香港醫學遺傳學會
Hong Kong Society of Medical Genetics

HKSMG Newsletter

Issue no. 2; Jan 2009

c/o 3/F Cheung Sha Wan Jockey Club Clinic, 2 Kwong Lee Rd., Shamshuipo, KLN., HKSAR
Official website: http://www.fmshk.com.hk/hksmg/index.htm, Email: hksmg.com@gmail.com

Message from the Editor

The Year of the Boar is now behind us and we have just welcomed the Year of the Ox. The last 12 months is very special for our society both intellectually and professionally. We started off with a very successful annual meeting and met a lot of very special and outstanding people and some very good new friends through organizing various conferences and scientific symposiums with sister societies. I want to send our special thanks for continued support from our members and to all the various event co-organizers that we work with. We couldn't have done it without you. The society will continue to promote the interest and knowledge in medical genetics during the coming year.

On behalf of the HKSMG, we wish you all a great Year of the Ox - let's all continue to grow personally and professionally, and let's make many more new friends along the way! (*Richard Choy*, Editor)

HKSMG council members at various occasions.
Dr. Ivan LO (Chairman, top second left). Dr. Stephen LAM (Ex-Chairman, second row 2nd from right)

Dr. Brian Hon-Yin CHUNG
MBBS

Graduated from University of Hong Kong

Appointments:
Assistant Professor in Department of Paediatrics, QMH

Scientific Subcommittee Member, HKSMG

Letter from Toronto

Dear Colleagues and Friends,

Hello! Seasonal greeting from Toronto!

Since 1st October, 2007, I have moved to Toronto for a 2-year fellowship in Clinical and Metabolic Genetics in the Hospital for Sick Children (HSC). It has been more than 1 year now and the experience has been great!

HSC offered a total of 3 genetic programs:

1) A 5-year residency program under the Royal College of Canadian Physicians,
2) A 2-year fellowship under the Canadian College of Medical Geneticists, and A 2-year master program in genetic counseling under the University of Toronto.

Among them, the fellowship is offered to trainees who would like to specialize in different areas including clinical genetics, metabolic genetics (clinical), cytogenetics, molecular genetics and metabolic genetics (laboratory). It is a structured program consists of 10 rotations and trainees need to complete a logbook of at least 200 patients whom they have participated in their management. To obtain the specialist qualification, they also need to sit for an examination held every 2 years with written and clinical components.

The rotations include:

1) Clinical genetics (in-patient and out-patient service) – at least 6 months
2) Metabolic Genetics (in-patient and out-patient service) – at least 2 months
3) Prenatal Genetics – at least 2 months
4) Adult Genetics – at least 1 month
5) Cancer Genetics – at least 1 month
6) Cytogenetic laboratory – at least 2 months
7) Molecular laboratory – at least 2 months
8) Metabolic laboratory – at least 2 months
9) Elective rotation – 2 months
10) Research rotation – 4 months.

Although the winter is very cold (-30C last February), the program has been very exciting! We are exposed to the state-of-art genomic technologies including oligo-arrays, methylation array, mitochondrial diagnostics, and tandem mass spectrometry. Thursdays are our academic days and we have teaching for the whole day including dysmorphology case conferences, difficult counseling cases, neurogenetic rounds (with radiology), fetal round (with feto-maternal medicine and high risk obstetrics) and the "seasonal specials" – short courses on cytogenetics, molecular genetics, genetic epidemiology and counseling courses are offered every other 3 months to deepen our knowledge in the respective areas.

The biggest "challenges" really come when you are on-call at night. It is because you are on-call not only for the hospital (as we are in Hong Kong) but you are on-call for all Genetic and Metabolic consults in the whole TORONTO area and you may even get calls from other cities (or towns) from all over ONTARIO!!! You might at 1 night receive a call for advices in managing hyperammonaemia in a 21-year-old man in Newfoundland (3 hours of flight from Toronto), while at other nights receive call for assessing a newborn with multiple congenital anomalies in NICU or you might need to talk to a family physician on what to do with an abnormal newborn screening report suggestive of galactossaemia in one of his/her patients (yes, these are all my personal experience)!!!!

