Congenital Hyperinsulinism due to pancreatic mosaicism for paternal uniparental disomy (pUPD) of all chromosome 11, with the additional finding of pancreatic mosaicism for trisomy 12.

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Case

- A term male (birthweight 3.7kg, 80th percentile) with diazoxide-unresponsive congenital hyperinsulinism (CHI) was born to unaffected parents
  - natural conception
  - non-consanguineous and no family history
- He did <u>not</u> have the *cardinal* Beckwith-Wiedemann spectrum[1] features of
  - macroglossia, exomphalos or lateralised overgrowth
- He did <u>not</u> have the *suggestive* Beckwith-Wiedemann spectrum[1] features of
  - polyhydramnios, macrosomia
  - facial naevus simplex, ear creases or pits
  - umbilical hernia, diastasis recti
  - nephromegaly or hepatomegaly
- Placenta was not retained to assess for size or mesenchymal dysplasia[1]
- A targeted massively parallel sequencing (MPS) panel identified a heterozygous maternally inherited K_{ATP} channel *ABCC8* variant (c.1332+4del) - minimal splicing effect predicted
  - classified as likely benign
- Intensive medical support was required and he could not be medically maintained with a trial of continuous subcutaneous octreotide
- [18F]-DOPA PET/CT imaging of the pancreas
  - unexpected finding of focal increased uptake in the pancreatic distal body/tail junction (Figure 1A)
- Histopathology of the subtotal pancreatectomy (day 22) showed (Figure 2)
  - focal adenomatous hyperplasia
    - ➢ trabeculae and islet nests composed of
      - ❖ regular, oval or columnar cells
      - ❖ lacking atypia or conspicuous nuclear enlargement
    - ➢ adjacent lobules had a relatively normal distribution of islets and exocrine acini
    - ➢ chromogranin highlighted the islets
    - ➢ aberrant p57 expression in islet cytoplasm
      - ❖ nuclear in normal islets and in diffuse hyperinsulinism
      - ❖ would be negative in focal CHI due to a pathogenic paternal K_{ATP} channel variant
- Within 2 weeks, medical support was again required with residual, increased [18F]-DOPA pancreatic uptake (Figure 1B)
- A second resection (5% left in-situ) (day 36) achieved normoglycaemia
- At 24 months of age
  - normoglycaemic with age-appropriate feeding (exocrine pancreatic supplements)
  - normal ultrasonographic appearance of liver and kidneys
  - normal neurodevelopmental progress

Objectives

- Extended genetic analyses in the context of
  - Congenital Hyperinsulinism
  - focal increased [18F]-DOPA PET/CT pancreatic uptake and
  - atypical histology

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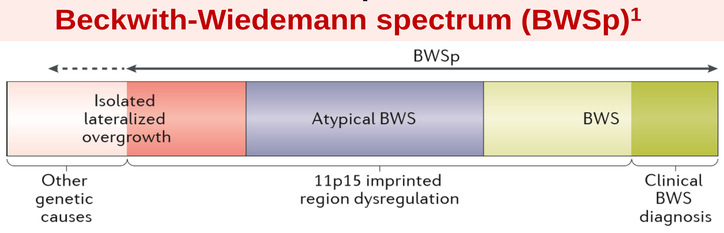
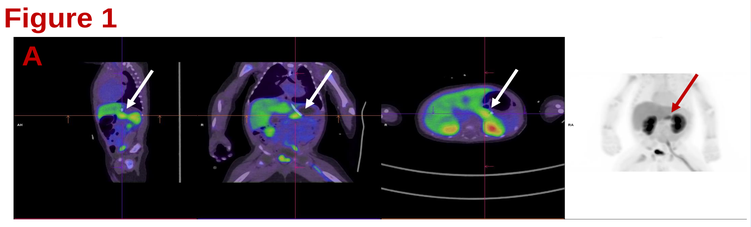
Beckwith-Wiedemann syndrome (BWS)

- A multisystem human genomic imprinting disorder with variable clinical expression and complex molecular aetiology[1]
- An international consensus statement has introduced the concept of Beckwith-Wiedemann spectrum (BWSp)[1]

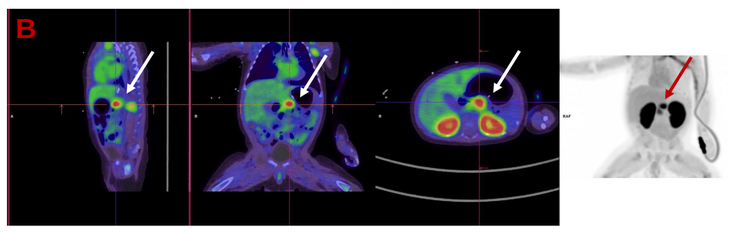


- Hyperinsulinaemic hypoglycaemia is common (30-60%) and usually resolves within a few days
  - persistent, severe cases refractory to medical management are usually associated with the paternal uniparental disomy (pUPD11) molecular defect
    - ➢ majority do not have a paternal inactivating K_{ATP} channel variant but those that do have even more refractory hypoglycaemia

