NEWSLETTER OF THE HONG KONG COLLEGE OF PATHOLOGISTS

PATHOLOGUE

The Hong Kong College of Pathologists, Incorporated in Hong Kong with Limited Liability

THE HONG KONG COLLEGE OF PATHOLOGISTS
SCIENTIA ILLUMINAT MEDICINAM
香港病理學專科學院

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Message from the President

I have been asked a few times about my plan since I took office last November. Though I have some ideas about the work, I must admit I have little time to set up any schedule. Perhaps this gives me a chance to write up some thoughts.

Over the past few years since I joined the College Council, there were major changes. We have a full-time College Secretary who helps to tidy up bits and pieces in our Chamber, including taking Council minutes, managing daily operation of the College, and assistance in CME/CPD. At present, Adrienne plays a crucial role in communication among Fellows, Councillors and the Academy. We discussed and implemented changes in standardizing score in examinations, examination formats in specialties, training requirements (such as in case of long sick leave, autopsy numbers), appeal mechanism, etc. All of these require the work of a team, not individuals, who share the view to better the College and our profession.

It has always been in my mind to recruit younger Fellows to participate in the work of the College. There are many new faces that I know little of other than during their rotation to my department. In order to continue the directive of training future specialists, we need to have new trainers and examiners who are familiar with the work of the Council, the administrative architecture of the College, the role of different committees, and our examination system. Though these are documented in our College Handbook, many Fellows are not familiar with the practical details. It is also important for us to have new ideas and criticism from those who went through the Fellowship Assessment not too long ago.

The general public has little knowledge on the work of pathologists – other than autopsy and working in laboratories. Through an opportunity of the Academy to promote public understanding on medical science this year, we are moving forward to meet the public. Having completed three one-hour live broadcast programmes on RTHK ("Hour of the Hong Kong College of Pathologists") in January and February, we look forward to involvement in columns of newspaper and television later this year to promulgate our work.

Scientists working in our laboratories contribute constantly to our service. I would like to establish a better link between them and the College. I understand the Australasian College is trying to do similarly; and shall explore on this in future.

The next ILCP (International Liaison Committee of Presidents) meeting will take place in Hong Kong in September. This yearly meeting of Presidents from major Colleges of Pathologists over the world provides a platform for discussion on the professional practice in different places, as well as future directions and our role. As host to this meeting, I solicit assistance from past presidents as well as the Council to organize and chair the meeting. It is a great opportunity to review our goal and practice. I also hope this will put us in an updated position with practices from our overseas colleagues.

Finally, I welcome your thoughts and comments, and am always available via the internet (suenwm@ha.org.hk).

Dr. Michael SUEN, the President

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*(**Please send comments to:***
Dr. CHAN Chak Lam Alexander (Chief Editor),
c/o the Department of Pathology, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, H.K.
***E-mail:** chancl@ha.org.hk*
***Fax:** 2385 2455)*

THE HONG KONG COLLEGE OF PATHOLOGISTS:

TOPICAL UPDATE

Volume 4, Issue 2 August 2009

The Hong Kong College of Pathologists, Incorporated in Hong Kong with Limited Liability

Editorial note: *Globin disorder is the commonest monogenic disorder and a major public health issue not only in high prevalence areas but worldwide, due to immigration. Genetic study is the cornerstone of prenatal diagnosis in disease prevention. It is also an indispensible supplement to conventional haemoglobin analysis in the diagnosis of complicated cases. Knowledge of the genotype allows the clinician to predict disease phenotype. In this article, Dr Jason So has provided a comprehensive account of the genetic approach to the diagnosis of globin disorders, especially highlighting issues of local relevance. We welcome any feedback or suggestions. Please direct them to Dr. Edmond Ma (e-mail: eskma@hksh.com) of Education Committee, the Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individuals, and are not necessarily those of the Hong Kong College of Pathologists.*

Genetic Diagnosis of Globin Gene Disorders

SO, Jason CC
Associate Professor, Division of Haematology, Department of Pathology, The University of Hong Kong, Queen Mary Hospital

Introduction

Globin gene disorders as a whole are the commonest group of monogenic disease in the world. In Southern China and Southeast Asia, alpha and beta thalassaemias, as well as specific types of haemoglobin (Hb) variants such as Hb E, are prevalent. Most people who have inherited these mutated globin genes are asymptomatic carriers. The number of severely affected patients is relatively small in developed regions where comprehensive antenatal screening and prenatal diagnosis programmes are in place. This is not the situation in less developed countries where the clinical, economical and social load of globin gene disorders is still heavily felt.

Phenotypic Diagnosis of Globin Gene Disorders

The clinical and haematological manifestations of different forms of thalassaemias are well known. The approach to phenotypic diagnosis is largely standardised among haematology laboratories. Complete blood counting reveals the degree of anaemia. A low mean corpuscular volume (MCV) of red cells serves as an important screening parameter for further testing. Quantitation of Hb A2 and F is performed for diagnosis of beta thalassaemia, delta-beta thalassaemia and hereditary persistence of foetal haemoglobin (HPFH). Demonstration of excess beta globin chains (Hb H) indicates alpha thalassaemia. When a Hb variant is suspected, its electrophoretic mobility is assessed and compared with thalassaemia known variants. The advent of technological advances, including sophisticated blood cell analysers, automated high performance liquid chromatography (HPLC), capillary electrophoresis and antibody-based assays has made the analysis of Hb quicker, more accurate and precise. In most cases, the diagnosis of thalassaemias and common Hb variants is straight forward.

Problems with Phenotypic Diagnosis

In certain situations, however, phenotypic tests are inadequate. Problems arise when tests results do not conform to a typical pattern for thalassaemia, when family study results appear discordant or when a Hb variant is suspected but its identity is not apparent on electrophoresis. Under these circumstances globin genotyping can reveal the nature of globin mutation(s) in the patient. Phenotypic testing is also inapplicable in prenatal diagnosis due to different developmental stages of globin production between embryonic, foetal and postnatal period. Moreover, foetal cells and nucleic acids are the usual specimens for prenatal analysis instead of foetal red cells. Haemoglobin study is simply impossible. Genetic testing is the only way to provide a diagnosis.

Globin genotyping as a clinical service has been available in Hong Kong for more than twenty years. To date this service encompasses patient diagnosis, family study, prenatal testing and pre-implantation genetic diagnosis.