I met Dr Stephen Lam in Philadelphia when we attended the 2008 American Society of Human Genetics Conference. I am so glad to learn from him that everyone is doing well in Hong Kong. I am looking forward to meeting all of you when I am back and we can, again, work together! Take care!

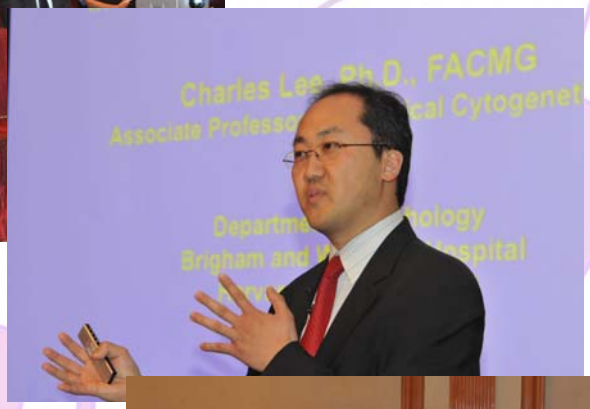
Happy Chinese New Year!!

Yours sincerely,
Brian

REPORT ON SCIENTIFIC ACTIVITY IN OCTOBER 2008

We are honored to have Dr. Charles Lee, the leader in genome copy number variations to deliver a dinner lecture entitled **"The impact of human structural genomic variation on a new era of prenatal genetic testing".** The lecture was co-organized by the Hong Kong Society of Cytogenetic and the Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong. It was held in the evening of 2nd Oct 2008 at the Marco Polo Hotel with over 50 attendees coming from different disciplines such as the universities, government units, Hospital Authority service units and other scientific professions. Dr. Charles LEE is the Director of Cytogenetics for the Harvard Cancer Center, Associate Professor of Pathology at Harvard Medical School, and an Associate Faculty Member of the Broad Institute of Harvard and MIT. He is also a board-certified clinical cytogeneticist at Brigham and Women's Hospital. He shared with the audience his discovery on identification of widespread structural variation (in the form of copy number variants - CNVs) in the human genome and how his finding now having a major impact on many areas of medicine and research, including cancer biomarker studies, medical genetic diagnostics, and personalized medicine.

The lecture was delivered by Dr. Charles LEE the youngest recipient of the Ho-Am Prize in Medicine (also referred to as the "Korean Nobel Prize").



A conference banquet was held at the Marco Polo Hotel on the evening of October 2, 2008 following the lecture. Most participants attended and had a memorable evening.

Genetic Study of CNS Diseases

Ivan F. M. Lo
Edgar W. L. Hau
Tony M. F. Tong
Stephen T.S. Lam
Clinical Genetic Service,
Department of Health, HKSAR

Correspondence: 3/F Cheung Sha Wan Jockey Club Clinic, 2 Kwong Lee Road, Kowloon, Hong Kong.
Email: dr.ivanlo@gmail.com

Introduction

Clinical Genetic Service (CGS) is the major service provider of genetic testing in Hong Kong. The development of various genetic investigations serves several purposes. First, genetic disorders can be confirmed, which has implications on prognosis and subsequent clinical management. Second, risk assessment during genetic counselling can be done more accurately, allowing patients or parents to make informed decisions on reproductive options. Third, the genetic defect can serve as a marker with which one can perform cascade screening in the family and prevent recurrence of the disease by means of prenatal diagnosis or even pre-implantation genetic diagnosis.

