Sudden death in an infant attributed to arrhythmia associated with Beckwith-Wiedemann Syndrome due to hypomethylation of imprinting control region 2 on chromosome 11p15.5

Grace Petkovic[1], **Aashish Sethi[1]**, Louise Apperley[1], Senthil Senniappan[1], Joanne Blair[1], George Kokai[2], Mohammed Didi[1]
Departments of Endocrinology[1]and Pathology[3], Alder Hey Children's Hospital, Liverpool,

Alder Hey Children's NHS Foundation Trust

Introduction

- Hypomethylation at the imprinting control region 2 (IC2) on chromosome 11p15.5 is the commonest identifiable cause of Beckwith-Wiedemann Syndrome (BWS).
- IC2 is located in KCNQ1 intron 10 and is associated with Long QT syndrome (LQTS).
- A recent consensus statement on BWS[1] recommends annual cardiac evaluation including electrocardiogram (ECG) in these patients.
- The natural history of LQTS secondary to hypomethylation at IC2 in BWS is unknown, despite it being the commonest etiology.
- It is also unknown whether adequate attention is paid to the risk of arrhythmias in patients with IC2 lesions by multidisciplinary teams managing patients with this condition.
- Sudden death due to ion channel disease is made on the strength of negative autopsy in addition to ECG, personal / family history or molecular diagnosis of ion channel pathology[2].
- We report to our knowledge, the first case of infant death attributed to arrhythmia associated with BWS.

Case Report

- A female neonate from in-vitro fertilisation, born to a primigravida mother with benign intracranial hypertension, presented with hypoglycemia on day four of life.
- Congenital hyperinsulinism was confirmed and responded to diazoxide (10mg/kg/day) and chlorothiazide (6.5mg/kg/day).
- BWS was suspected and genetic tests confirmed BWS with hypomethylation at KCNQ1OT1: TSS-DMR located within 11p15.5
- She had gastroesophageal reflux disease, which responded to ranitidine. A swallow assessment showed safe swallow.
- Cardiac assessment was normal, including ECG on day 5 of life.
- She tolerated a six hour fast prior to discharge and following this, blood glucose control was excellent.
- At four months of life, the mother was playing with the child in her arms when she suddenly became floppy and blue.
- Resuscitation failed and she was pronounced dead.
- Hypoglycemia was excluded and an autopsy, including toxicology found no cause for the death.
- There was no milk in the tracheo-bronchial tree and no histological abnormalities in the lungs or esophagus.
- The pancreas showed the histology of diffuse hyperinsulinism.
- Cause of death was considered to be due to arrhythmia.

Figure 1: Diagram of the normal 11p15 imprinting cluster

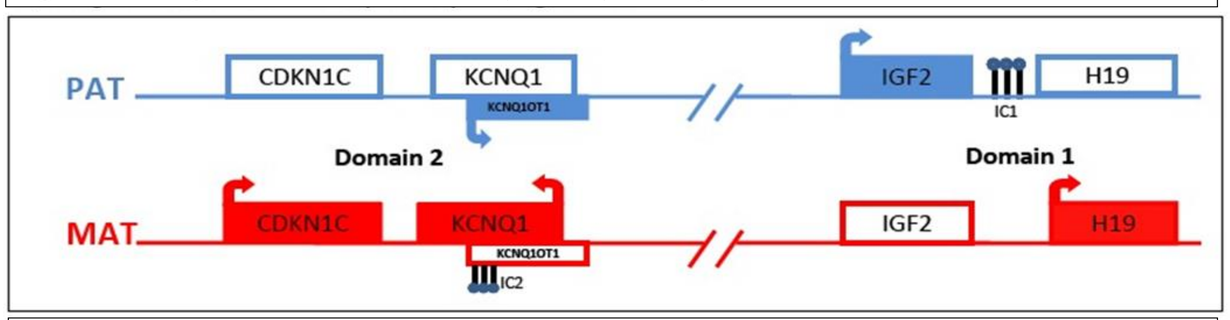
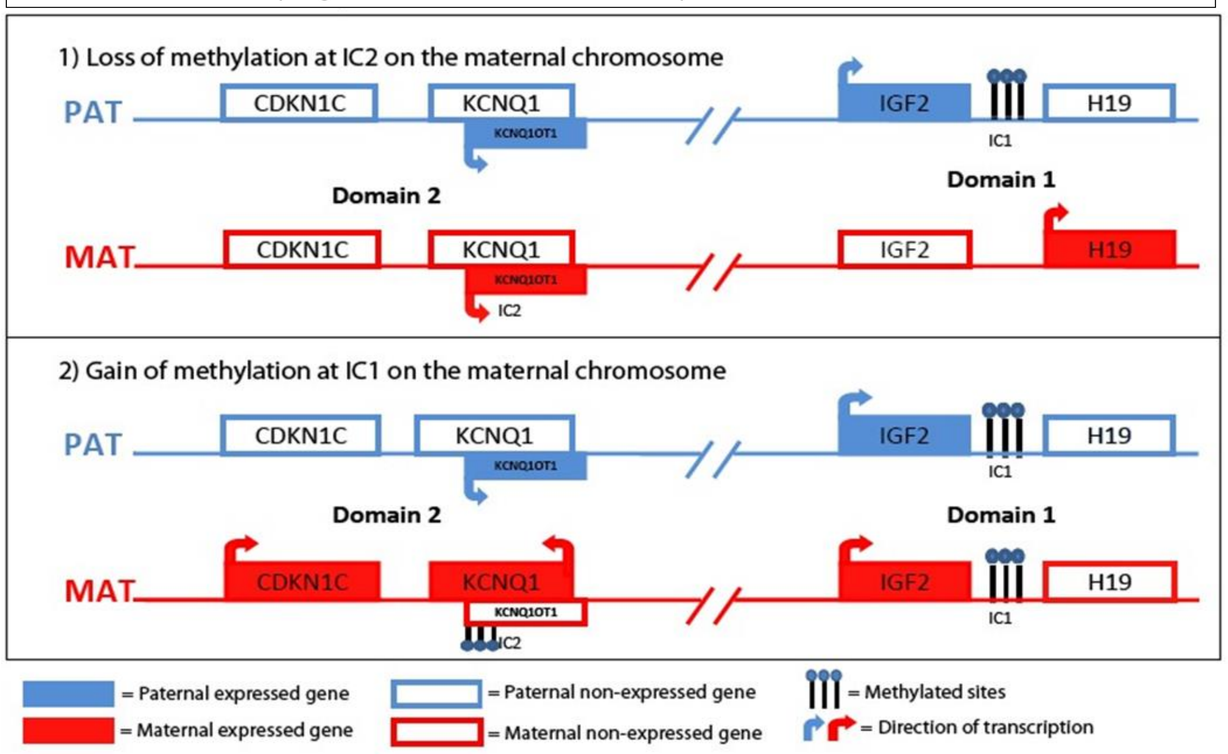