Globin genotyping can reveal the nature of globin mutation(s) in atypical cases of thalassaemia. It is also the only method for prenatal testing.

Atypical Phenotypes in Thalassaemia

When the phenotype of a patient does not fit into any typical form of thalassaemia or haemoglobinopathy, one has to consider the co-existence of multiple globin mutations or other inherited or even acquired red cell disorders. In populations where mutations in different globin genes are found, such genetic interactions are to be expected. These interactions may alter the Hb composition and the degree of anaemia, thereby masking the true nature of the underlying globin disorder(s). Although family study may provide clues as to the number and nature of globin gene defect in an index patient, it will not be helpful if any of the globin gene defects is phenotypically silent. Apart from interaction between different globin gene mutations, atypical thalassaemic phenotypes can also be due to unusual globin gene mutations. Some typical examples of atypical phenotypes are shown in Table 1. Globin genotyping is helpful in making a correct diagnosis in these cases.

Table 1. Examples of globin gene interactions leading to atypical phenotypes

Atypical phenotype	Possible cause due to genetic interaction	Possible cause due to unusual globin mutation
Beta thalassaemia trait with markedly raised Hb F	Heterozygous beta thalassaemia mutation + HPFH	Some deletional beta thalassaemias or promoter mutation of beta globin gene
Beta thalassaemia trait with near normal MCV	Heterozygous beta thalassaemia mutation + masked single or two alpha globin gene deletion	Very mild beta thalassaemia mutation
Beta thalassaemia trait with significant anaemia	Heterozygous beta thalassaemia mutation + silent triplicated alpha globin gene configuration	Dominant beta thalassaemia
Hb E trait with low percentage of variant	Heterozygous Hb E mutation + alpha thalassaemia	Anti-Lepore Hong Kong (beta-delta fusion gene) [1]
Thalassaemic red cell indices with reduced Hb A2	Heterozygous beta thalassaemia mutation + delta thalassaemia mutation	Delta-beta thalassaemia
Double heterozygous alpha and beta thalassaemia trait with significant anaemia	Heterozygous beta thalassaemia mutation + masked Hb H disease	

Uncommon Haemoglobin Variants

Haemoglobin variants that are relatively common in a population can usually be diagnosed with confidence from characteristic red cell indices, HPLC retention time and electrophoretic mobility. However, identification of uncommon variants can be problematic. This is particularly true for unstable Hbs and Hbs with altered oxygen affinity. They former can be too unstable for electrophoretic analysis and the latter may not show abnormal mobility on routine electrophoresis. Even in cases demonstrating an abnormal electrophoretic pattern similar to reported rare variants, its low prevalence in the population will still mean a very low positive predictive value. Mutation analysis is the only way to ensure diagnostic certainty in these cases.

Common Globin Gene Defects in Chinese

Globin mutations are very heterogeneous. To date, there are over 70 alpha and around 240 beta thalassaemia mutations reported [2]. The number of haemoglobin variants is even greater, with around 360 and 530 variants deposited in public databases for alpha and beta chain, respectively [2]. They are jointed by less common globin mutations, including delta-beta thalassaemias, HPFH, fusion mutants, delta thalassaemias and others. In any population, however, only a relatively small number of mutations account for most globin disorders. Therefore, a cost-effective and efficient genetic diagnostic service requires knowledge of the types and prevalence of different mutations in a population. A large population study has established the high prevalence of both alpha and beta thalassaemia carriage and the dominant mutation types in Hong Kong Chinese [3]. Our database is strengthened by cumulative experience from clinical service and research in this field. This information is invaluable in guiding the laboratory approach of mutation detection and our interpretation of test results.

According to this large population screening study, alpha and beta thalassaemia carriage in Hong Kong Chinese is 5% and 3.1%, respectively. Eighty-seven percent of alpha thalassaemia mutations is due to a two-alpha-globin gene deletion of the Southeast Asian type ($--^{SEA}$). Single alpha-globin gene deletion of 3.7 kb ($-\alpha^{3.7}$, 6%) and 4.2 kb ($-\alpha^{4.2}$, 3%) account for most of the remaining. Non-deletional alpha globin gene mutations are very uncommon. Notable examples found in Chinese are Hb Constant Spring, Hb Quong Sze, codon 30 (△GAG) deletion and Hb Q-Thailand. On the contrary, beta thalassaemias are mostly point mutations or small insertion/deletion in the beta globin gene. Four mutations account for 93% of all defects detected in a large cohort of over 200 Chinese beta thalassaemia trait subjects - codons 41-42 (-CTTT), 46%; IVSII-654 (C→T), 28%; nt -28 (A→G), 13% and codon 17 (A→T), 6% [author's unpublished data].

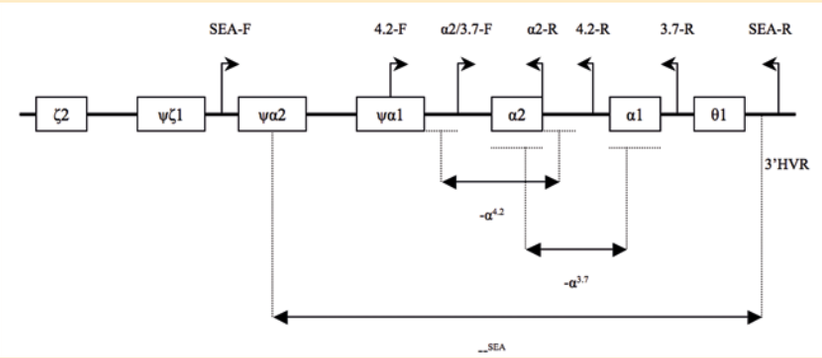
A cost-effective and efficient genetic diagnostic service requires knowledge of the types and prevalence of different mutations in a population.