Chromosomal disorders

A lot of patients are referred to CGS for Central Nervous System (CNS) diseases. Particularly, children with developmental delay, autism, and mental retardation constitute a major category of referrals. Karyotyping has been an important investigation in this group of patients, because a small but significant percentage of these patients are caused by various chromosomal abnormalities. From 1991 to 2007, 184 (6.6%) chromosomal abnormalities were detected in ~2791 patients referred for these reasons, not counting Down syndrome and other microdeletion syndromes (22q11.2 deletion syndrome, Williams syndrome, Smith-Magenis syndrome, etc.) that require fluorescence in-situ hybridization (FISH) for confirmation. Over the last 10 years or so, it became more and more recognized that cryptic subtelomeric chromosomal aberrations account for 5-10% of idiopathic mental retardation. It is important to identify these cases, because recurrence is not uncommon in these families. However, being "cryptic" means that these subtelomeric aberrations are difficult to detect with traditional cytogenetic techniques. In CGS, a combined molecular and FISH approach is adopted. A small study was done and detected 3 (15%) subtelomeric deletions among 20 unrelated MR patients.[1]

Fragile X syndrome

Fragile X syndrome is regarded as the commonest hereditary MR syndrome with an incidence of 1/4,000 – 1/6,000 males and accounts for 1-2% of MR patients. However, it is not so easily recognizable clinically. It is so named because in these patients the X chromosome may bear a fragile site at Xq27.3 region and the detection of this fragile site by cytogenetic technique was mainstay of diagnosis till early 90's. It is the first genetic disease found to be caused by trinucleotide repeat expansion. There is a polymorphic stretch of CGG trinucleotide repeats in the 5'UTR of exon 1 of the FMR1 gene. In normal people, the number of CGG repeats is in the range of 6-54. Individuals with 55-200 CGG repeats are said to have a premutation; meiotic instability may occur, resulting in contraction or further expansion of the repeats in the offspring. Individuals with >200 CGG repeats are said to have a full mutation. Full mutations are almost invariably associated with abnormal methylation of the gene and transcriptional silencing, with the result of a Fragile X syndrome phenotype. All males with full mutation manifest variable degree of mental retardation, whereas about half of the female full mutation carriers manifest. Therefore, Fragile X syndrome is said to be inherited in an X-linked semidominant fashion. In our genetic laboratory, Fragile X is detected by an initial screening with polymerase chain reaction (PCR) followed by confirmation with Southern blotting. A total of 34 index cases were identified since 1987. There was a positive family history of MR in about half of the patients. Mothers who had been tested were confirmed to be either premutation or full mutation carriers.

Rett syndrome

Rett syndrome (RS) is an interesting neurodevelopmental disorder. It predominantly affects females. The typical presentation is apparently normal development in the first 18 months, followed by developmental regression with loss of learned hand use and language skills, seizures, gait apraxia, deceleration of head growth, and midline stereotypic hand movements. The gene implicated in RS has been

elusive until 1999, when Amir et al. (1999) found mutations in the MECP2 gene in some patients with RS.2 As a result of collaboration with the research group from Stanford University, a RS patient from Hong Kong was among the first patients who had the causative *MECP2* mutations identified.3 Soon Lam et al. (2000) reported 6 *MECP2* mutations in 13 local patients with classical RS.4 CGS has been providing *MECP2* gene analysis for patients with suspected Rett syndrome since 2001. Up to now, 14 different mutations were identified in 18 unrelated patients. The mutations are heterogeneous, including *MECP2* gene deletion, single exon deletion, missense mutations, nonsense mutations, frameshift mutations and in-frame deletion. All these confirmed cases were sporadic and were females. None of the mothers who underwent testing carried the mutation. It is now known that *MECP2* mutations not only cause a classical RS phenotype in female, it also causes a severe encephalopathic phenotype in male. On the other hand, atypical or milder cases of RS were also found to be due to *MECP2* mutations, which aroused the debate whether routine *MECP2* testing should be offered to children with non-specific mental retardation or autism. So far evidence showed that *MECP2* mutations probably account for no more than 1% of these cases.