Figure 2: Diagrams of the 11p15 imprinting cluster illustrating two molecular mechanism underlying Beckwith-Wiedemann Syndrome



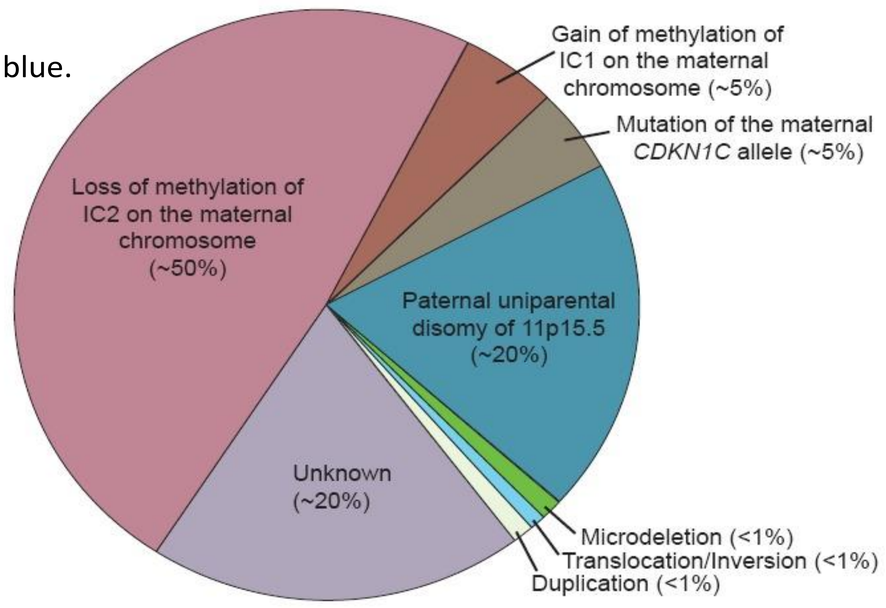


Figure 3: Genetic causes of Beckwith-Wiedemann Syndrome

Discussion

- Hereditary LQTS is an autosomal dominant disorder of cardiac rhythm.
- LQT1, the most common variant, is caused by loss-of-function, heterozygous mutations in *KCNQ1*, which encodes a protein with structural features of a voltage-gated potassium channel.
- BWS is caused by dysregulation of the expression of imprinted genes in the 11q15.5 region (Figure 1,2 & 3) which also includes *KCNQ1.*
- Hereditary LQTS has been reported in two families (adults) with BWS harboring an intragenic deletion and a translocation at IC2 leading to inactivation of the *KCNQ1* gene and sudden death[1,3,4].
- However, to the best of our knowledge it has not been reported in association with infant death.
- Initial normal cardiac evaluation in this patient raises the need for a critical evaluation of the timing and scheme for cardiac assessments in BWS patients.

Conclusion

- This is to our knowledge, the first report of an infant death attributed to arrhythmia associated with BWS.
- Prospective studies are required to examine the natural history of cardiac arrhythmia in BWS patients with IC2 abnormalities.
- Given the location of IC2 in the KCNQ1 gene it is possible that mutations, both genetic and epigenetic, may give rise to both BWS and LQTS.

References:

1. Nature Reviews Endocrinology volume 14, pages 229–249 (2018)
2. Basso C. Postmortem diagnosis in sudden cardiac death victims: macroscopic, microscopic and molecular findings. Cardiovascular Research 50: 290–300, 2001.
3. Kaltenbach, S. et al. Beckwith-Wiedemann syndrome and long QT syndrome due to familial-balanced translocation t(11;17)(p15.5;q21.3) involving the KCNQ1 gene. Clin. Genet. 84, 78–81 (2013).
4. Gurrieri, F. et al. Mild Beckwith-Wiedemann and severe long-QT syndrome due to deletion of the imprinting center 2 on chromosome 11p. Eur. J. Hum. Genet. 21, 965–969 (2013).

Acknowledgement: The presented work resulted from collaboration made possible through the Merck sponsored educational programme "ESPE Clinical Fellowship".

Conflict of Interest: The authors have no real or perceived conflicts of interest in any matters, including financial issues, relating to this work.