香港兒童腦科及體智發展學會
HKCNDP

The Hong Kong Society of
Child Neurology & Developmental Paediatrics

# Annual Scientific Meeting

21 - 24 November 2008
Hong Kong

# Neuro-Genetics

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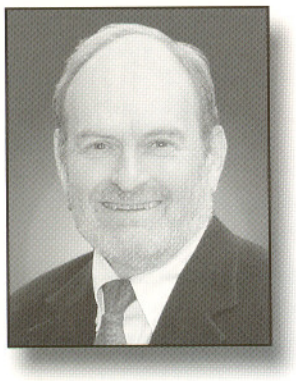
# Course Director



Alan Percy, M.D., Professor of Pediatric Neurology joined the UAB School of Medicine Faculty from the Baylor College of Medicine in 1992 as Director of Sparks Clinics and Director of Pediatric Neurology. Prior to leaving Baylor, Professor Percy was Director of the Rett Center, NICHD-funded interdisciplinary project, devoted to research and care of females with Rett Syndrome (RS). Professor Percy is an internationally known researcher on RS and presently directs the UAB Sparks Clinics Rett Syndrome Research Programme. Professor Percy has more than 30 years of experience in neurodevelopmental and related disorders and is recognized nationally and internationally for his achievements in this field. Professor Percy has taken prominent leadership positions in academic neurological societies. Since 1998, Professor Percy has served as Director of the American Board of Psychiatry and Neurology. He is a Fellow in both the American Academy of Pediatrics and American Academy of Neurology and is actively involved in many national and international pediatric and neurology societies. Professor Percy is also active in many areas of research including the UAB Mental Retardation Research Center (MRRC), where he serves as an MRRC Scientist. Professor Percy was recently named one of the American's Best Doctors on the www.bestdoctors.com. Only 4% of American's doctors are recognized in these listings based on surveys sent to leading specialists around the world.

| Date | Time | Session | Topic | Speaker |
|---|---|---|---|---|
| 21 Nov (FRI) | 1800 - 2000 | *Registration and Light Buffet Dinner* | | |
| | 2000 - 2200 | Seminar I | Rett Syndrome: Understanding the Gene, MECP2 | Professor Alan Percy |
| 22 Nov (SAT) | 1230 - 1400 | *Registration and Light Buffet Lunch* | | |
| | 1400 - 1500 | Seminar II | Rett Syndrome: Medical Issues | Professor Alan Percy |
| | 1500 - 1530 | *Tea Break* | | |
| | 1530 - 1600 | Case Presentation I | Genetic Complexity of Angelman Syndrome in Chinese | Dr. Ivan Lo |
| | 1600 - 1700 | Seminar III | The Leukodystrophies: Diagnosis and Treatment | Professor Alan Percy |
| 23 Nov (SUN) | 0900 - 0930 | *Registration* | | |
| | 0930 - 1030 | Seminar IV | The Storage Diseases: Diagnosis and Treatment | Professor Alan Percy |
| | 1030 - 1130 | Free Paper Session | Outcome of Paediatric Epileptic Surgery Measured by Classification of Outcome and WeeFIMs | Ms. Connie Hui |
| | | | A Review of Pathology Results in a Local Epilepsy Surgery Series | Dr. Josephine Chong |
| | | | Genetic Analyses of Developmental Dyslexia in Hong Kong Chinese Children | Professor Mary Waye |
| | | | An Infant with Persistent Respiratory Failure | Dr. Wai-lan Yeung |
| | 1130 - 1200 | *Tea Break* | | |
| | 1200 - 1330 | Local Presentation | Neurogenetics Services in HA | Dr. Albert Chan |
| | | | Molecular Basis of Dopa-responsive Dystonia in Hong Kong | Professor Ching-wan Lam |
| | | | Molecular Diagnosis in Neurological Diseases: Usefulness and Dilemma from a Clinician's Perspective | Dr. Cheuk-wing Fung |
| | 1330 - 1500 | *Light Buffet Lunch* | | |
| | 1500 - 1600 | Case Presentation II | Local Data on Neurogenetics and Neuro-developmental Genetics | Dr. Edgar Hau |
| | | | Genetic Diagnosis of Hereditary Spastic Paraplegias | Dr. Doris Ching |
| | 1600 - 1630 | *Tea Break* | | |
| | 1630 - 1710 | Seminar V | Expanded Newborn Screening: Implications for Our Field | Professor Alan Percy |
| 24 Nov (MON) | 1830 - 1900 | *Registration* | | |
| | 1900 - 2000 | Keynote Lecture | Exploring the Neurogenetics of Mental Retardation | Professor Alan Percy |
| | 2000 - 2200 | *Chinese Banquet* | | |

