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Human trisomy 21 fibroblasts rescue methotrexate toxic effect after treatment with 5-methyl-tetrahydrofolate and 5-formyl-tetrahydrofolate.

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Abstract

Trisomy 21 causes Down syndrome (DS), the most common human genetic disorder and the leading genetic cause of intellectual disability. The alteration of one-carbon metabolism was described as the possible metabolic cause of the intellectual disability development in subjects with DS. One of the biochemical pathways involved in the one-carbon group transfer is the folate cycle. The cytotoxic drug methotrexate (MTX) is a folic acid (FA) analogue which inhibits the activity of dihydrofolate reductase enzyme involved in the one-carbon metabolic cycle. Trisomy 21 cells are more sensitive to the MTX effect than euploid cells, and in 1986 Jérôme Lejeune and Coll. demonstrated that MTX was twice as toxic in trisomy 21 lymphocytes than in control cells. In the present work, the rescue effect on MTX toxicity mediated by FA and some of its derivatives, tetrahydrofolate (THF), 5-formyl-THF, and 5-methyl-THF, in both normal and trisomy 21 skin fibroblast cells, was evaluated. A statistically significant rescue effect was obtained by 5-formyl-THF, 5-methyl-THF, and their combination, administered together with MTX. In conclusion, trisomy 21 fibroblast cell lines showed a good response to the rescue effects of 5-formyl-THF and 5-methyl-THF on the MTX

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Plasma and urinary metabolomic profiles of Down syndrome correlate with alteration of mitochondrial metabolism.

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Abstract

Down syndrome (DS) is caused by the presence of a supernumerary copy of the human chromosome 21 (Hsa21) and is the most frequent genetic cause of intellectual disability (ID). Key traits of DS are the distinctive facies and cognitive impairment. We conducted for the first time an analysis of the Nuclear Magnetic Resonance (NMR)-detectable part of the metabolome in plasma and urine samples, studying 67 subjects with DS and 29 normal subjects as controls selected among DS siblings. Multivariate analysis of the

NMR metabolomic profiles showed a clear discrimination (up to of 80% accuracy) between the DS and the control groups. The univariate analysis of plasma and urine revealed a significant alteration for some interesting metabolites. Remarkably, most of the altered concentrations were consistent with the 3:2 gene dosage model, suggesting effects caused by the presence of three copies of Hsa21 rather than two: DS/normal ratio in plasma was 1.23 (pyruvate), 1.47 (succinate), 1.39 (fumarate), 1.33 (lactate), 1.4 (formate). Several significantly altered metabolites are produced at the beginning or during the Krebs cycle. Accounting for sex, age and fasting state did not significantly affect the main result of both multivariate and univariate analysis.

Partial trisomy 21 map: Ten cases further supporting the highly restricted Down syndrome critical region (HR-DSCR) on human chromosome 21.

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Abstract

BACKGROUND:

Down syndrome (DS) is characterized by the presence of an extra full or partial human chromosome 21 (Hsa21). An invaluable model to define genotype-phenotype correlations in DS is the study of the extremely rare cases of partial (segmental) trisomy 21 (PT21), the duplication of only a delimited region of Hsa21 associated or not to DS. A systematic retrospective reanalysis of 125 PT21 cases described up to 2015 allowed the creation of the most comprehensive PT21 map and the identification of a 34-kb highly restricted DS critical region (HR-DSCR) as the minimal region whose duplication is shared by all PT21 subjects diagnosed with DS. We reanalyzed at higher resolution three cases previously published and we accurately searched for any new PT21 reports in order to verify whether HR-DSCR limits could prospectively be confirmed and possibly refined.

METHODS:

Hsa21 partial duplications of three PT21 subjects were refined by adding array-based comparative genomic hybridization data. Seven newly described PT21 cases fulfilling stringent cytogenetic and clinical criteria have been incorporated into the PT21 integrated map.

RESULTS:
The PT21 map now integrates fine structure of Hsa21 sequence intervals of 132 subjects onto a common framework fully consistent with the presence of a duplicated HR-DSCR, on distal 21q22.13 sub-band, only in DS subjects and not in non-DS individuals. No documented exception to the HR-DSCR model was found.
CONCLUSIONS:
The findings presented here further support the association of the HR-DSCR with the diagnosis of DS, representing an unbiased validation of the original model. Further studies are needed to identify and characterize genetic determinants presumably located in the HR-DSCR and functionally associated to the critical manifestations of DS.