Approach to Globin Genotyping

a) *Alpha globin genotyping*

As the precise extent of deletions for the common alpha thalassaemias are known, multiplex gap polymerase chain reaction (PCR) using primer pairs flanking these deletions is a fast and simple way for their detection (Figure 1). Presence of PCR products of expected sizes on post-PCR gel electrophoresis indicates presence of the specific deletions (Figure 2). Simultaneous detection of the more common non-deletional alpha globin gene mutations can be done using specifically designed mutation-specific PCR primers in a multiplex amplification refractory mutation system (ARMS). Again the presence of PCR products of expected sizes indicates presence of the specific mutations (Figure 3). These simple techniques have proven to be very effective in alpha globin genotyping in a clinical setting [4]. Rarer point mutations are readily detected by direct nucleotide sequencing, a technique which is fully automated and widely available in clinical molecular laboratories. The relatively small size of all globin genes (~2 kb) renders them particularly amenable to direct sequencing.

Figure 1. Forward and reverse gap PCR primers for detection of common alpha globin gene deletions

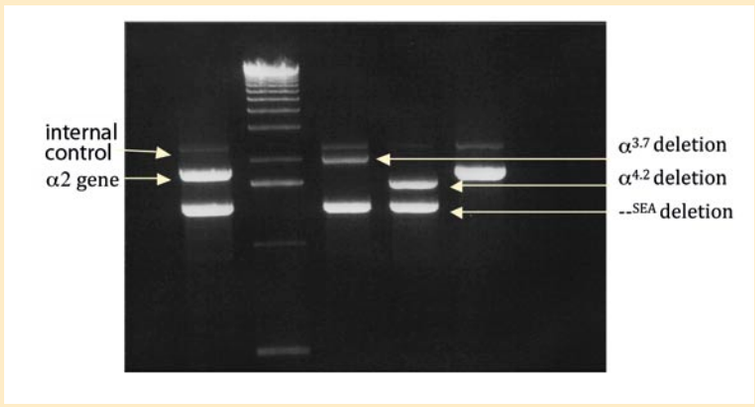


b) *Beta globin genotyping*

The same technique of multiplex ARMS can be applied to detect the common beta globin gene point mutations. Depending on the availability of expertise and specific instruments, a multitude of other molecular techniques are also used. These include heteroduplex detection, microarray and mini-sequencing followed by denaturing high performance liquid chromatography detection. Direct nucleotide sequencing is used to screen for uncommon mutations.

In the prenatal diagnosis and pre-implantation genetic diagnosis setting where foetal DNA in maternal plasma and blastomeres are studied, more sensitive techniques such as quantitative PCR and single cell PCR protocol with or without whole genome amplification are required.

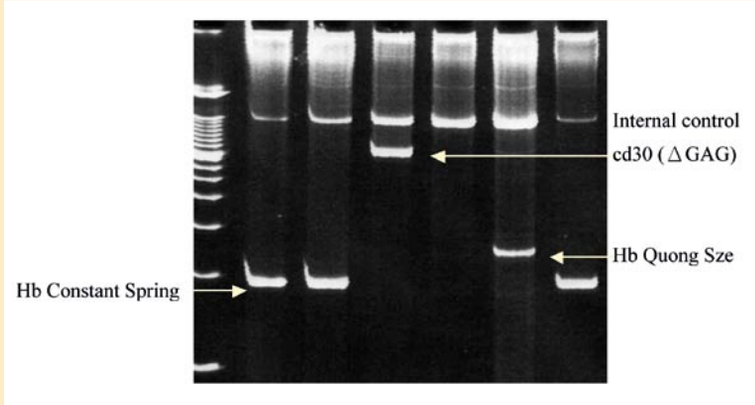
Figure 2. Electrophoretic results of multiplex gap PCR for three common alpha thalassaemia deletions



c) *Detection of uncommon deletions in globin genes*

Alpha globin gene deletions other than (--^{SEA}), (-$\alpha^{3.7}$) and (-$\alpha^{4.2}$) and deletion in beta globin gene cluster are rarely reported in Chinese. Deletions of greater than 1 kb in the beta globin gene cluster are reported in deletional HPFH and most delta-beta thalassaemias but are distinctly uncommon in β thalassaemias. Screening for larger deletions is technically difficult. Routine PCR-based techniques target only known deletions, while direct nucleotide sequencing of promotors, exons and exon-intron junctions is not helpful in this setting as a normal allele is present. Deletions can be screened by Southern blotting, array comparative genomic hybridization, quantitative PCR, fluorescence in-situ hybridization with tiling probes and conventional cytogenetics. However, these techniques all have disadvantages of low resolution, high cost, poor throughput, or complex test design and data readout. Because of these limitations, the prevalence and nature of beta globin gene cluster deletions in many populations remains uncharacterised. This hinders the development of a comprehensive diagnostic algorithm and the provision of genetic counselling and prenatal diagnosis.

Figure 3. Electrophoretic results of multiplex ARMS for three non-deletional alpha globin gene mutations



Multiplex ligation-dependent probe amplification (MLPA) is a recently described method that can detect mid-size deletions down to a few hundred bases or single exon level [5]. A series of probes are designed that recognise target sequences along a genetic region of interest. Each probe consists of two separate oligonucleotides that bind adjacent to each other at their target sequence. In this closely apposed position a ligation reaction takes place to generate an intact probe. All probes have the same primer recognition sites at their ends so intact probes can be amplified in a PCR using one single set of labelled primers. A stuffer sequence of a different length is inserted into each probe at synthesis. Amplification products from different probes therefore differ in size, which can be separated and recognised after capillary electrophoresis in a standard sequencer. The peak height/area of a probe represents the amount of amplification product, which is in turn proportional to the copy number of target sequence recognised by the probe in the sample. This technique is fast and reliable. It can be applied to many hereditary and acquired diseases caused by gene dosage changes.

A local study was performed to detected large deletion in the beta globin gene cluster using a commercial MLPA kit [6]. It contains 25 probes spanning a 68.7 kb region of the beta globin gene cluster from 5' of locus control region to 3' of the beta globin gene. One hundred and six Chinese patients suspected to harbour such deletions were screened. Seventeen heterozygous deletions were detected. Subsequent mapping revealed only 3 types of deletion, each with its distinct phenotypic features. The commonest one was Chinese $(^{A}\gamma\delta\beta)^{0}$ thalassaemia which showed a classical delta-beta thalassaemia phenotype in heterozygous state with low MCV, normal Hb A2 and raised Hb F of >10%. The next commonest was Southeast Asian (Vietnamese) deletion. Heterozygous carriers of this deletion had a hybrid phenotype of beta thalassaemia trait and HPFH (low MCV, raised Hb A2 but markedly raised Hb F to over 20%). The last one was Thai $(^{A}\gamma\delta\beta)^{0}$ thalassaemia (HPFH-6), a typical HPFH mutation leading to markedly raised Hb F. With this knowledge simple diagnostic tests based on gap PCR have been developed for their specific detection.