Figure 1

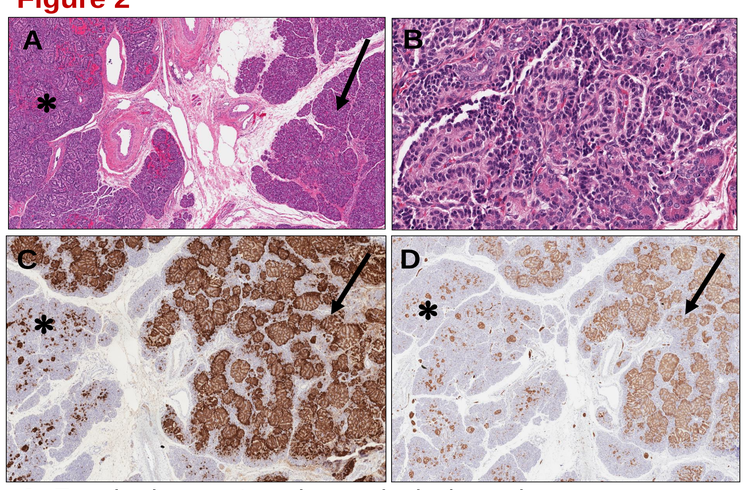


A. *Focal moderate-intense [18F]-DOPA uptake at the pancreatic body/tail junction (arrows), consistent with site of hypermetabolic tissue, with a faint focus of [18F]-DOPA uptake at the uncinate process which is more likely physiologic*



B. *Focal moderate-intense [18F]-DOPA uptake at the subtotal pancreatectomy resection margin (arrows), suggesting that significant residual hypermetabolic tissue had not been resected*

Figure 2



A. *Focal adenomatous hyperplasia (arrow), normal pancreas (∗) H&E,10x*

B. *Islet hyperplasia, H&E, 20x*

C. *Chromogranin expression in hyperplastic islets (arrow), normal islets (∗), 4x*

D. *p57 expressed in hyperplastic islets (arrow) and normal islets (∗), 4x*

References

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2. Kalish JM *et al.* Clin Cancer Res 2017; 23(13):e115-e122
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4. Kalish JM *et al.* J Med Genet, 2016; 53(1):53-61
5. Hong B *et al*. Am J Med Genet A, 2017; 173(6):1681-1686

Methods

1. Pancreas (region of islet hyperplasia)
   - i. Targeted MPS hyperinsulinism panel with mosaic variant calling programme on the sequence data (detects variants to level of 1%)
     - ▪ *KCNJ11, ABCC8, AKT2, GLUD1, GCK, GPC3, HADH, HNF4A, INSR, KDM6A, KMT2D, SLC16A1, CACNA1D, PMM2, TRMT10A, HNF1A*
   - ii. Single-nucleotide polymorphisms (SNP) array analysis (Affymetrix Cytoscan 750K)
2. Peripheral blood and buccal cells
   - i. SNP array analysis

Results

1. Pancreas
   - i. Targeted MPS hyperinsulinism panel
     - ▪ maternal *ABCC8* variant that was identified in blood was again detected, but only in a small number of reads with skewed allelic frequency → suggesting mosaicism
   - ii. SNP array analysis
     - ▪ mosaic loss of heterozygosity (LOH) was observed for chromosome 11
     - ▪ observed pattern suggested high-level mosaicism for a cell line with whole-chromosome isodisomic UPD for chromosome 11, as well as a normal biparental cell line
     - ▪ Trio analysis suggested the UPD to be paternal in origin (isodisomic UPD11 pat)
     - ▪ a mosaic gain of one copy of chromosome 12 was also detected, consistent with mosaic trisomy 12 (mosaicism level 50%)
2. Peripheral blood and buccal cells
   - i. SNP array analysis
     - ▪ no mosaic paternal uniparental disomy (pUPD) or trisomy 12 identified (cannot exclude low-level mosaicism of <10%)

Conclusions

Pancreatic mosaicism for pUPD11

- Most likely cause of CHI
- With 2 cardinal BWSp features
  - hyperinsulinism >1 week duration, escalating treatment and pancreatic adenomatosis

  the BWS clinical diagnosis is met[1]
- In BWSp, pUPD11 predicts a high risk for Wilms tumour and hepatoblastoma, with 3-monthly ultrasound recommended for 7 years[1]
- α-fetoprotein screening is debated[1,2]
- <u>Even in the absence of overt 11p overgrowth features, BWSp due to pUPD11 should be considered if</u>
  - persistent, severe CHI without an identified pathogenic K_{ATP}-channel mutation(s)
  - large focal pancreatic lesions (with/without a K_{ATP} mutation) or
  - atypical histology[3,4]

Pancreatic mosaicism for trisomy 12

- Unreported previously → significance unknown
- Embryonic lethal when not in mosaic form
- A patient with trisomy 12 in 25% of peripheral blood cells has been reported
  - mild dysmorphic features at birth
  - normal development at 6 months of age[5]