**Venues:**

**21 - 23 November 2008**
Lecture Theatre, 7/F., Block H, Princess Margaret Hospital, 2 - 10 Princess Margaret Hospital Road, Lai Chi Kok

**24 November 2008**
Jade Ballroom, 2/F., Eaton Hotel Hong Kong, 380 Nathan Road, Jordan

# Synopsis - Seminar I

## Rett Syndrome: Understanding the Gene, MECP2

*Professor Alan Percy*
*Civitan International Research Center, The University of Alabama at Birmingham, USA*

Rett syndrome (RTT) (MIM 312750) is a unique neurodevelopmental disorder caused by a **novel pathogenetic mechanism**, i.e. disturbance of epigenetic gene regulation via DNA methylation. First recognized as a distinct clinical entity in 1966, RTT is a leading cause of cognitive, communication, and motor impairments in females. RTT, recognized almost exclusively in females following apparently normal psychomotor development during the first six months of life, occurs in all ethnic groups as a sporadic disorder secondary to *de novo* mutations in *MECP2*. This X-linked gene encodes methyl-CpG-binding protein 2 (MeCP2). Presence of a mutation in the *MECP2* gene confirms the clinical diagnosis. Children fulfilling clinical criteria for RTT may (95% or more) or may not have *MECP2* mutations. Specific phenotype-genotype correlations have been developed from a number of different investigative groups. *MECP2* mutations may also be seen in children who do not have classic RTT.

MeCP2 mediates transcriptional silencing through its methyl-CpG-binding (MBD) and transcriptional repression (TRD) domains. Switching on a silenced *MECP2* gene in the knockout animal model for RTT achieved complete or nearly complete reversal of the clinical phenotype. This study provides proof of principle that the neurodevelopmental abnormalities in RTT may be reversible, in whole or in part. Alterations in chromatin remodeling due to loss of MeCP2 function underscore the notion that complex molecular pathways mediate pathogenesis in RTT and that a single intervention is unlikely to ameliorate every feature of the disorder. For example, recent evidence from the Zoghbi lab using a knockout mouse model demonstrated enhanced corticosterone release and corticotropin-releasing hormone (Crh) expression. Enhanced Crh expression was noted not only in the hypothalamus, but also in the amygdala and stria terminalis, structures associated with anxiety and fear. Wildtype Mecp2 binds to the Crh promoter, acting as a potential regulator of its expression; mutant Mecp2 does not. These results suggest a critical role for Mecp2 in the hypothalamic-pituitary-adrenal axis and forebrain neural structures with important downstream connections in the brainstem regarding the behavioral and autonomic manifestations of RTT. The results also suggest therapeutic interventions to address anxiety directly. Lacking a direct cure, a valid alternative treatment strategy would be to target specific components of the phenotype such as stress, anxiety, osteopenia, seizures, sleep disorders, and potential hormonal/metabolic abnormalities. The apparently normal period of early development in RTT provides a window of opportunity whereby interventions such as anxiety and stress reducing therapies might significantly change the outcome.

**References:**

1) Percy AK, Lane JB. Rett Syndrome: Model of Neurodevelopmental Disorders. J Child Neurol 2005;20:718-721.
2) Kankirawatana et al. Early Progressive Encephalopathy in Boys and MECP2 Mutations. Neurology 2006;67:164-166.
3) Percy AK, Lane JB, Childers J, Skinner S, Annese F, Barrish J, Caeg E, Glaze DG, MacLeod P. Rett Syndrome: North American Database. J Child Neurol 22:1338-1341,2007.
4) Percy AK. Rett Syndrome: Recent Research Progress. J Child Neurol 23:543-549,2008 (available on-line December 3, 2007).
5) Neul JL, Fang P, Barrish J, Lane J, Caeg E, Smith EO'B, Zoghbi HY, Percy A, Glaze DG. Specific Mutations in Methyl-CpG-Binding Protein 2 Confer Different Severity in Rett Syndrome. Neurology 70:1313-1321,2008.
6) Bebbington A, Anderson A, Ravine D, Fyfe S, Pineda M, de Klerk N, Ben-Zeev B, Yatawara N, Percy A, Kaufmann WE, Leonard H. Investigating genotype phenotype relationships in Rett syndrome using an international dataset. Neurology 70:868-875,2008.

