

Down syndrome mouse models and response to the NMDA antagonist MK-801

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We are combining bioinformatics and experimental approaches to predict pathways relevant to learning/memory that are perturbed in DS and to identify the chromosome 21 genes responsible for the perturbations. For each chr21 protein, pathways are defined by identifying (1) mammalian protein interactions from curated databases and the primary literature, and (2) orthologous protein interactions in model organisms. We also extract chr21 protein information from large scale functional genomics and proteomics datasets. All data are compiled in the chr21/DS gene function database (<http://chr21db.cudenver.edu>) Data predict perturbations in many inter-related pathways, among them MAPK, calcineurin, and NMDA receptor signaling, plus direct and indirect interactions among several chr 21 proteins. To test predictions, we have compared levels of selected chr 21 and non-chr21 proteins from hippocampus and cortex of the major DS mouse models, the chr16 segmental trisomies, Ts65Dn and Ts1Cje. We have examined naive mice and mice that have been treated with the NMDA receptor antagonist, MK- 801. We have identified treatment-dependent abnormalities in the activation levels and/or localizations of critical pathway components, including pAkt, pErk1/2 and pGSK3B, plus the transcription factor Elk, and the chr21 proteins, TIAM1 and DYRK1A. These data are consistent with predictions of perturbed MAPK and calcineurin activity, in turn affecting function of NMDA receptors. Data suggest that the molecular phenotype of DS is characterized by (1) abnormalities in basal levels of protein activities and (2) failures in the dynamics of responses to stimuli. Identifying key points of dysregulation in pathways critical for learning and memory will suggest targets for the testing of potential therapeutics.

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