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Functional consequences of Genomic Abnormalities

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Abstract

The widespread use of whole genome chromosome microarrays led to the discovery of a large number of recurrent and unique copy number changes (CNV) as the cause of an abnormal phenotype in 15% of cases with developmental delay and congenital anomalies. Typically, genomic changes are correlated with abnormalities at the "whole body" level, however, the functional consequences of genomic abnormalities at the cellular level, and how they can be linked to the phenotype are rarely investigated. Our recent interest is to determine if genes integral to CNVs show abnormal function in patient cells by testing whether their expression at the RNA and protein level and known cellular functions is impaired. We identified abnormal cellular function of genes from CNVs from 1q21.1, 2p13.2 and Xq21.1 facilitating thus phenotype-genotype correlation. In case of the 1q21.1 CNV, the copy number change of its integral genes *CHD1L* and *PRKAB2* resulted in perturbed chromatin remodeling and AMPK function. These genes have a role in cellular and environmental stress response which could explain the phenotypic variability in subjects that carry the 1q21.1 CNV. In subjects with recurrent 2p13.2 CNV, the impaired early morphogenesis, symmetry as well as craniofacial, skeleton and brain development could be associated with the dysfunction of retinoic and notch signaling pathway, implicating two CNV genes: *CYP26B1* and *EXOC6B*, respectively. Finally, the CNV from Xq21.1 disrupted the MAGT1 gene, which has a role in Mg homeostasis, and resulted in reduced Mg influx in patient cells. This could explain the severe skin phenotype (pruritus) seen in carriers of this CNV as Mg homeostasis is essential for skin health. Studying functional defects of CNVs is important as it identifies cellular pathways that are defective and offers treatment strategies to minimize their functional defects (e.g. restricted vitamin A diet in case of an abnormal retinoic acid metabolism in patients with 2p13.2 CNV or reducing the skin defects by adding Mg to the diet or as ointment in patients with *MAGT1* CNV). Our work allows the establishment of a closer link between the genomic abnormality and its cellular and clinical consequences, and offers opportunities for treatment for some of the phenotypic defects.

Biography

Dr. Evica Rajcan-Separovic is an Associate Professor at the University of British Columbia and a Career Scholar funded by the Michael Smith Foundation of Health Research and the Canadian Institutes of Health Research (CIHR). Dr Rajcan-Separovic has a broad interest in the field of genomic abnormalities and their role in abnormal prenatal and postnatal human development. She has served on the review panels for agencies including Welcome Trust, MRC England and CIHR.