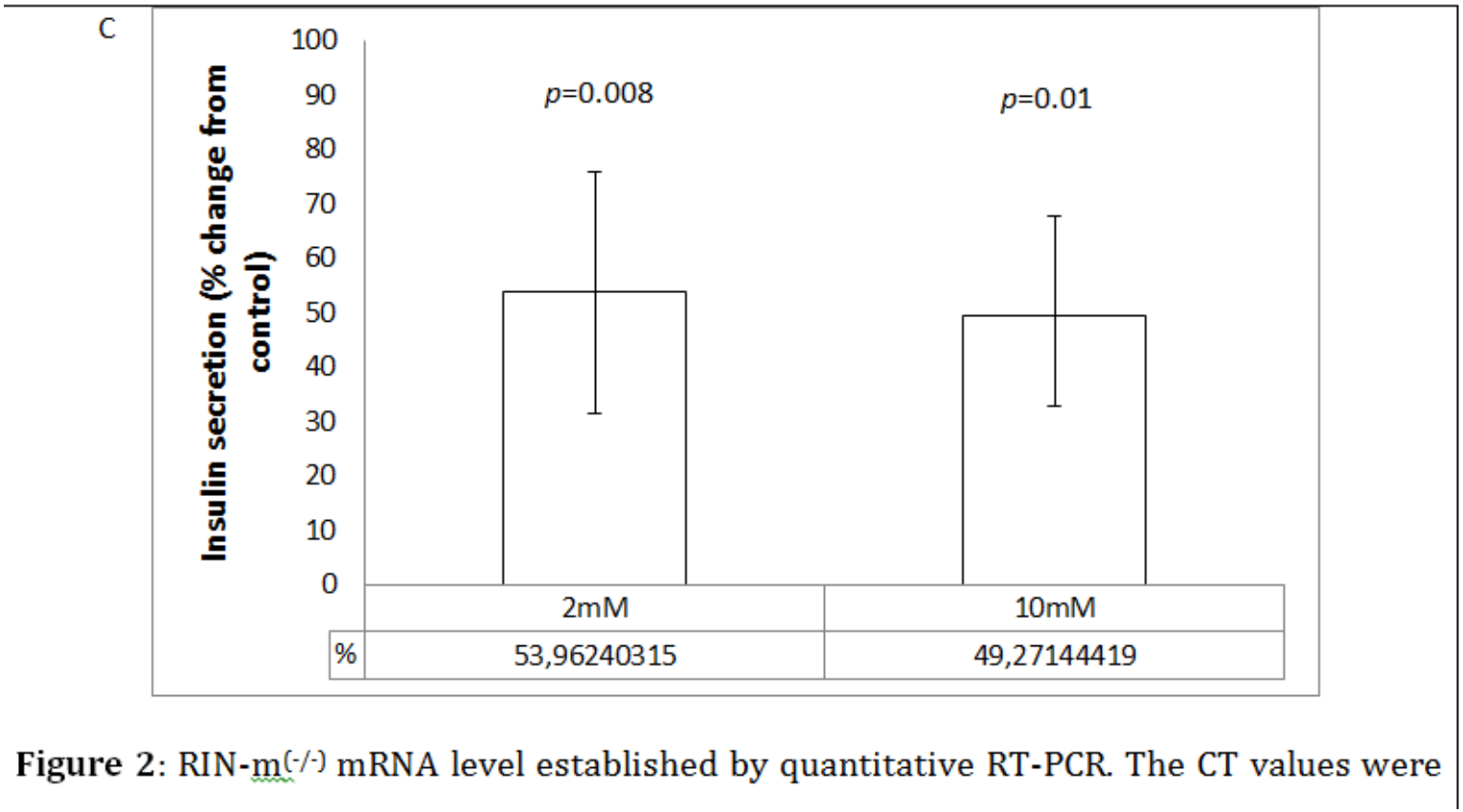


Figure 2: RIN-m$^{(-/-)}$ mRNA level established by quantitative RT-PCR. The CT values were

