AB085. Imprinting mutation of CDKN1C in Beckwith-Wiedemann Syndrome: inheritance, genetic counselling and surveillance

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Background: Beckwith-Wiedemann Syndrome (BWS), a genetic overgrowth disorder is typified by exomphalos, macroglossia and neonatal gigantism. The molecular basis is known in approximately 80% of patients and is heterogeneous involving epigenetic and genetic changes at chromosome 11p15.5. An uncommon cause is a point mutation at CDKN1C found in approximately 5% of cases. When found, 1/3 of CDKN1C mutation is familial. We describe the first Malaysian family with CDKN1C mutation c.232C>T (Q78X), their clinical features, issues related to genetic counselling and subsequent follow-up.

Case presentation: Fifteen children fulfilling the clinical criteria for the diagnosis of BWS were included in a research study to uncover their genotype. One patient was found to carry the CDKN1C mutation c.232C>T (Q78X). This patient was the first child born to unrelated parents at 30.6±4.0 gestation. He was large for gestational age with a birth weight of 2.21 kg. He had an exomphalos, bilateral dysplastic kidneys and facial dysmorphism consistent with BWS. After a stormy neonatal period, he succumbed on day 17 of life. Before his molecular analysis was completed, his mother gave birth to a girl at 37+1/40 gestation; birth weight was 3.4 kg. This child was antenatally diagnosed with exomphalos and amniocentesis revealed normal karyotype. At birth, she had features of BWS, cleft palate and normal kidneys. Her exomphalos was surgically corrected on day 3 of life, after which she progressed well albeit with mild developmental delay. Their mother is phenotypically normal and carries the said pathogenic CDKN1C mutation. She is currently pregnant with her third child. Genetic counselling was provided and she fully comprehends the recurrence risk of 50% in this pregnancy.
as well as the availability of prenatal diagnostic testing. Prenatal testing was declined.

Discussion and conclusions: The diagnosis of BWS can be confidently achieved with well-established clinical criteria. However, molecular diagnosis is of utmost importance for accurate genetic counselling because of the high recurrence risk of maternally inherited CDKN1C point mutation. Surveillance on follow-up can also be tailored with the knowledge of molecular diagnosis as CDKN1C mutation is associated with the lowest risk of embryonal tumours commonly unaffected genotype. In this report, we have shown a phenotypically unaffected mother with a pathogenic CDKN1C mutation.

This mutation could have occurred de novo or inherited from her father as it is silent in the paternal allele. In the latter scenario, genetic counselling should be offered to all her sisters so that they may make informed choices with regards to their reproduction.

Keywords: CDKN1C; imprinting; overgrowth


AB086. Chromosomal microarray analysis—detection of both duplication and deletion in patients with multiple congenital anomalies and/or developmental delay

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Background and objective: Chromosomal microarray analysis (CMA) is recommended as first-tier genetic testing for patients with multiple congenital anomalies, developmental delay/intellectual disability and/or autism spectrum disorder. It detects chromosomal imbalance at a higher resolution than conventional chromosomal analysis. CMA diagnostic service was launched in our hospital in February 2014. The aim of this report is to review the incidence of detecting both duplication and deletion in patients referred for this test.

Methods: DNA was extracted using Gentra Puregene Blood Kit. CMA was performed using the Agilent 4x180 K CGH + SNP array and analysed with Agilent CytoGenomics. G-banding analysis was carried out on stimulated lymphocytes culture. Targeted fluorescence in-situ hybridization (FISH) was performed using locus specific probes.

Results: From 1 February 2014 to 31 May 2015, a total of 205 patients were tested. Seven (3.4%) were identified to have both duplication and deletion of chromosomal segments that were pathogenic (5) or of uncertain clinical significance (2). We present a case of a 1-day-old Chinese girl with oligohydramnios, prematurity (35+3 weeks) and multiple congenital anomalies including heart defect, cleft palate, ear anomalies, microcephaly, vaginal skin tag, bilateral clinodactyly and wide anterior fontanelle.

Karyotyping and FISH analysis for 22q11 deletion were normal. CMA revealed a pathogenic gain of 2.143 Mb at 16p13.3 and a pathogenic loss of 0.271 Mb at 16q24.2q24.3. The gain at 16p13.3 affects 67 genes including CREBBP. The 16p13.3 duplication syndrome is a contiguous gene syndrome characterized by normal to moderate intellectual disability, normal growth, mild arthrogryposis, frequently small and proximally implanted thumbs, characteristic facial features and occasionally, developmental defects of the heart, genitalia, palate or eyes. The 0.271 Mb deletion at 16q24.3 affects four genes including ANKRD11 and CDH15. The clinical features of 16q24.3 microdeletion syndrome include facial dysmorphisms, cognitive impairment, autism, structural anomalies of the brain and seizures. The patient’s reported phenotypes overlap with clinical features seen in both the 16p13.3 duplication syndrome and the 16q24.3 microdeletion syndrome.

Conclusions: CMA helps to identify clinically significant chromosome anomalies that are too small to be detected by karyotyping. Of the seven cases reported with both duplication and deletion, six would not have been picked up by karyotyping. Through CMA, the hospital care team is able to make an accurate genetic diagnosis for the patients.