Prader-Willi and Angelman syndromes

Prader-Willi syndrome (PWS) and Angelman syndrome (AS) are clinically distinct disorders that are the result of similar genetic defects. These genetic defects involve the chromosome region 15q11-13. Owing to the presence of low copy repeats, this region is prone to deletion or duplication. To complicate it further, this region contains imprinted genes. Genomic imprinting is a term that describes the phenomenon of differential gene expression dependent upon the parent of origin of the alleles. Some genes express only when they are inherited from the father, while some others express only when they are inherited from the mother. About 70% of both PWS and AS patients are caused by microdeletion of this region. A PWS phenotype occurs when the microdeletion happens on the paternally inherited chromosome 15; an AS phenotype results when the microdeletion happens on the maternally inherited chromosome 15. The rest of the PWS or AS patients are caused by other genetic or epigenetic defects like uniparental disomy 15 (UPD15) and imprinting defects. For AS, about 10% of patients are caused by mutations of a gene known as UBE3A. CGS has been using FISH to detect 15q11-13 microdeletion in cases of suspected PWS/AS since mid-90's. With the subsequent advances in molecular techniques, we are now able to diagnose over 98% of the PWS and about 90% of AS cases. At present, we have confirmed the diagnosis of 56 PWS and 38 AS patients. The genetic defects in the PWS patients are microdeletion (59%), matUPD15 (39%), and imprinting defect (2%). The genetic defects in the AS patients are microdeletion (66%), patUPD15 (11%), imprinting defect (5%), UBE3A mutation (13%) and undefined (5%).

Hereditary neurodegenerative diseases

This is a group of neurological disorders that usually present in adulthood and show anticipation, a phenomenon in which disease severity is increased and disease onset is pushed to an earlier age when the disorder is transmitted from one generation to the next. Quite a number of them are caused by polyglutamine tract expansion as a result of CAG trinucleotide repeat expansion in the respective genes. There are at least 10 disorders due to this kind of mutation. In our laboratory, we are testing for Huntington disease, spinal cerebellar ataxias (SCA type 1, 2, 3, 6, 7, 8, 12), dentatorubropallidoluysian atrophy (DRPLA), and Kennedy disease. With the exception of the X-linked recessive Kennedy disease, these disorders are of autosomal dominant inheritance. To date, we have confirmed the molecular defect of over 78 local families of SCA. SCA3 is the commonest type, with over 56 positive families. Among these neurodegenerative disorders, DRPLA may be of particular interest to paediatric neurologists, because in all three DRPLA families that we have confirmed, there are affected individuals who presented before 18 years of age.5 Other neurodegenerative disorders which we have seen disease onset before 18 years are SCA3 (3/54 families) and Huntington disease (1/22 family).

Congenital central hypoventilation syndrome

Congenital central hypoventilation syndrome (CCHS) is a rare autosomal dominant disorder of the autonomic nervous system (ANS) characterized by an abnormal autonomic ventilatory response to progressive hypercarbia and sustained hypoxemia. Patients typically present in the newborn period with hypoventilation or apnea asleep, awake, or both, without any associated cardiac, pulmonary, neuromuscular or brainstem lesions. Rarely, some patients may present at a later age and are diagnosed to have late onset central hypoventilation syndrome (LOCHS). The central hypoventilation can occur as an isolated feature or in association with anatomic defects of the ANS. Notably Hirschsprung's disease (Haddad

syndrome) was also present in 16-50% of patients; and tumours of the sympathetic nervous system such as neuroblastoma, ganglioneuroblastoma, and ganglioneuroma, were found in 5-10% of patients. PHOX2B gene defects cause >90% of cases, and more than 90% of the mutations result in polyalanine tract expansion. We reported three local male patients with CCHS ascertained because of persistent hypoventilation in the absence of primary pulmonary, cardiac, neuromuscular, brainstem and metabolic causes. Two of them also had Hirschsprung's disease. PHOX2B gene analysis detected a single nucleotide insertion and two other mutations that led to polyalanine tract expansion.6 Two more patients, a boy and a girl, were diagnosed subsequent to that report.

Pelizaeus-Merzbacher disease

Pelizaeus-Merzbacher disease (PMD) is an X-linked disorder caused by PLP1 gene defects. PLP1 encodes the myelin proteolipid protein, an important component of CNS myelin formation. Patients, usually males, present with severe hypotonia of neonatal or infantile onset, nystagmus, and cognitive impairment, with progression to spasticity and ataxia at the later stage. MRI scan of the brain typically shows reduced white matter and myelination. The most common PLP1 mutation is gene duplication. At CGS, 7 local PMD patients were confirmed, with 4 PLP1 duplications and 3 point mutations.