**Rett syndrome database resources:**

RettBase: Dr. John Christodoulou
MECP2 Mutation Repository
www.mecp2.chw.edu.au

InterRett: Dr. Helen Leonard
Clinical information repository from parents and physicians
www.ichr.uwa.edu.au

**Current NIH-funded Natural History Study:**

Data collected at the enrollment sites are transmitted electronically as confidential information to the Data Technology Coordinating Center (DTCC) at the University of South Florida in Tampa. The DTCC maintains an active public website that accepts disease specific contact registrants (www.rarediseasesnetwork.epi.usf.edu/).

**Current enrolling sites:**

Baylor College of Medicine:
Site PI: Daniel Glaze, MD
Coordinator: Judy Barrish, RN, BSN

Greenwood Genetic Center:
Site Co-PI: Mike Friez, PhD
Site Co-PI: Steve Skinner, MD
Coordinator: Bridgette Aufmuth, MS

University of Alabama at Birmingham:
Site PI: Alan Percy, MD
Coordinator: Jane Lane, RN, BSN

## Rett Syndrome: Medical Issues

*Professor Alan Percy*
*Civitan International Research Center, The University of Alabama at Birmingham, USA*

The diagnosis of Rett syndrome (RTT) (MIM 312750) is based on specific clinical criteria. Consensus criteria for classic RTT include apparently normal early development, postnatal deceleration of head growth in most, loss of purposeful hand skills, stereotypic hand movements, psychomotor regression including communication dysfunction, early, short-term presence of autistic features, and gait dysfunction characterized by dyspraxia and jerky truncal ataxia. RTT remains a clinically rather than genetically defined condition. Presence of a mutation in the *MECP2* gene confirms the clinical diagnosis. Children fulfilling clinical criteria for RTT may (95% or more) or may not have *MECP2* mutations. *MECP2* mutations may also be seen in children who do not have classic RTT. Revised clinical guidelines should provide for accurate and reliable diagnosis by primary care providers and clinical investigators.

Studies of individuals with RTT and relevant mouse models indicate that RTT is a complex, multisystem disorder involving a variety of phenotypes that result from dysfunction of multiple pathways. Phenotypes related to *MECP2* mutations in females vary from normal or mild learning disability to classic RTT, depending on mutation type and pattern of X chromosome inactivation (XCI) as well as unknown factors; phenotypes in males vary from fatal infantile encephalopathy to familial X-linked mental retardation. Rarely, classic RTT occurs in males who have somatic mosaicism or Klinefelter syndrome.

Medical issues related to RTT reflect the multi-systemic nature of the syndrome. These include growth and nutrition, epilepsy, sleep, scoliosis, gastrointestinal function from top to bottom, behavior, motor system function, respiratory function, cardiac conduction, and sexual maturation. Because girls with RTT commonly survive into adulthood, this disorder produces a significant societal burden, underscoring the need for effective therapies. We know that symptomatic therapy is currently altering the natural history of RTT, exemplified by improvements in the management of nutritional and gastrointestinal issues, scoliosis, seizures, and sleep. This conclusion is based on data gathered in our on-going natural history study with current enrollment in excess of 675 participants. We have examined many of these medical issues with respect to their occurrence in the eight common point mutations and in two other mutation groups (large deletions and c-terminal deletions). These results will be presented and summary recommendations made.

