Frontotemporal Dementias: Clinical Correlates to Cellular Substrates
Thursday, May 11, 2:30 PM–5:00 PM
Location: Toronto
Chair: Anand Kumar
Co-Chair: Ralph Nixon

24. CLINICAL, NEUROPATHOLOGICAL AND NEUROIMAGING CORRELATES OF FRONTOTEMPORAL DEMENTIA (FTD)
A. Kumar
U.C.L.A. School of Medicine, Neuropsychiatric Institute, Los Angeles, CA 90024-1759

Frontotemporal dementias (FTD) comprise a heterogeneous group of neurobehavioral disorders characterized by behavioral aberrations and progressive cognitive decline. The behavioral features typically include disinhibition, verbal outbursts, and apathy. The cognitive abnormalities comprise of decline in memory, language and executive functions. Visual-spatial functions are noticeably spared. The pathological correlates of FTD include neuronal atrophy, gliosis and spongiosis in the frontal and temporal lobes with sparing of the more posterior regions. Neuritic plaques and neurofibrillary tangles are characteristically absent in FTD. Neuroimaging studies with single photon emission computed tomography and Xenon inhalation techniques demonstrate deficits in perfusion largely restricted to the frontal and anterior temporal regions. Both sporadic and familial forms of the disorder have been described and extrapyramidal features occur in certain, though not all, subgroups. FTD is a compelling model of behavioral disorders with clear-cut neurologic and neurobiological underpinnings. They comprise approximately 15 percent of early onset degenerative disorders and their clinical impact in getting increasing recognition. This presentation will focus on new developments within the clinical and neuropathological realm, and emphasize the neurobiological implications of the clinical and genetic heterogeneity frequently encountered in FTD. It will also serve as a broad based introduction to the other components of this panel—which will underscore the genetic, cellular and gene therapeutic aspects of FTD and closely related neurodegenerative disorders.

25. NEUROGENETICS OF FTD—RECENT DEVELOPMENTS
D. Geschwind
U.C.L.A. School of Medicine, Department of Neurology, Los Angeles, CA 90024-1759

There is a striking genetic predisposition to FTD, as from 40 to 50% of patients have a family history of an FTD spectrum disorder, and most are consistent with dominant transmission. Genetic analysis has determined that a series of disorders related clinically and pathologically to frontotemporal dementia (FTD), collectively labeled FTD-P-17 disorders, are etiologically related. The relationship between these disorders although initially based on linkage analysis, has been confirmed by the discovery of causal mutations in the tau gene in some families with FTD-P-17 disorders. Mutations affecting the expression or structure of the microtubule binding domain of the tau gene have been found about 25% of large families with chromosome 17q21-22-linked disease, but rarely in sporadic cases. Functional studies implicate alterations in the microtubule binding domain in various splice isoforms of tau, but other genes are likely to be involved. Remarkable heterogeneity in clinical and pathological presentations can be seen, even among those with the same mutation. The basis for this variability is unknown. The functional implications of known mutations will be emphasized and the phenotype-genotype correlations will be discussed.

26. THE PATHOBIOLOGY OF TAU PROTEIN IN NEURODEGENERATIVE DISEASES
R.A. Nixon, K. Duff, Y. Matsuoka
Nathan Kline Institute and New York University School of Medicine, Orangeburg, NY 10962