Mitochondrial disorders

Suspected mitochondrial disorder is a fairly common reason of referral to CGS. This group of disorders are not easy to diagnose and probably are very much under-diagnosed currently for a number of reasons. There is a wide spectrum of clinical phenotypes. Some patients present with the well defined phenotypes of MELAS, MERRF, NARP, LHON, KSS and CPEO; while many others have non-specific phenotypes. Clinical severity also varies with the level of heteroplasmy and the distribution of the mutant in the body. Biochemical and even histological evidence of mitochondrial dysfunction are sometimes just secondary changes. Apart from those that cause the aforementioned, well defined phenotypes, mutations are generally heterogeneous. Furthermore, mitochondrial disorders are not necessarily caused by mtDNA mutations; mutations of nuclear encoded genes, notably those encoding subunits of the respiratory chain complexes, also cause mitochondrial dysfunction. So far, 10 families with MELAS, 2 families with NARP, 1 family with MERRF and 1 with LHON have been confirmed by CGS.

Conclusion

During the last 15 years, genetic study of CNS diseases has moved from the cytogenetic era into the molecular era. This is not to say that cytogenetics is dispensable; it remains an essential tool for the diagnosis of chromosomal disorders. With the completion of the Human Genome Project, knowledge of disease causing genes is growing with unprecedented pace. Together with advances in molecular technologies, genetic diagnosis for single gene disorders is more readily available. The demand for genetic study is ever increasing; CGS is prepared to meet the demand from the public.

References

1. Lam AC, Lam ST, Lai KK, Tong TM, Chau TC. High rate of detection of subtelomeric aberration by using combined MLPA and subtelomeric FISH approach in patients with moderate to severe mental retardation. Clin Biochem 2006 Mar;39(3):196-202. Epub 2006 Feb 23.
2. Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nature Genet 23: 185-188, 1999.
3. Wan M, Lee SSJ, Zhang X, Houwink-Manville I, Song HR, Amir RE, Budden S, Naidu S, Pereira JLP, Lo IFM, Zoghbi HY, Schanen NC, Francke U. Rett syndrome and beyond: recurrent spontaneous and familial MECP2 mutations at CpG hotspots. Am J Hum Genet 65: 1520-1529, 1999.
4. Lam CW, Yeung WL, Ko CH, Poon PMK, Tong SF, Chan KY, Lo IFM, Chan LYS, Hui J, Wong V, Pang CP, Lo YMD, Fok TF. Spectrum of mutations in the MECP2 gene in patients with infantile autism and Rett syndrome. J Med Genet 37: E41, 2000.
5. Yam WK, Wu NS, Lo IF, Ko CH, Yeung WL, Lam ST. Dentatorubral-pallidoluysian atrophy in two Chinese families in Hong Kong. Hong Kong Med J 2004 Feb;10(1):53-6.
6. Or SF, Tong MF, Lo FM, Law CW, Miu TY, Trochet D, Lam TS. PHOX2B mutations in three Chinese patients with congenital central hypoventilation syndrome. Chin Med J (Engl) 2006 Oct 20;119(20):1749-52.

Forthcoming Scientific Activity

Institute of Biomedical Science, HK Branch
Hong Kong Society of Cytogenetics
Hong Kong Society of Medical Genetics

A Joint Seminar

On

"MARKER" - CHROMOSOMES

Will be delivered by

Prof. Konstantin Miller

Head of the Clinical Cytogenetic Laboratories
Institute of Human Genetics
Hannover Medical School
Germany

Date : 4 February 2009 (Wednesday)
Time: 7:00 – 8:00 PM
Venue: The Federation of Medical Societies of Hong Kong
Duke of Windsor Social Service Building,
4/F, 15 Hennessy Road, Wanchai, Hong Kong

MLT Board CPD Code: 12095111 Awarding 1 CPD Point

ALL ARE WELCOME