

Identification of human chromosome 21 genes involved in learning and memory: bioinformatics challenges in Down Syndrome research

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Down syndrome (DS), the most common genetic cause of intellectual disability (ID), is due to an extra copy of chromosome 21 (chr21) and the consequent increase in expression of the genes encoded by it. Recent reannotation of the genomic sequence of chr21 identified >500 genes. The central challenge in DS basic research is to determine the subset of genes that make major contributions to ID, to identify the pathways in which they function and, from this information, to predict potential targets for therapeutics. To do this effectively requires “systems” analysis integrating experimental and bioinformatics based approaches. The latter efforts are broadly described as prediction and analysis of expression, function and interactions of chr21 protein coding and functional RNA genes, and development of the “Chr21 gene function and pathway database” (<http://chr21db.cudenver.edu>) including posting of all data and analysis tools.

Current information on chr21 gene functions and interactions, and the potential for therapeutic interventions, will be described. This will be followed by discussion of short and medium terms goals in bioinformatics and their integration with experimental work. Topics include: (i) the genetic basis of phenotypic variation in Down syndrome: the functional and expression/translation consequences of chr21 SNPs with incorporation of data from orthologous chimpanzee proteins; (ii) the genetic basis for phenotypic variation in mouse models of Down syndrome using a similar SNP analysis for orthologous mouse genes plus RNA expression variation from hippocampal microarray data (WebQTL: <http://www.webqtl.org>); (iii) drug responses that involve chr21 gene expression predicted using data from the Connectivity Map (Lamb et al 2005; Lamb 2007); (iv) the contributions of paralogous genes of chr21 proteins and mouse orthologs: predicting functional differences and overlaps based on expression patterns from dbEST, WebQTL, the Allen Brain data, etc; (v) protein structure/function predictions: developing criteria to predict protein coding vs. functional RNA genes from annotation of chr21 and orthologous mouse genomic regions, including contributions of intrinsically disordered proteins; (vi) chr21 genes contributing to hearing impairment, seizures or speech impairments in DS: several chr21 proteins, when mutated, cause these deficits in the non-DS population; use SNP, RNA expression, and protein interaction data to generate pathways in which these proteins function and predict pathway perturbations that will occur due to increased gene expression in DS. Results of these analyses will improve our ability to predict targets for effective therapeutics, which can then be tested in mouse models of DS for correction of learning and memory deficits. While the focus of each of these projects is on the genes of chr21, all analyses are generalizeable to the whole human and other genomes.