Aggregates of the tau protein in the form of paired-helical filaments are one of the hallmark lesions of Alzheimer’s Disease. The significance of tau to mechanisms of neurodegeneration is now underscored by the identification of mutations of tau causing frontotemporal dementia (FTD). As one of a diverse group of microtubule-associated proteins (MAPs), tau binds and stabilizes microtubules (MT), which serve as structural elements and as tracks for the axonal transport of vesicular organelles, thereby supporting axon function and synaptic transmission. The six isoforms of tau generated by alternative splicing of a single gene vary in their affinity for MT and efficiency in inducing the polymerization of tubulin to form MT. FTD-causing mutations alter the proportions of tau isoforms and result in tau proteins with reduced ability to promote MT assembly although this effect alone is unlikely to account for the autosomal dominant nature of FTD. When the tau gene is deleted in mice, only subtle phenotypic changes are seen suggesting that other MAPs can substitute for tau function. These and other findings support a toxic gain of function, rather than loss of tau function, as the underlying effect of FTD-related mutations. In this regard, recent studies suggest that FTD-mutant tau may bind abnormally and disassemble MT, which might then lead to axonal transport failure. Another property of tau is its proclivity for aggregating into inclusions with distinctive morphologies (eg. NFT in AD, ribbon-like filaments in FTD). As in other human neuronal inclusion diseases, the role of aggregation in the degenerative mechanism (eg. protection vs toxicity) is unclear. Tau undergoes complex phosphorylation during development. In human tauopathies, tau is hyperphosphorylated, which decreases its association with MT and promotes its aggregation. Recently, tau has been found to interact with the non-receptor tyrosine kinase fyn and other src family tyrosine kinases and is tyrosine phosphorylated suggesting a role for tau in signal transduction. A host of tau transgenic mouse models are being developed to investigate tau pathobiology and new findings on these models and their relationship to FTD in humans will be discussed.

27. REVERSAL OF SPONTANEOUS ATROPHY OF CHOLINERGIC BASAL FOREBRAIN NEURONS IN THE AGED PRIMATE BY EX VIVO GENE THERAPY
D.E. Smith (1), J. Roberts (2), F. Gage (3), M.H. Tuszyinski (4)
(1) Department of Neurosciences, University of California at San Diego, La Jolla, CA; (2) California Regional Primate Research Center, University of California at Davis, Davis, CA; (3) Salk Institute for Biological Studies, La Jolla, CA; (4) Veterans Affairs Medical Center, San Diego, CA

Recent pre-clinical developments in gene therapy in primates could have practical implications for degenerative disorders such as frontal temporal dementias (FTD) in humans. Ex vivo gene therapy is a
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


(1) Department of Genetics and (2) Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, California; (3) Department of Human Genetics, UCLA School of Medicine, Los Angeles, California; (4) Child Development and Rehabilitation Center, Oregon Health Science University, Portland, Oregon; (5) Kennedy Krieger Institute, Johns Hopkins Medical Institutions, Baltimore, Maryland; (6) Hospital General do Portao, Curitiba, and (7) Department of Psychiatry, Federal University of Parana, Curitiba, Parana, Brazil; (8) Clinical Genetic Service, Department of Health, Hong Kong; (9) Departments of Pediatrics, (10) Molecular and Human Genetics and (11) Howard Hughes Medical Institute, Baylor College of Medicine, Houston, Texas

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 leaning 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 identified 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

C. Colantuoni (1,2), O.-H. Jeon (1,2), C.M. Bouton (1,2), A.E. Purcell (1,2), K. Hyde (3), A. Chenchik (3), A.H. Khimani (4), R.H. Yolken (5), S. Zeger (6), W.E. Kaufmann (7,8,9), S. Naidu (9,10), J. Pevsner (1,2)

(1) Department of Neurology, Kennedy Krieger Institute, 707 N. Broadway; (2) Department of Neuroscience, Johns Hopkins University School of Medicine, 725 N. Wolfe St., Baltimore, Maryland 21205; (3) CLONTECH Laboratories, Inc., Palo Alto, California 94303; (4) NEN Life Science Products, Inc., Boston, Massachusetts 02118; (5) Stanley Division of Developmental Neurovirology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21287; (6) Department of Biostatistics, Johns Hopkins University; (7) Department of Cognitive Neurology, Kennedy Krieger Institute; (8) Departments of Pathology and Psychiatry and Behavioral Science and (9) Departments of Neurology and Pediatrics, Johns Hopkins Hospital; (10) Department of Neurogenetics, Kennedy Krieger Institute, Baltimore, Maryland 21205

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