Multiplex ligation-dependent probe amplification can also be applied to detect uncommon alpha globin gene deletions using appropriate probes. It is noteworthy that the same setup is also able to detect gene amplification, including alpha globin gene triplication and segmental duplication of the whole alpha globin gene cluster [7]. Alpha globin gene amplification leads to alpha and beta globin chain imbalance. Its detection will provide a genetic explanation in some patients who present with beta thalassaemia intermedia phenotype with a single beta thalassaemia mutation found on genotyping.

The Problem of Raised Hb F

It has long been observed that the level of Hb F varies among normal individuals and patients with beta globin disorders. This variation is of considerable clinical importance in severe beta globin disorders such as beta thalassaemia major and sickle cell anaemia, where a raised Hb F can ameliorate disease severity through elevation of Hb level, reduction of alpha and beta globin imbalance in thalassaemia and interference of abnormal Hb polymerisation in sickle cell disease.

There are several genetic determinants within the beta globin gene cluster that are associated with increased Hb F in adult life. Large deletions (deletional HPFH) are very rare in Chinese [6]. The *Xmn1* promoter polymorphism at nt – 158 (C→T) of the $^{G}\gamma$-globin gene is common in normal Chinese (19%) [8]. Although this polymorphism favours a higher Hb F response in severe beta globin disorders, it has little effect on Hb F level in normal or beta thalassaemia trait subjects. Gain of function gamma globin promoter mutations are associated with raised Hb F but data in Chinese is scarce [9]. Likewise, mutations in the 5' beta locus control region or the 3' HS-1 regulatory sequence may be important in controlling Hb F level. However, these regulatory regions are not the targets of most current diagnostic protocols. Therefore, little is known of the causes that lead to raised Hb F in many Chinese patients. An extensive sequencing project targeting at these regulatory sites in the beta globin gene cluster is underway in the author's laboratory to determine their roles in HPFH in Chinese.

There are also genetic determinants responsible for enhanced Hb F output unlinked to the beta globin gene cluster. A genome-wide single nucleotide polymorphism (SNP) association study using over 300,000 markers showed that chromosome regions 6q23 and 2p15 are quantitative trait loci influencing Hb F production in normal Caucasians [10]. These findings have been subsequently validated in Chinese with beta thalassaemia trait, Sardinians with beta thalassemia and African Americans with sickle cell disease [8, 11, 12]. Data are coming out to indicate that either the gene product from these loci (*BCL11A* at 2p15) is directly implicated in developmental control of Hb F expression [13] or the genetic region (*HBS1L-MYB* intergenic region at 6q23) has potential erythroid-specific regulatory roles similar to the beta locus control region at the beta globin gene cluster [14]. An association of these SNPs with Hb F

level and disease severity in beta thalassaemia [15] and with Hb F level and pain crisis in patients with sickle cell disease have been demonstrated by clinical correlation studies [16]. If these findings can be validated by further clinical studies, SNP genotyping will certainly be incorporated into future diagnostic panel for better prediction of disease severity in patients who have inherited severe globin gene mutations.

Conclusion

Genetic diagnosis of globin gene disorders has become widely available in many parts of the world. It provides a definitive diagnosis when phenotyping results are unusual, complicated or unavailable. A cost-effective service requires knowledge of globin gene mutations present in the tested population. Further studies in the genetics of globin mutation and regulation will certainly enhance our ability to diagnose globin gene disorders and predict their severity.

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Out of the Whitecoat:

Living in the 'Second World' through Writing

Dr. Gavin CHAN,
Department of Pathology,
Queen Mary Hospital

▲ *Dr. Gavin Chan (first from left) pictured during a book prize presentation ceremony, organized by the Hong Kong Education City.*

If the world is where we experience reality, the second world is a virtual one which you find in arts, music, novels or movies. I am blessed that I can enter into my 'second world' through writing.

Writing has become part of my life since my junior secondary school. Because of the encouragement from my Chinese Language teacher, I started to contribute to newspapers and magazines, and participated in essay competitions as well. It opened a magic door for me – I entered into a fantasyland interacting with various figures in the stories. How wonderful if you can explore a fascinating world created by yourself! As Alice in Wonderland I enjoy the adventures of this second world, and through this telescope I learn to see the reality in different perspectives. During writing I find my retreat from the stress and discouragements of the daily life.

Writing itself is a lonely path. You work on a story by yourself. However it is so amazing when one day you receive feedbacks, realizing that there are readers getting connected with you because of your books. These readers from different places, of different age and in different events of life pick up your works. They start to read, entering into your virtual world and sharing your thoughts. It will be a most gratifying experience if anyone is moved and influenced by your stories.

Life is full of possibilities. It is beyond my imagination that I can write books for teenagers when I was still young, thanks to my Chinese Language teacher, my many supporting friends and readers. These books are gifts from God witnessing my thoughts, my growth and my perspectives in life. Writing is not an easy path, but a very rewarding input of my life.

(Editor's note: Dr. Gavin Chan is the writer of 12 books outside the field of pathology. His latest work, entitled 嘉薰醫生7移兇, published by 突破出版社 (ISBN:978-962-8996-52-0), is currently available in various major bookstores. He is under the pseudonym 陳嘉薰.)

▲ *Dr. Gavin Chan speaking during a book prize presentation ceremony co-organized by the Hong Kong Public Libraries, the Hong Kong Professional Teachers Association and the Radio Television Hong Kong.*

THE HONG KONG COLLEGE OF PATHOLOGISTS:

TOPICAL UPDATE

Editorial note:

Family history has long been known to be an important risk factor of breast cancer. In this issue of Topical Update, Dr. Ui Soon Khoo gives us an update on the two major susceptibility genes associated with this disease, and discusses on the practical aspects. We welcome any feedback or suggestions. Please direct them to Dr. Polly Lam (e-mail: lamwy@ha.org.hk) of Education Committee, the Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individuals, and are not necessarily those of the Hong Kong College of Pathologists.