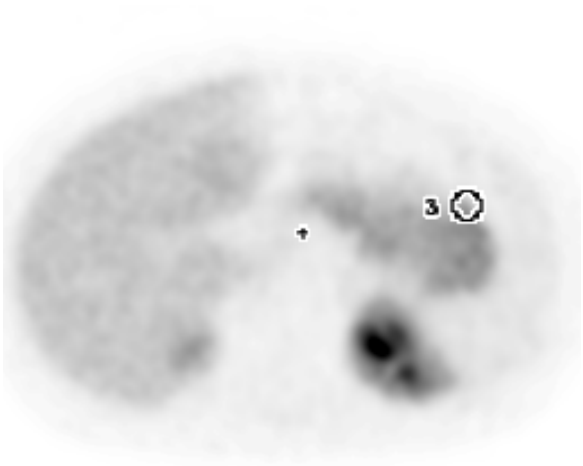
Submitted

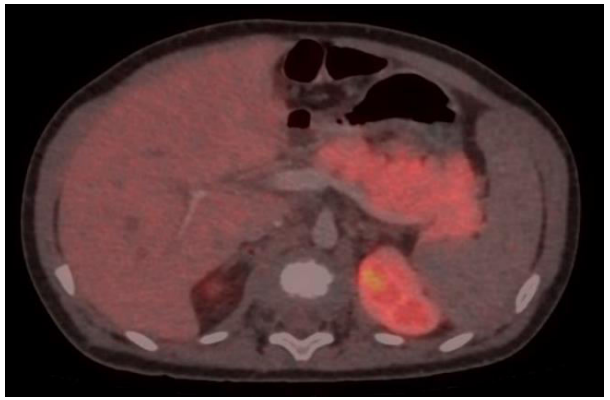
No mutations by CHI NGS panel

- Syndromic?
- Germline mutations in novel genes?
- Somatic pancreatic mutations?
  - known or novel genes

Elen, Armenia

- paternal *ABCC8* p.Val1497Met. Predicted focal

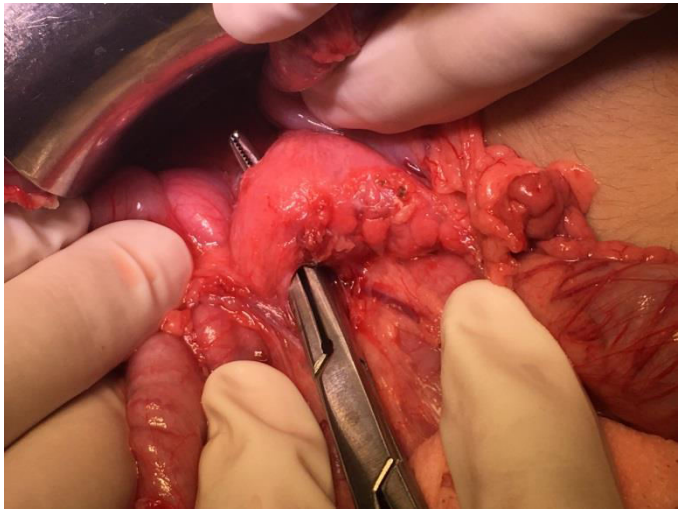


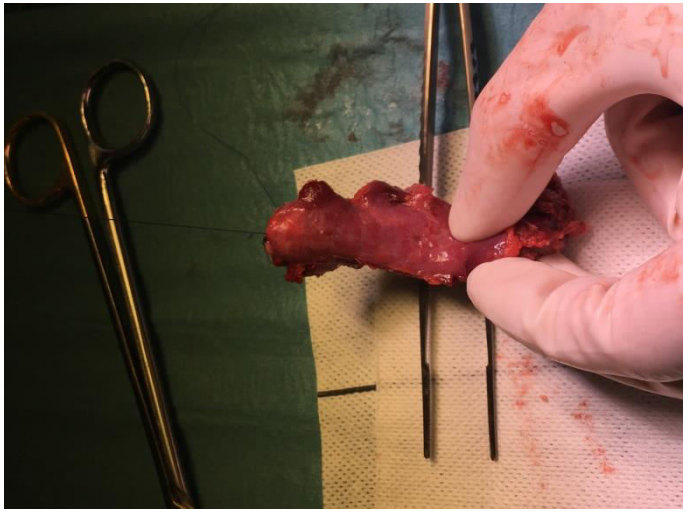


Atypical PET/CT

Elen, Armenia

- Giant, fibrous left 2/3 of pancreas, resected -> cure





- Blood DNA: No BWS
- Pancreatic tissue:
  1) abnormal methylation pattern 11p15 (“somatic BWS”)
  2) mosaic loss of p57

Somatic novel gene mutation

- Caroline, onset of HI age 9 years
  - No insulinoma; DOPA PET/CT: atypical tail
  - tail resection -> cure
- No CHI panel mutations blood or tissue
- No WES mutations of interest in blood
- WES pancreatic tissue:
  - Novel gene ”X” frameshift mutation
    - Islet growth (CRISPR/Cas9 knock out cells)
    - Hypersecretion of insulin (bioinformatic, to be proven)

Unpublished

Conclusion

- CHI heterogeneous –> Individualized treatment

- Major needs:
  - Better prompt recognition and treatment modalities
  - Referral/early contact to highly specialized multidisciplinary centers
  - More research