

PATHWAY ANALYSIS FOR THE COGNITIVE FEATURES OF DOWN SYNDROME.

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Down syndrome (DS) is the most common genetic cause of intellectual disability. It is due to an extra copy of human chromosome 21 (chr21) and the increased expression, due to gene dosage, of the genes encoded by it. Many phenotypic features of DS, including intellectual disabilities, develop postnatally, and this suggests that pharmacotherapeutics may be practical. We are combining bioinformatics and experimental approaches to identify pathways relevant to learning/memory that are perturbed in DS.

Bioinformatics approaches: Mouse is *the* model organism for DS research, from basic science studies to preclinical assessment of potential therapeutics. To exploit mouse most effectively, it is necessary to understand the similarities and differences from human chr21 in gene content. We have therefore updated the annotation of human chr21 for gene content and analyzed conservation in mouse. A total of 539 genes were identified within human chr21, and 434 genes within the orthologous regions of mouse chr16, 17 and 10. We established a ten-level classification scheme to provide for each gene, and its splice variants, an unambiguous description of biologically relevant features, with the goal to facilitate prediction among novel genes of those that are most likely to be protein coding vs. functional RNA and/or to be conserved among mammals. We believe that these analyses, which have been posted to our Chr21 Gene Function and Pathway Database (<http://chr21db.ucdenver.edu>; <http://chr21.egr.vcu.edu:8888>), provide DS and chr21 researchers with important information relevant to the creation and use of mouse models of Down syndrome. Species-specific genes and regulatory sequences can now be considered when designing and interpreting phenotypic features of mouse models and in predicting their relevance to the human phenotypes.

Experimental approaches: We have completed the first phase of the systems biology approach to pathway analysis. We have defined molecular perturbations, in the Ts65Dn and Ts1Cje mouse models of DS, in the responses to the NMDA receptor antagonist, MK-801. Two key observations are: (i) basal levels of phosphorylation of key signaling molecules, Erk1/2, Akt, Creb, GSK3B and ELK, are all abnormally low in cortex and/or hippocampus, and (ii) in responses to MK-801, normal dynamic changes in the levels of these proteins and in localization of chr21 proteins are absent. These proteins are known to be essential components of pathways required for learning and memory, in particular, pathways required for normal hippocampal function, and therefore are highly relevant to DS. This work is important because it demonstrates that, from functional information on chr21 proteins, we can correctly predict non-chr21 protein and pathway perturbations. This in turn will allow prediction of targets for potential therapeutic intervention.