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The Hong Kong College of Pathologists, Incorporated in Hong Kong with Limited Liability

Hereditary Breast and Ovarian Cancer – the *BRCA1* and *BRCA2* genes

KHOO, Ui Soon
Professor, Department of Pathology,
The University of Hong Kong,
Queen Mary Hospital

Background

Breast cancer is the leading female cancer in Hong Kong. Now at 52.1 per 100,000 (Hong Kong Cancer Registry, 2008) its incidence has been steadily rising over the last few decades, and is the highest reported in Asian regions. There are two major breast and ovarian susceptibility genes, *BRCA1* and *BRCA2*. About 30-70% of patients with hereditary breast/ovarian cancer and about 5-10% of all breast and/or ovarian cancer cases harbor a germline mutation in these genes[1]. The defective gene is inherited in autosomal dominance pattern. Individuals carrying a mutation in the *BRCA1* or *BRCA2* genes have a 85% lifetime risk of breast cancer, and a lifetime risk for ovarian, fallopian tube or primary peritoneal cancer that ranges from 35-60% for *BRCA1* and 10-27% for *BRCA2*[2].

BRCA1 and BRCA2 mutations increase susceptibility to breast and other cancers.

BRCA mutation carriers tend to develop breast cancer at a young age, may have bilateral breast cancer or have a personal history of both breast and ovarian cancer. There is also an increased risk for prostate and pancreatic cancer as well as male breast cancer in *BRCA2* mutation carriers. Other features of increased likelihood of hereditary susceptibility include the presence of two or more individuals in the family with breast cancer, the presence of both breast and ovarian cancer in the family, breast cancer in one or more male family members, and one or more members with two primary cancers. To estimate the probability of heritable genetic mutation in a family, one has to take into account the age of onset of breast cancer, the number of affected relatives, biological relationships of affected relatives, the ratio of affected to unaffected relatives as well as the presence/absence of associated malignancies and ethnic background.

Clinical and pathologic features

Gene expression microarray profiling of breast cancer has identified a distinct subtype called basal-like cancer which is characterized by an expression signature that is similar to basal/myoepithelial cells of the breast[3]. Basal-like cancer is the subtype observed in *BRCA1*-related breast cancers, representing 80-90% of breast cancers arising in *BRCA1* mutation carriers and about 15% of sporadic breast cancers associated with reduced *BRCA1* mRNA expression[4].

80-90% of breast cancers arising in BRCA1 mutation carriers are of basal-like cancer subtype, which is associated with poorer clinical outcome.

Although there is as yet no internationally accepted definition for basal-like cancers, basal cytokeratin markers, singly or in combination, such as CK5/6, CK14, and CK17 by immunohistochemistry have been used to identify basal phenotype[5]. These cancers are usually of high histological grade, with features of medullary-like cancers. Most metaplastic cancers also display basal-like phenotype. Basal-like cancers typically do not express hormone receptors or HER-2 (triple negative phenotype). Ductal carcinoma in-situ (DCIS) with basal-like phenotype has been reported, suggested to be the precursor lesion to invasive basal-like cancer.

TP53 mutations have been found at high frequency in breast cancers with germ-line *BRCA1* mutations (97%) as well as in sporadic basal-like breast carcinomas (92%) independent of *BRCA1* status[6]. DCIS with basal-like phenotype was also found strongly associated with p53 accumulation.

Patients with basal-like cancer are usually younger and associated with poorer clinical outcome with development of metastases within the first 5 years, shorter survival and relatively high mortality rate. They are more strongly associated with family history, more frequently "interval cancers" (i.e. cancers arising between annual mammograms), and with specific mammographic features demonstrating rapid progression. They also show a specific pattern of distant metastases to brain and lung.

A significant proportion of tubular and lobular carcinoma occur in BRCA2 related breast cancers.

BRCA2 related breast cancers contain a significant proportion of tubular and lobular carcinoma not commonly found in *BRCA1* mutation carriers. These cancers tend to be of medium to high grade, more often estrogen receptor positive and more commonly associated with ductal carcinoma in-situ. *BRCA1* and *BRCA2* related ovarian carriers tend to be advanced stage high-grade serous carcinomas.

Genetic testing

Genetic testing aims at identifying the mutation that predisposes the individual or the family to cancer. In families where germ-line mutations in *BRCA1* and *BRCA2* have been identified, estimates for breast cancer risk can be made with greater accuracy. Both *BRCA* genes are very large genes. Several hundred different mutations have been identified but only a few of these mutations have been found repeatedly in unrelated families.

Identification of a specific mutation in a family, therefore, is a complex process and must usually begin by testing a blood sample from a family member who has had breast or ovarian cancer, called "index" testing. If a specific mutation is identified through index testing, then "carrier" testing is possible for family members who wish to learn whether or not they have inherited that mutation and the associated cancer risks.

Identification of a specific mutation in a family is a complex process. Genetic testing includes "index" and "carrier" testing.

A negative result from families where no mutation has been identified cannot exclude the possibility that other genes, as yet unknown, may be involved in that family.

Although basal-like breast cancer appears associated with *BRCA1* mutations, there is as yet no recommendation that genetic test be carried out on these cases. The recommendation is against routine referral for genetic counseling and *BRCA* testing for women without specific family history patterns.

The benefits of routine screening for mutations have to be balanced with adverse ethical, legal and social consequences.

Testing for mutations of inherited cancer susceptibility genes raises many issues for the individual and family, with medical, psychological, and social implications. Hence the benefits of routine screening for mutations have to be balanced with adverse ethical, legal and social consequences that could result from this. Individuals are strongly recommended to receive genetic counseling prior to testing. Blood samples for genetic testing are accepted only after informed consent has been given.

Local findings

The frequency of *BRCA* mutations and the magnitude of cancer risks vary across different populations[7]. For familial breast/ovarian cancer families, the prevalence of *BRCA1* and *BRCA2* mutations in Caucasians and African Americans (42.2%, 27.9% respectively) is much higher compared with Asians (5-20%)[8].

The frequency of BRCA mutations varies across different populations.

On the other hand, for sporadic ovarian cancer, the 11.3% incidence of *BRCA1* mutations in Chinese is one of the highest reported worldwide[9]. Founder mutations, presumed to have arisen in a single ancestor of a specific ethnic group many generations ago, have been identified in many ethnic groups including the Chinese population[10].

