in reciprocal social interactions and communication in conjunction with Autism is a severe, lifelong behavioral disorder characterized by deficits in cDNA microarray technologies to measure the expression of thousands of genes expressed in the neurons and glia of the brain. The expression of several genes was found to be consistently abnormal in RS. The expression of an overlapping population of genes is highly correlated with the expression of MeCP2, whose expression levels range from normal to half of normal in the RS subjects studied here. In addition to the microarray analysis, we used subtractive hybridization techniques as an “open-ended” approach to identify mRNAs differentially expressed in RS. In addition to confirmation of differential expression using RT-PCR and conventional biochemistry, data from microarray and subtractive hybridization experiments were cross validated. Analysis of these large gene expression datasets indicate a global impact of MeCP2 mutations on cellular gene expression. These findings demonstrate the feasibility of high throughput gene expression analysis in human postmortem brain tissue, and the utility of cDNA microarrays in the identification of differentially expressed genes that are secondary to a primary genetic defect, but central to neuropathological mechanisms. Such approaches may become useful in the identification of diagnostic and therapeutic targets in RS as well as other human brain diseases.

30. GENETICS OF AUTISM


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Concordance rates for monozygotic and dizygotic co-twins of autistic probands indicate that there is a profound genetic component to autism and that inheritance is likely to be non-Mendelian. We have ascertained families with two or more individuals with autism or the related disorders of pervasive developmental disorder (PDD) and Asperger’s syndrome. Blood samples were collected from affected, parents, and unaffected siblings and used for a genome-wide linkage study. A two-stage design was adopted in which genotyping is first carried out with markers at an average density of 10 cM in one set of families and markers demonstrating evidence for linkage passing threshold (HLOD or NPL > = 1) are then genotyped in an additional sample. In our initial sample of ~60 families, over 30 markers surpassed the threshold. Second stage screening for an additional ~60 families is underway and will be followed by analyses of flanking markers in the entire sample for markers passing threshold in both samples. Attempts to replicate other studies indicating linkage to chromosomes 6, 7, 13 and 15, or allelic disequilibrium to chromosome 15 are being carried out in the combined sample. In the first sample, no evidence of linkage to chromosome 6, 13, or 15 were observed. In contrast, allelic disequilibrium with GABAR markers in was observed in the larger sample.

31. MOLECULAR CHARACTERIZATION OF THE AUTISTIC BRAIN USING THE HIGH-DENSITY MICROARRAY TECHNIQUE

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Autism is a severe, lifelong behavioral disorder characterized by deficits in reciprocal social interactions and communication in conjunction with restricted and stereotypic behaviors and interest. Presently the neurological basis of autism is not well established. The most consistent observations are those based primarily on postmortem neuropathological studies, which associated autism with a reduction in the number of Purkinje cells in the cerebellum. Accumulating evidence suggests the cerebellum may have a significant role in a variety of nonmotor functions including sensory and motor integration, learning and modulation of affect, motivation and social behavior. Thus cerebellar neuropathology likely contributes to autistic behavioral dysfunction. There is little information at the molecular level on how the structure and function of the cerebellum is affected in autism. To extend our understanding of how cerebellar changes may contribute to autistic dysfunction, we have initiated a program to identify and characterize genes with abnormal patterns of expression in the cerebellum of autistic patients. Our strategy is to compare the gene expression profile of postmortem cerebellar specimens from autistic patients against normal age-matched, non-demented control subjects using the microarray hybridization technology. Using this process, we are analyzing 5,700 genes of known function and will be able to identify autism-related genes. We will categorize these genes into functional clusters defined by their cellular and biochemical functions. Results from our studies are expected to provide insight into the cellular and biochemical pathways underlying the relationship between autistic neuropathology and symptomatology.

32. BEHAVIOR GENETICS OF THE SEROTONIN TRANSPORTER: SEARCHING FOR EPISTATIC INTERACTIONS

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The serotonin transporter (5HTT) is critical to the subsistence of brain serotonin (5HT) homeostasis. It is the initial target for both antidepressant compounds and drugs of abuse. A polymorphism in the 5'-flanking regulatory region of the 5HTT gene that results in allelic variation in 5HTT expression and function is associated with anxiety-, depression-, and aggression-related personality traits and is likely to influence syndromal dimensions of various psychiatric disorders associated with these traits.

The relative influence of genetic and environmental factors on human temperamental and behavioral differences is among the most prolonged and contentious controversies in the intellectual history of man. Although current views emphasize the joint influence of genes and environmental sources, the complexities of gene-gene and gene-environment interaction represents a research area which has barely been touched empirically. Investigation of epistatic interactions in rhesus monkeys and humans as well as gene inactivation studies in mice support the view that adaptive 5HT uptake function is essential for brain development, neuroplasticity, and complex behavior. Despite evidence for a substantial contribution of the 5HTT to the formation of synaptic connections in the mammalian brain during development, adult life, and old age, detailed knowledge of the molecular mechanisms involved in these fine-tuning processes are...