**References:**

1) Percy AK, Lane JB. Rett Syndrome: Model of Neurodevelopmental Disorders. J Child Neurol 2005;20:718-721.
2) Kankirawatana et al. Early Progressive Encephalopathy in Boys and MECP2 Mutations. Neurology 2006;67:164-166.
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Coordinator: Bridgette Aufmuth, MS

University of Alabama at Birmingham:
Site PI: Alan Percy, MD
Coordinator: Jane Lane, RN, BSN

## The Leukodystrophies: Diagnosis and Treatment

*Professor Alan Percy*
*Civitan International Research Center, The University of Alabama at Birmingham, USA*

The leukodystrophies represent a group of inherited disorders affecting the formation of myelin and should be distinguished from disorders characterized by demyelination such as multiple sclerosis, inflammatory disorders, or toxic processes. As such, the leukodystrophies can be categorized as dysmyelinating (abnormal myelin formation), hypomyelinating (failure of myelin formation), or vacuolating (dissolution of myelin). The leukodystrophies are associated typically with infants and children, but adult variants are recognized with increasing frequency. As a group, the leukodystrophies have an incidence of 1:50,000, based on data from Germany. This number should be regarded as a minimum figure as underdiagnosis is likely. Efforts to provide useful screening tools have focused on cranial MRI and CSF analyses. Indeed, careful MRI analysis has yielded an excellent classification scheme. No consistently effective treatment is available for the entities described below although bone marrow stem cell replacement strategies have been employed for some.

A number of leukodystrophies, such as metachromatic leukodystrophy, globoid cell leukodystrophy, adrenoleukodystrophy and its variants, cerebrotendinous xanthomatosis, Sjögren-Larsson syndrome, and Canavan disease, represent inherited neurometabolic disorders affecting white matter predominantly. More recently, the molecular bases of other nonmetabolic inherited leukodystrophies have been demonstrated. These, however, differ from the inherited neurometabolic group in the sense that the relevant genes encode structural proteins rather than proteins involved directly in cellular metabolism. This group of disorders includes Pelizaeus-Merzbacher disease (PMD), an X-linked disorder due to mutations in the gene, *PLP*, located at Xq22; Alexander disease, a rare disorder of white matter associated with mutations in glial fibrillary acidic protein (GFAP) gene, *GFAP*; and vanishing white matter (VWM) disease, also called childhood ataxia with diffuse hypomyelination (CACH) syndrome, a rare, autosomal recessive disorder involving hypomyelination and recently mapped to both 3q27 and 14q24.

Laboratory diagnosis of the leukodystrophies employs a variety of biochemical, enzymatic, and molecular methodologies as well as clinical neurophysiology, neuroimaging, and histopathology. Careful clinical assessment should allow a quite precise and tailored approach. However, for this to occur, a high index of suspicion for an inherited neurodegenerative process is essential.

**References:**

1) van der Knaap MS, Leegwater PAJ, Konst AAM, Visser A, Naidu S, Oudejans CBM, Schutgens RBH, Pronk JC. Mutations in Each of the Five Subunits of Translation Initiation Factor eIF2B Can Cause Leukencephalopathy with Vanishing White Matter. Ann Neurol 2002:51:264-270.
2) Percy AK. The Leukodystrophies. In Principles and Practice of Pediatrics, McMillan J, DeAngelis, C, Feigin, RD, Warshaw, JB (eds), 5th Edition, J.B. Lippincott Williams & Wilkins, Philadelphia, 2006, pp. 2346-2353.
3) Bizzi A, Castelli G, Bugiani M, Barker PB, Herskovits EH, Danesi U, Erbetta A, Moroni A, Farina I, Uziel G. Classification of childhood white matter disorders using proton MR spectroscopic imaging. Am J Neuroradiol 2008;29:1270-1275.
4) Sedel F, Tourbash A, Fontaine B, Lubetzki C, Baumann N, Saudubray J-M, Lyon-Caen O. Leukoencephalopathies associated with inborn errors of metabolism in adults. J Inherit Metab Dis 2008;31:295-307.

## The Storage Diseases: Diagnosis and Treatment

*Professor Alan Percy*
*Civitan International Research Center, The University of Alabama at Birmingham, USA*

The storage diseases represent but one possible explanation of neurodegen-erative disease. One must exclude other relevant etiologies including the toxic encephalopathies, chronic viral infections, the immunopathic disorders (systemic lupus erythematosis and related conditions), brain neoplasms, psychiatric or behavioral disorders including autistic spectrum disorder and environmental deprivation, or other metabolic conditions such as diabetes mellitus or porphyria.