The majority of germline mutations in the *BRCA* genes lead to truncated protein which disrupts the function of the encoded proteins. Somatic mutations in *BRCA1* and *BRCA2* are rare[11]. Reduced expression of BRCA1 protein and promoter hypermethylation have been demonstrated in both breast and ovarian cancer. On the other hand, increased BRCA2 protein expression with promoter hypomethylation has been found in sporadic ovarian cancer[12].

Interventions offered

The interventions that can be offered to women with *BRCA1* or *BRCA2* mutation carriers include intensive screening, chemoprevention, prophylactic mastectomy and/or oophorectomy.There remains insufficient evidence on the effectiveness of intensive surveillance with mammography or the benefits of chemoprevention with selective estrogen receptor modulators in improving health outcomes for women with *BRCA1* or *BRCA2* mutations[13].Although the use of MRI, ultrasonography, and mammography in combination has a high sensitivity of 95%, the effect of this increased detection on morbidity and mortality remains unclear[14]. There is however fair evidence that prophylactic surgery for these women significantly decreases the incidence of breast and ovarian cancer[15]. Oophorectomy reduced ovarian cancer risk by 85-100% and reduced breast cancer risk by 53-68%.

Origin of high-grade serous malignancies

The acceptance of prophylactic oophorectomy as the treatment strategy for women with *BRCA* mutations and at high risk for the development of ovarian carcinoma led to the recognition of clinically occult tubal carcinomas and serous tubal intraepithelial carcinoma (STIC) originating in the distal fallopian tube, particularly the fimbriae, making an important contribution to determining the ultimate site of origin of pelvic high-grade serous malignancy[16].

Clinically occult tubal carcinomas and serous tubal intraepithelial carcinoma originating in the distal fallopian tube have been recognized.

Detailed examination of prophylactic salpingo-oophorectomies has revealed the presence of serous tubal intraepithelial carcinoma (STIC) in approximately 5% of cases, with about 80% of these early carcinomas originating in the distal fallopian tube, particularly the fimbrae[17].Tumors arising from this region are extremely small and previously often went unrecognized, emphasizing the importance of complete histologic sampling of fallopian tubes and ovaries in all salpingo-oophorectomy specimens. Detailed routine pathological examination of the fimbria following the protocol "Sectioning and Extensively Examining the FIMbrial end" (SEE-FIM)[17] is now the recommended method of handling prophylactic salpingo-oophorectomy specimens for *BRCA* mutation carriers (Table 1)[18] as the outcome and management of these individuals would depend on the status of her fallopian tubes.

The importance of complete histologic sampling of fallopian tubes and ovaries in all salpingo-oophorectomy specimens from these patients has been demonstrated.

The American College of Obstetricians and Gynecologists now recommend that women with *BRCA1* or *BRCA2* mutations, aged above 40 years or when childbearing is complete, should be offered risk-reducing bilateral salpingo-oophorectomy with microscopic examination of ovaries and fallopian tubes for occult cancer and thorough visualization of the peritoneal surfaces with pelvic washings.

Table 1. The SSS-FIM Protocol for examining the fallopian tubes of prophylactic salpingo-oophorectomy specimens.

1. Fix tubes and ovaries in formalin for 1-2 hours to reduce risk of exfoliation during sectioning. Submit the entire tube and ovary for histology in the following manner:
2. Amputate the distal 2 cm of tube, which is to be sectioned sagitally into 4 sections.
3. Serially section the remaining portion of tubes at 2 to 3 mm intervals.
4. Serially section the ovaries at 2 to 3 mm intervals.
5. Perform p53 and MIB-1 immunostaining for areas showing cytological atypia and loss of cilia.

Tubal carcinomas originating in the distal fallopian tube have since been identified irrespective of *BRCA* status and have also been shown to be the source of one half of primary peritoneal serous carcinomas. STICs have significant cytological atypia, absence of cilia, are highly proliferative, and in 80% of cases highlighted by nuclear accumulation of mutated p53 protein, with *TP53* mutations found in almost all cases.

p53 immunostaining has also revealed "p53 signatures", probably the earliest lesion in a continuum of tubal serous carcinogenic sequence.

p53 immunostaining has also revealed the presence of small linear p53 positive foci in non-neoplastic mucosa of the distal fallopian tube, called "p53 signatures". Evidence suggests that these "p53 signatures" are a precursor of pelvic serous carcinoma, and probably the earliest lesion in a continuum of tubal serous carcinogenic sequence. These are now shown to be a relatively common finding in the fallopian tube, its prevalence in *BRCA* mutation carriers similar to that in women with unknown *BRCA* status. Such findings have important clinical implications which include recommending salpingectomy at the time of simple hysterectomy.

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The 18th Annual General Meeting 2009 and the 18th T.B. Teoh Foundation Lecture

▲ *The 18th AGM. From left to right: Dr. Raymond Yung , Dr. Michael Chan, Dr. WF Ng, Dr. Cindy Tse and Dr. Michael Suen.*

The 18th Annual General Meeting (AGM) was held after the 5th Trainee Presentation Session on 7th November, 2009. Three new Council Members, Dr. CHAN Chak Lam Alexander, Dr. LO Yee Chi Janice and Dr. TANG Wai Lun, were elected. We would like to take this opportunity to thank the immediate past President Dr. NG Wing Fung, immediate past Council Members Dr. LEE Kam Cheong, Dr. LUK Wei Kwang and Prof. TO Ka Fai for their contribution to the College.

In the conferment ceremony, 1 Honorary Fellow, 5 Fellows and 12 Members were admitted to the College. The honourable guests included Prof. LIANG Hin Suen Raymond (President of the Hong Kong Academy of Medicine) and Dr. Hon. LEUNG Ka Lau (Member of the Legislative Council of Hong Kong, Medical Functional Constituency). College President Dr. SUEN Wang Ming Michael shared with the audience a personal story to highlight the importance of inter-disciplinary efforts in contributing to a healthy society.

The 18th T.B. Teoh Foundation Lecture was delivered by Prof. MAK Tak-Wah (Ontario Cancer Institute, Princess Margaret Hospital, Toronto, Canada). In the lecture "Cancer Metabolism: Back to the Future", Prof. Mak enlightened us on a tactic for combating cancer – shoot the carriage rather the horses. The subsequent College banquet dinner provided a relaxed environment for reunion and socializing for the guests, senior fellows and junior members.

