### Case

- A term normosomic male was born via assisted vaginal delivery due to failure to progress and fetal distress
  - Maternal history of diet-controlled gestational diabetes
  - Neonatal hypoglycaemia requiring intravenous dextrose for 24 hrs
- Diazoxide-responsive hyperinsulinaemic hypoglycaemia diagnosed at 11 months during a gastrointestinal illness
  - Ammonia and acetyl carnitine profile normal
  - Hyperinsulinism ongoing at 9 yrs (7.5mg/kg/day diazoxide)
- Renal tract anomalies diagnosed following a urinary tract infection at 7 weeks
  - Right grade IV vesicoureteric reflux
  - Right bifid collecting system
  - Small right kidney, reduced function
- Persistent low postnatal weight and Body Mass Index (BMI) with continuing selective and restrictive eating behaviours (Figure)
- Head circumference in normal range
- Other phenotypic features:
  - Developmental delays
  - Learning difficulties
  - Anxiety
  - Autistic Spectrum Disorder
  - Attention Deficit Hyperactivity Disorder
- A dilated aortic root was identified at 6 years during cardiac surveillance following prolonged diazoxide use
  - 17 gene aortopathy panel negative
- Both parents clinically unaffected

### 16p11.2 Copy Number Variants

- **16p11.2 microdeletion** and duplication syndromes have been described\(^1\)
  - *de novo* and inherited cases
  - Spectrum of clinical manifestations
  - Incomplete penetrance
  - Variable expressivity
- **Shared** phenotypic features\(^1,^2\)
  - Autism
  - Developmental delay
- **Mirrored** phenotypic features\(^1,^2,^3\)
  - Deletions
  - Obesity
  - Hyperphagia
  - Macrocephaly
  - Duplications
  - Underweight
  - Feeding / eating disorders
  - Microcephaly

### Genetic Investigations

- Targeted screening of 16 genes known to cause hyperinsulinaemic hypoglycaemia did not identify a pathogenic variant
  - KCNJ11, ABCC8, AKT2, GLUD1, GCK, GPC3, HADH, HNF4A, INSR, KDM6A, KMT2D, SLC16A1, CACNA1D, PMM2, TRMT10A, HNF1A
- A heterozygous interstitial duplication of ~551Kb at chromosome 16p11.2 (Chr16:29,647,342 - 30,198,151) was detected by SNP array (Illumina Whole-Genome Infinium CytoSNP 850K Array)
  - The duplicated region contains at least 30 known genes of which 5 are OMIM listed disease causing genes
    - KIF22, PRT2, ALDOA, TBX5, CORO1A
  - This result conformed a diagnosis of chromosome 16p11.2 duplication syndrome
  - The duplication was paternally inherited

### Conclusions

- Our case expands the clinical spectrum of phenotypic abnormalities observed in the 16p11.2 duplication syndrome
- The two reported cases of hyperinsulinaemic hypoglycaemia in 16p11.2 microdeletion syndrome were diagnosed neonatally and ceased Diazoxide within 15 months
  - In one of these patients (Case 2), it was postulated that the deletion of SH2B1 may have been contributory\(^4\)
  - SH2B1 has been associated with developmental delay; and implicated in the regulation of energy balance, body weight and glucose metabolism\(^5\)
  - In our case, SH2B1 was not within the duplicated region
- Hyperinsulinaemic hypoglycaemia may be a rare feature of 16p11.2 copy number variants.
- The biological mechanisms are unclear

### References


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*Poster presented at:*

- Presented at the Annual European Society of Paediatric Endocrinology Meeting, Vienna, Austria, September 2019.
- Poster presented at: A/Prof Louise S. Conwell, Louise.Conwell@health.qld.gov.au

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**Figure**

- Height for Age
- Weight for Age
- BMI for Age

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**Presented at:**

- The Annual European Society of Paediatric Endocrinology Meeting, Vienna, Austria, September 2019.