Typically, storage diseases represent disordered lysosomal function and comprise a group of diverse disorders, which have in common the abnormal accumulation or **storage** of disease-specific macro-molecules or metabolites derived from them in lysosomes, the subcellular organelle responsible for their degradation. Lysosomes contain an array of hydrolytic enzymes (hydrolases), which are crucial for catabolism of the broad array of cellular macromolecules. In a sense, the lysosome functions as the cell's sanitary engineer. When lysosomal function is deficient, the substrate for the defective enzyme(s) accumulates often leading to organomegaly. Ultimately, the lysosome fails completely, and cell death results. In addition, the stored material, itself, may be cytotoxic. In some, the specific enzyme is normal, and disease is due to deficient activator protein required for enzyme function. These macromolecules are normal tissue components of cell membranes. For example, GM1 ganglioside is a membrane receptor for cholera toxin; sulfatide is a membrane receptor for HIV. Similarly, sulfatide and gangliosides have been implicated in a variety of immune-mediated neuropathic disorders involving so-called molecular mimicry. In the nervous system, sphingolipids, particularly the gangliosides, may function as cell-recognition markers critical for cell-cell interaction and development of synaptic contacts. Still others such as sphingosine and ceramide appear to be important modulators of cytotoxicity and apoptosis.

As a group, the lysosomal storage diseases represent the most common inherited neurometabolic diseases with an incidence of about 1:6-8,000 births. For most of these disorders, the biochemical and molecular abnormalities have been established; for some, the molecular defect is unknown and clinical diagnosis still presents a significant challenge. Remarkable clinical heterogeneity exists within individual disorders, the full spectrum of which continues to emerge. Diseases of lysosomal function are categorized according to the accumulated material, namely, sphingolipidoses, mucopolysaccharidoses, mucolipidoses, glycoproteinoses, sialic acid storage disease, cholesterol ester lipidosis, Niemann-Pick Type C, glycogen storage disease Type II (Pompe disease), sialidoses, and neuronal ceroid lipofuscinoses. Treatment strategies include enzyme replacement, substrate reduction, and bone marrow stem cell transplantation.

**References:**

1) Beutler E. Lysosomal storage disease: Natural history and ethical and economic aspects. Mol Genet Metab 2006;88:208-215.
2) Bach G, Zeigler M, Zlotogora J. Prevention of lysosomal storage disorders in Israel. Mol Genet Metab 2007;90:353-357.
3) Sands M, Haskins ME. CNS-directed gene therapy for lysosomal storage disease. Acta Paediatrica 2008:97:22-27.
4) Matern D. Newborn screening for lysosomal storage disorders. Acta Paediatrica 2008:97:33-37.

## Expanded Newborn Screening: Implications for Our Field

*Professor Alan Percy*
*Civitan International Research Center, The University of Alabama at Birmingham, USA*

In 1999, the American Academy of Pediatrics (AAP) newborn screening task force indicated a need for greater uniformity for newborn screening and recommended that the US **Health Resources and Services Administration** (HRSA) should engage in "a national process involving government, professionals, and consumers to advance the recommendations of this Task Force and assist in the development and implementation of nationally recognized newborn screening system standards and policies." As such, a task force was created to develop "nationally recognized newborn screening system standards and policies." This group included experts in the various disorders as well as experts in primary care, health policy, law, ethics, and public health, and also included consumers. They created a uniform panel of screening tests and a follow-up system. What emerged was the recommendation that State newborn screening programs mandate **screening** for all core panel conditions and **reporting** of all secondary target conditions including any abnormal results that may be associated with clinically significant conditions, including the definitive identification of carrier status. This program emerged from advanced technology of tandem mass spectrometry (MS/MS), the most significant advance in newborn screening in 35 years allowing early identification and treatment of these disorders and decreased infant morbidity and mortality.