We would like to thank Prof. CHIU Wai Kwun Rossa for being the Mistress of Ceremonies in the AGM. We thank Dr. Cycles SP POON, Dr. Amanda KAN, Dr. KH YIU, Dr. KF CHAN and Dr. Victor TANG for taking photos of the AGM, conferment ceremony, T.B. Teoh Foundation Lecture and banquet. We would also like to express our gratitude towards our College Secretary, Ms. Adrienne YUNG, as well as Ms. Maizie CHAN and Ms. Heidi CHU, for their continuous support in organizing the AGM.

Looking forward to seeing you all in the coming AGM!

▲ *The AGM went swiftly, then Dr. WF Ng relayed the presidency to Dr. Michael Suen.*

▶ *Prof. Tak W Mak was admitted as Honorary Fellow to the College.*

▶ *Forensic pathologists and anatomical pathologists are close siblings, in terms of examining gross organs and minute DNA molecules.*

▲ *The AGM provides a good chance for inter-hospital gathering.*

◀ *A great day to share with family.*

▼ *Dr. Michael Suen presented a souvenir to Dr. WF Ng for his invaluable contribution to the College.*

▲ *Congratulations to the young doctors!*

▲ *Let's get rejuvenated to tackle the swine flu challenge.*

▼ *Salute to Dr. Joanna Ho (front row, right 2nd), our highly respected mentor.*

▶ *Amiable smiles are everywhere.*

▼ *Thanks to Prof. Tak W Mak for the inspiring lecture.*

THE FIFTH TRAINEE PRESENTATION SESSION (2009)

The 5th Trainee Presentation Session was held before the 18th Annual General Meeting of the College on 7 November 2009. Five trainees participated in this year's session, including Dr. Emily HUNG, who delivered a baby on the morning of last year's Trainee Presentation Session day and thus could not make it to the event a year ago. This year, the five trainees from different specialties delivered presentations which were of very high standard on all aspects, including scientific content and presentation skills. The Question and Answer time was especially stimulating. We gratefully thank our panel of five judges from different specialties (Prof. Philip BEH, Dr. Eudora CHOW, Dr. Chloe MAK, Prof. TO Ka Fai and Dr. Raymond YUNG) for their time and generosity in sharing with the trainees suggestions for enhancement. The winner of the Best Presentation Prize this year is Dr. Emily HUNG from the Department of Chemical Pathology, Prince of Wales Hospital. Congratulations to Dr. HUNG, who despite not being able to attend the session last year, supported the event enthusiastically again this year. The prize included a plaque, a certificate of Best Presentation and HK$1,000. Each participant was also awarded a Certificate of Appreciation.

With the endorsement by the College and the Hong Kong Academy of Medicine on the requirement for all trainees registered on or after 16 October 2008 to make two presentations within their six years of recognized training (at least one of which must be at the Trainee Presentation Session or conferences organized by the College), we look forward to increasing participation in this meaningful activity. The next Trainee Presentation Session will again take place before the College Annual General Meeting in 2010. We appeal to all Fellows and trainees to mark your diaries and show your support for the event. The Education Committee also welcomes any suggestions for improvement: please direct them to the College Secretary (hkcpath@hkam.org.hk).

Dr. Janice LO
Education Committee

▲ *Group photo of judges, trainees and organizers.*

▶ *Dr. Emily HUNG receiving the prize from the Chairman of the Education Committee.*

Presence of donor-derived DNA and cells in the urine of sex-mismatched hematopoietic stem cell transplant (HSCT) recipients: implication to the transrenal hypothesis

HUNG ECW[1,2], SHING TKF[2], CHIM SSC[3], YEUNG P[2], CHAN RWY[4], CHIK KW[5], LEE V[5], LI CK[5], WONG SC[6], CHIU RWK[1,2], LO YMD[1,2]

[1]Li Ka Shing Institute of Health Sciences, Departments of [2]Chemical Pathology, [3]Obstetrics & Gynaecology, [4]Accident & Emergency, [5]Paediatrics, [6]Clinical Oncology, The Chinese University of Hong Kong, Prince of Wales Hospital

BACKGROUND: Transrenal DNA has been postulated to originate from the passage of cell-free plasma DNA through the kidney barrier. While this may provide an attractive, completely non-invasive source of nucleic acids for molecular diagnosis, its existence remains controversial.

METHODS: Donor-derived DNA in blood and urine samples were studied in 22 HSCT recipients by fluorescence *in situ* hybridization (FISH), PCR, mass spectrometry and immunofluorescent detection.

RESULTS: All subjects exhibited high amounts of donor-derived DNA in plasma. Male, donor-derived DNA was detected in cell-free urine supernatants (CUS) from all five sex-mismatched HSCT female recipients. Surprisingly, the amount of DNA in CUS had no correlation with the plasma value. DNA fragments over 350bp which were not detected in plasma were found in CUS. FISH analysis demonstrated donor-derived polymorphs in urine and, coincidentally, donor-derived cytokeratin-expressing epithelial cells in 3 out of 10 cases up to 14.2 years post-transplant.

CONCLUSION: This is the first demonstration of donor-derived DNA in HSCT recipients' urine. However, such DNA is shown to have substantial contribution from donor-derived cells, rather than from the transrenal passage of cell-free plasma DNA. The novel discovery of donor-derived cytokeratin-expressing epithelial cells raises interesting biological and therapeutic implications, e.g., the capacity of marrow stem cells as an extra-renal source for renal tubular regeneration.

Acknowledgement: This project is supported by an Earmarked Research Grant (CUHK4436/06M) from the Hong Kong Research Grants Council.

Experience on participation in the 5th Trainee Presentation Session by the winning trainee: Afterthoughts from Dr. Emily HUNG

It was an honour for me to be awarded the Best Presentation Award in the 5th Trainee Presentation Session. The project was accomplished with concerted efforts from different departments, namely, Chemical Pathology, Paediatrics, Obstetrics & Gynaecology, and Oncology from the Prince of Wales Hospital, and Pathology from the Queen Elizabeth Hospital, in particular, Ms. Elena LO and Ms. KWAN Man Yee from the Anatomical and Pathology Laboratory. I am deeply indebted to the leader of the project, Prof. Dennis LO, and the members of the team who have made this project a success. My participation in the trainee presentation session was to raise the awareness of the project findings amongst our colleagues, and to collect new ideas from the audience. This event is truly meaningful and enjoyable, and would not have been possible without Dr. Wei-Kwang LUK and Dr. Janice LO's excellent coordination. Last but not least, my heartfelt thanks go to Dr. Michael CHAN and Prof. Rossa CHIU, our trainers in PWH, for their generous time, patience and support.

