From Molecular Genetics to Gene Expression Profile Analysis in Mental Retardation—Making Sense Out of Sequence  
Thursday, May 11, 2:30 PM–5:00 PM  
Location: Acapulco  
Chair: Giulio Maria Pasinetti  
Co-Chair: Eric London


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Rett syndrome (RTT) is a progressive neurodevelopmental disorder with an incidence of 1 in 15,000. Girls with classic RTT appear to develop normally until 6–18 months of age, then gradually lose speech and purposeful hand use and develop microcephaly, growth retardation, seizures, ataxia, intermittent hyperventilation and stereotypical hand movements. RTT occurs sporadically in 99.5% of cases. Exclusion mapping studies of a few familial RTT cases, assuming X-linked inheritance, mapped the locus to Xq28. By positional candidate gene testing, we identified mutations in the gene encoding the X-linked methyl-CpG-binding protein 2 (MeCP2) as the cause of Rett syndrome. MeCP2 selectively binds to 5-methylcytosines in CpG dinucleotides and mediates transcriptional repression through interaction with the histone deacetylase/Sin3a silencing complex. All missense mutations are de novo and affect evolutionarily conserved amino acids in the region encoding the methyl-binding domain (MBD) and/or the transcriptional repression domain (TRD). Mutations causing premature termination of translation include nonsense and frameshift mutations that predict the synthesis of truncated proteins. Both nonsense (R168X, R255X) and missense (R106W, R306C) mutations have been found with multiple recurrences. The R168X mutation was identified in six unrelated sporadic cases as well as in two affected sisters and their normal mother. All nucleotide substitutions involved C to T transitions at CpG hotspots. This mechanism would account for preferential paternal origins of de novo MeCP2 mutations. A 806delG deletion causing a V288X stop in the TRD was identified in a woman with motor coordination problems, mild learning disability and skewed X inactivation; in her sister and daughter affected with classic RTT; and in hemizygous son who died from congenital encephalopathy. Thus, some males with RTT-causing MeCP2 mutations may survive to birth and female heterozygotes with favorably skewed X inactivation patterns may have little or no involvement. Therefore, MeCP2 mutations are not limited to clinically defined RTT and may be implicated in a much broader phenotypic spectrum. Current work aims to identify the target genes of MeCP2-dependent silencing that may be abnormally expressed as a result of MeCP2 mutations.

29. DIFFERENTIAL GENE EXPRESSION IN HUMAN POSTMORTEM RETT SYNDROME BRAIN REVEALED BY cDNA MICROARRAY

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Rett Syndrome (RS) is a developmental neurological disorder which has been described virtually exclusively in females. Previous studies have described gross anatomical and neurochemical pathology in RS, while genetic linkage analysis has identified Xq28 as the chromosomal region harboring the primary genetic defect in RS. Recently, it has been discovered that mutations in the MeCP2 gene cause RS. Despite this intense investigation, the molecular basis of RS neuropathology remains unclear, and there exists no effective therapy for RS. In order to gain