TO WHAT EXTENT DOES GENE DOSAGE MATTER?

Several technologies allow the detection of copy number variations (CNVs) such as gene deletions and duplications using well-known procedures in Cytogenomics laboratories. These anomalies cause dosage alterations of the genes annotated to the affected region. In the case of deletions, hemizygosity can lead to a wide range of effects, from abnormal phenotypes (haploinsufficiency) in the worst scenario to the absence of any phenotypic effects in the best. Besides differences in penetrance, time in life when effects appear is also highly variable, from congenital deffects to adult-onset diseases. In this paper from Trends in Genetics, the author has performed an outstanding review of the phenotypic effects of 238 non-recurrent gene deletions affecting chromosome 18. As expected, the most frequent result is the lack of clinical effects suggesting that dosage insensitivity and dosage compensation are the most frequent situations. Nevertheless, hemizygosity also produces a wide spectrum of effects including highly penetrant phenotypes (19 genes), low penetrance phenotypes (9 genes), conditional effects (49 genes) and risk factors for polygenic disorders (15 genes). All these data are summarized in Table 1 and could be useful for accurate and predictive clinical management of the affected patients.

The author also provides an interesting discussion about the molecular mechanisms behind haploinsufficiency. Factors based on the presence of conserved gene sequences, the alteration of topologically associated domains (TADs), the presence of ~~honologs~~ homologous genes, and the functionality of dosage sensitive genes are discussed. Finally, ~~it is~~ the paper also addresse~~d~~s the association between ~~a~~ variable penetrance, gene dose compensation and epigenetic modifications.