Dr. Emily HUNG
Department of Chemical Pathology
Prince of Wales Hospital

THE MUSEUM IN THE MID-LEVELS

Situated on the slope of Sheung Wan, in the historic district of Tai Ping Shan where plague broke out over a century ago, the Hong Kong Museum of Medical Sciences (HKMMS) was opened in 1996. It is a unique institution that charts the development of medicine in Hong Kong. The Museum is housed in a declared monument, the Old Pathological Institute. It was originally named the Bacteriological Institute at the time of its opening in 1906, and is probably one of the most intact and original of Hong Kong's declared monuments and heritage buildings.

The Museum occupies over 3,000 square metres, comprising 11 exhibition galleries which present in a variety of ways to arouse interest and to help members of the community know more about health and disease, including the unique development of western and traditional Chinese medicine, past conquests of epidemics, medical advances of local importance as well as promotion of the vital message of how to stay healthy.

▲ *Laboratory for investigation of the plague bacillus.*

HERITAGE CONSERVATION

The Museum is a project of the HKMMS Society, a non-profit and non-government organisation. Together with friends and supporters, the HKMMS Society has developed and maintained the historic building and made it possible for the public to enjoy the building while learning about the development of medicine in the region. For their efforts in most-appropriately revitalising one of Hong Kong's rare declared monuments, the HKMMS Society was awarded in 2004 the Award of Merit in Heritage Preservation and Conservation.

▶ *Wooden table for immunization of cows with the vaccinia virus.*

▼ *Herbal garden in the Museum.*

HONG KONG MUSEUM OF MEDICAL SCIENCES
Address: 2 Caine Lane, Mid-Levels, Hong Kong
Tel: 2549 5123
Website: www.hkmms.org.hk
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Tue to Sat 10 am – 5 pm
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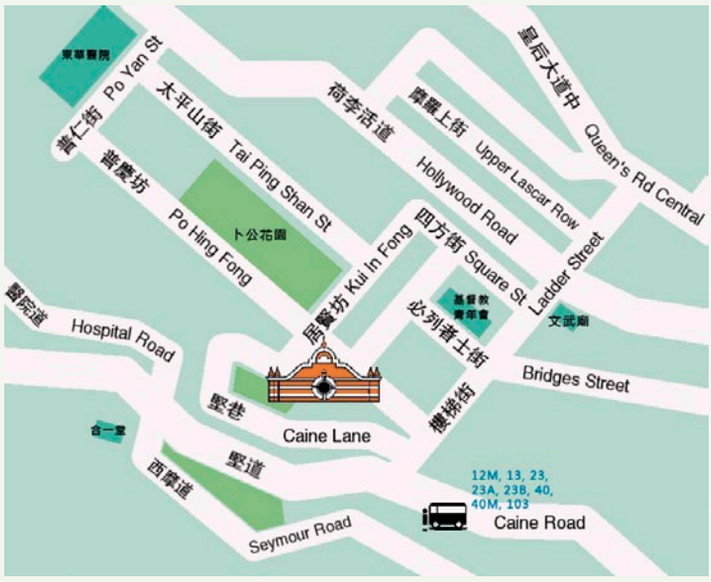

Route 1: By taxi / private vehicle
From Hollywood Road, turn right at Man Mo Temple into Square Street, pass Blake Garden and alight at the junction of Kui In Fong and Po Hing Fong. Walk up the stairs to Museum. Parking spaces with parking metres are available on Po Hing Fong.

Route 2: By bus or minibus
Take any bus or green minibus service running via Caine Road and alight at Ladder Street. Descend Ladder Street and turn left after the first flight of steps into Caine Lane. The Museum is down Caine Lane, on your right.
** From Central/ Wanchai to Caine Road (Buses: 3B, 12, 12M, 13, 23, 23A, 23B, 40, 40M, 103) (Green Minibuses: 8, 10, 10A, 11, 22, 28, 31)*
**From Pok Fu Lam to Caine Road (Buses: 40M, 103) (Green Minibuses: 8, 10, 10A, 11, 22, 28, 31)*

Route 3: By "Central – Mid-Levels Escalator"
Visitors can use the Mid-Levels Escalator from Central to Caine Road, and walk westwards along the pavement for around 10 minutes till you reach Ladder Street. Descend Ladder Street and turn left after the first flight of steps into Caine Lane. The Museum is down Caine Lane, on your right.

PLANNING A PARTY? LOOKING FOR A SPECIAL VENUE?

The Museum can offer the unique settings of a historical monument.

Purpose	Area	Charges
Seminars & Conferences	47 sq. m.	$350/hr during museum opening hours ; $500/hr during museum non-opening hours
Exhibition	47 sq. m.	$5,000 for 1 week ; $20,000 for 1 month ; $50,000 for 3 months
Private Party	50 sq. m.	$600/hr for Mon – Fri ; $900/hr for Sat - Sun
Personal Wedding Photos		$500

- Discount may be provided for charitable organizations and HKMMS Society members. For enquiries please contact Ms. Amelia CHIANG at 2549 5123.

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CALL FOR APPLICATION: CHAN WOON CHEUNG EDUCATION AND RESEARCH FUND IN PATHOLOGY

In 1991, friends, colleagues and former students of the late Dr. CHAN Woon Cheung endowed a fund in his memory to promote education, training and research in Pathology. This fund shall only be applied towards the promotion of education, training and research in Pathology, such as research grants for studies in Pathology, or grants to support training in Pathology, including passage fees and subsistence, where the training is conducted in Hong Kong or the applicant is currently working in Hong Kong. Local and overseas workers in Pathology, both members and non-members of the Hong Kong College of Pathologists, may apply for the grants for the purposes set out above.

For those who are interested, please download the application form from our College website (www.hkcpath.org) and return the completed application form to the Registrar. **The deadline for application submission is 31 May 2010.**

Visit our homepage at: www.hkcpath.org