The Molecular Bases for Beckwith-Wiedemann Syndrome and Russell-Silver Syndrome.

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ABSTRACT

Beckwith-Wiedemann (BWS) and Russell-Silver syndromes (RSS) are clinically and genetically heterogeneous syndromes which cause gigantism and growth retardation, respectively. BWS is also known to be associated with increased risk of childhood cancers. Mutations, genomic imprinting errors and uniparental disomy in chromosomes 7 and 11 have been reported before. The imprinted 11p15 region consists of two imprinted domains: imprinting centre (IC) 1 which regulates the expression of IGF2 and H19, and IC2 which controls the expression of CDKN1C, KCNQ1OT1 and KCNQ1. We aim to study the molecular basis for BWS and RSS. We report the preliminary results of our analyses. Whole blood samples were collected from 8 BWS and 15 RSS patients based on clinical proforma and the genomic DNA was extracted. The DNA samples were subjected to multiplex ligation-dependent probe amplification (MLPA) to detect the copy number status in imprinted genes of chromosome 11 for BWS and RSS. Two designated controls were included as reference. The resulting PCR products were sent for fragment analyses. With BWS, all 8 samples carried duplication involving IC2. KCNQ1OT1 is a paternally expressed untranslated transcript, read in an antisense direction with respect to KCNQ1 which is required for silencing of imprinted genes. CDKN1C is a maternally expressed imprinted gene encoding a cyclin-dependent kinase inhibitor that regulates prenatal and postnatal growth and development. With RSS, 4 of the 15 samples carried duplications in both IC1 and IC2, whereas 11 showed duplication in IC2 alone. In addition, 1 patient had mutations in all the studied genes in the IC1 and IC2 regions; 1 patient showed mutation of 1 gene each at IC1 and IC2; and 3 patients showed mutations at IC2 alone. The patients in this study present with duplication in BWS, and duplication and mutation in RSS, in different imprinted genes, emphasizing the heterogeneity of the two growth syndromes. Further confirmation is ongoing.