Germline Mutation in *NLRP2* (*NALP2*) in a Familial Imprinting Disorder (Beckwith-Wiedemann Syndrome)

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Abstract

Beckwith-Wiedemann syndrome (BWS) is a fetal overgrowth and human imprinting disorder resulting from the deregulation of a number of genes, including *IGF2* and *CDKN1C*, in the imprinted gene cluster on chromosome 11p15.5. Most cases are sporadic and result from epimutations at either of the two 11p15.5 imprinting centres (IC1 and IC2). However, rare familial cases may be associated with germline 11p15.5 deletions causing abnormal imprinting *in cis*. We report a family with BWS and an IC2 epimutation in which affected siblings had inherited different parental 11p15.5 alleles excluding an *in cis*

maternal *CDKN1C* expression [7–9]. Apparent hypomethylation of IC2 may, in rare cases, result from a germline IC2 deletion [10]. However, most BWS patients with IC2 methylation defects appear to have an epimutation of unknown cause (although there is an increased risk of BWS with IC2 epimutation in children conceived by assisted reproductive technologies) [11–13]. In order to gain insights into the factors responsible for IC2 imprinting defects, we

containingNLRP2and NLRP7at 19q13.4.NLRP7

of the two affected children with BWS was homozygous for a NLRP2 mutation and, by analogy with FHM caused by NLRP7

observations and the apparently milder phenotypic effects of maternal *NLRP2* inactivation than *NLRP7* inactivation (Beckwith-Wiedemann syndrome and molar pregnancy respectively) it might be predicted that clinical heterogeneity/incomplete penetrance would be a feature of maternal *NLRP2* inactivation. Although maternal *NLRP2* mutations appear to be a rare cause of familial BWS, the identification of these cases is important, as the inheritance pattern differs from the autosomal dominant inheritance (with parent of origin effects) associated with other inherited forms of BWS. The inheritance of *NLRP2*-associated BWS has similarities to other autosomal recessive disorders in which homozygous mothers are well, but there is a high risk to their offspring (e.g. FHM and treated maternal phenylketonuria).

References

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Author Contributions

Conceived and designed the experiments: EM ERM. Performed the experiments: EM DL LJT FR. Analyzed the data: EM DL LJT FR ERM. Contributed reagents/materials/analysis tools: SP JRWY CGW. Wrote the paper: EM ERM. Revised and approved the paper: DL SP LJT FR JRWY CGW RW.