The benefits of the program include presymptomatic diagnosis, particularly the detection of disorders of fatty acid oxidation and later onset (milder) disorders of protein metabolism (urea cycle disorders, amino acidemias, and organic acidemias). Limitations of the program include the inability to detect all inherited disorders of metabolism (such as glycogen storage diseases, nonketotic hyperglycinemia, some mitochondrial disorders, and carbohydrate deficient glycoprotein disorders); some patients will be clinically ill, perhaps critically, before results are available, especially early onset urea cycle disorders and some organic acidemias and amino acidemias; detection of disorders of unknown, if any, clinical significance (such as 3- methylcrotonylCoA carboxylase deficiency, SCAD, and some MCAD); false positives will occur and increase costs with respect to their evaluation and the resultant family morbidity including anxiety, altering their view of their child, etc.; and results may not be valid if the infant is on total parenteral nutrition, is premature, had a transfusion, or is due to poor timing of test.

In summary, comprehensive newborn screening should be offered to all. We must be cognizant of limitations, time for results to return, false positives, conditions for which it does not screen, and positive tests for clinically insignificant conditions.

**References:**

1) Jones PM, Bennett MJ. The changing face of newborn screening: diagnosis of inborn errors of metabolism by tandem mass spectrometry. Clinica Chimica Acta 2002;324:121-128.
2) US General Accounting Office, Newborn Screening: Characteristics of State Programs, GAO 03-449, March 2003. http://www.gao.gov/new.items/d03449.pdf.

## Exploring the Neurogenetics of Mental Retardation

*Professor Alan Percy*
*Civitan International Research Center, The University of Alabama at Birmingham, USA*

Mental retardation or significant cognitive impairment is defined by the presence of both low IQ and limitations in adaptive daily living functions and may be classified as syndromic or non-syndromic. Severity may vary from borderline to profound. In most syndromic forms, characterized by the presence of abnormal clinical, laboratory, or imaging features, IQs range from moderate to severe although some may be profound. Genetic explanations may be chromosomal or gene-based, the latter X-linked, autosomal or multifactorial. Until recently, the major clinical and molecular focus has been on X-linked mental retardation (XLMR). However, tools are now emerging to examine autosomal forms.

The principal chromosomal disorders to be discussed are Down syndrome, Prader-Willi syndrome, and Angelman syndrome. Down syndrome is the most common genetic disorder, characterized by moderate to severe cognitive impairment and median survival of about 50 years. Prader-Willi syndrome (PWS) is due to deletion of paternally-derived chromosome 15q11-13. Recent evidence links PWS to specific mutations of noncoding small nucleolar RNAs (snoRNAs), although other genes may play a role. The propensity for obesity responds well to growth hormone replacement. Angelman syndrome (AS) is caused by deletion of maternally-derived chromosome 15q11-13 or mutation (5-10%) in E3 ubiquitin protein ligase gene (*UBE3A* gene). Diagnosis of PWS and AS is based on methylation analysis of chromosome 15q11-13 with FISH analysis to confirm deletion and microsatellite probes to detect uniparental disomy. If negative in AS, mutation analysis of *UBE3A* gene should be conducted.

Predominant attention to X-chromosome disorders is related to familial recurrences and association with expanded syndromes. About two-thirds of XLMR not associated with specific syndrome, a number that is likely to diminish as molecular understanding increases. Examples include fragile X syndrome and Rett syndrome. Fragile X syndrome, a trinucleotide repeat disorder, is the most common inherited mental retardation (1:5,000). Behavior problems include poor attention and hyperactivity and autism occurs in 60%.

Autosomal MR is likely to be more common XLMR, but due to rarity of large families of affected individuals, progress has been slow. Only a handful of genes have been associated with autosomal recessive MR, and it is possible that only a small number of genes will be responsible. Screening of large consanguineous families may be required. Current approaches to identification will benefit from the implementation of comparative genomic hybridization techniques. For example, submicroscopic deletions may account for 7% of MR of unknown cause. CGH screening could hasten identification and understanding of this group. This may be a particularly fruitful approach for autosomal dominant forms of MR by identifying candidate genes.

**References:**

1) Roper and Hamel. X-linked Mental Retardation. Nature Reviews Genetics 2005;6:46-57.
2) Billuart et al. Oligophrenin-1 encodes a rhoGAP protein involved in X-linked mental retardation. Nature 1998;392:923-926.