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**Biography**

Dr THONG Meow Keong is a Professor of Paediatrics and Consultant Clinical Geneticist at the University of Malaya Medical Centre, Faculty of Medicine, University of Malaya. He is a board-certified clinical geneticist by the Human Genetics Society of Australasia.

He pioneered and established the first Genetics Clinic in 1995 and the Genetics & Metabolism Unit at the Department of Paediatrics, Faculty of Medicine, University of Malaya. He worked closely with the Ministry of Health Malaysia in developing the counselling module for thalassaemia and clinical practice guidelines on inherited disorders and was invited by the World Health Organization and March of Dimes to prepare a monograph on management of individuals with birth defects and haemoglobinopathies. He also contributed to the Oxford Monograph in Medical Genetics: Genomics and Health in the Developing World, published by the Oxford University Press in 2012

Dr Thong received numerous awards in the past 10 years. He was a Fulbright scholar and past winner of the 8<sup>th</sup> Royal College of Physicians of London and Academy of Medicine of Malaysia Annual Research Award, recipient of the Australia-Malaysia Fellowship in Research Excellence award by the Australia-Malaysia Institute, as well as Travel Award by the Asian Society for Pediatric Research, Japan. He and his team were gold medallist at the "Biotechnology Asia 2006" and 18<sup>th</sup> I.TEX Exhibition.

He has served for many administrative roles in University of Malaya. He was awarded the University of Malaya Distinguished Service awards. He was the Head, Department of Paediatrics, University of Malaya from 2009-2011. He is also an Associate Editor for two journals, reviewer for journal manuscripts and research grant applications as well as a theses examiner for national and international examinations.

Currently, he holds many leadership roles in medical associations. Dr Thong is the President of the Asia-Pacific Society of Human Genetics, Vice President of the Medical Genetics Society of Malaysia, Chairman of the Clinical Genetics subspecialty committee of the National Specialist Register Malaysia and President of the College of Paediatrics, Academy of Medicine of Malaysia.

Dr Thong's current research interests included rare disorders, preventive and curative strategies for genetic disorders, genetic counselling and inborn errors of metabolism. He has published over 60 peer-reviewed publications on genetic disorders that hitherto have not been documented in Malaysia, authored 4 books and 10 book chapters and presented in many national and international conferences. One of his most featured books includes "Rare Journeys of Love", entailing real-life stories of Malaysian patients and their families in coping and living with rare genetic conditions. His passion in improving the quality of life and care for these courageous young children has inspired many younger generation of clinicians and scientists.



# GENES, MEDICINE AND SOCIETY: FROM PAEDIATRICS TO GENETIC COUNSELLING AND BEYOND

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## **ABSTRACT:**

The story of Clinical Genetics is a relatively new one, first spearheaded by Paediatrics but increasingly, has taken root in all branches of medicine leading to 'Personalised Medicine'. There are expectations that this revolution in genetics will pave the way to genomic medicine and a cure for all inherited disorders. The development of the field of Clinical Genetics and Genetic Counselling in Malaysia is still in its infancy. Using evidence-based data on genetic disorders such as birth defects, inborn errors of metabolism, genetic syndromes, neurological disorders and hereditary cancers, that hitherto have not been well documented in Malaysia, this review article will focus on findings and issues that will present a unique insight and opportunity to understanding the complex genetic counselling issues related to Clinical Genetics in Malaysia.

**Keywords:** *Medical genetics, genetic counselling, developing country, genomics.*

## **INTRODUCTION**

The story of medical genetics is a relatively new one, emerging with the dawn of the 20<sup>th</sup> century leading to the successful elucidation of the DNA double helix structure by Watson and Crick about 60 years ago, and witnessing the successful completion of the Human Genome Project in 2003. It is not surprising that there are a lot of expectations that this revolution in genetics will pave the way to genomic medicine and to a cure for all inherited disorders (1).

### **New Genetics and Personal Genomics**

Since then, new information emerged on how individual genes, or groups of genes interacting together with external factors, increased our predisposition to certain diseases such as birth defects, cancers, coronary heart diseases, infertility and psychiatric illnesses. It is also expected that identification of 'good' genes may protect us from these diseases. Pharmacogenomics will lead to more targeted prescribing which is more effectively tailored to the needs of the individual. For example, the US Food and Drug Administration (FDA) released a warning to health professionals and patients that carbamazepine associated Stevens-Johnson syndrome may occur with the use of carbamazepine in patients positive for the *HLA-B\*1502* allele and recommended genetic

screening for patients of Asian ancestry before initiation of carbamazepine therapy (2). Genetic testing which has become faster and more accurate and cheaper and easily available to general practitioners may become an integral part of health care.. In short, genetics has been permeating all fields of medicine (3, 4).

The early perception that medical genetics was a specialty of minor practical relevance changed with the development of new diagnostic and therapeutic possibilities. Paediatrics had largely spearheaded the development of medical genetics. After the completion of the Human Genome Project, many researchers from various medical specialties turned their attention to investigating the role genes play in health and disease.

David Comings, editor of the American Journal of Human Genetics commented in 1980 on a then novel approach for mapping the human genome, "*Since the degree of departure from our previous approaches and the potential of this procedure are so great, one will not be guilty of hyperbole in calling it the 'New Genetics'*" (5). Sir David Weatherall in his book 'New Genetics and Clinical Practise 1982 edition' predicted how medical practices will change with new developments but he also lamented "very few genetic diseases can be treated effectively" (6). Fortunately, over the period of 30 years, much has changed. Without a doubt, the greatest advances in translational medicine

over the past 2 decades had been in the area of genetics and now genomics. The range of treatment options available to manage patients with genetic disorders ranged from genetic counselling to organ transplantation. These approaches paved the way for the next wave of advances made in genetic medicine – personalised medicine with the information gained from genomics research (7).

Like any medical conditions, the reduction of the impact of genetic diseases requires both curative and preventive approaches. Treatment of genetic disorders requires the characterisation of the mutations of the genetic diseases and the understanding of the pathophysiology of these changes. With these information made available and validated, effective treatments can be instituted. Therapeutic options include specific dietary manipulation for inborn errors of metabolism, drug therapy to augment gene function such as hydroxyurea in sickle cell anaemia, enzyme or protein replacement therapy and the replacement or removal of abnormal tissues. Recombinant DNA technology has enabled biosynthetic materials such as Factor VII, vaccines and insulin to be produced in large quantities. Stem cell transplantation is successfully used to cure a number of genetic disorders, such as  $\beta$ -thalassaemia major and childhood malignancy. With the curative options steadily increasing, the number of conditions treated in this manner has been increasing (8).

Somatic gene therapy was considered a promising curative option but had remained largely experimental due to a number of technical difficulties (9). The failure of gene therapy to deliver its earlier promise of cure had been due to a number of factors. Firstly, the number of protein variants outnumbers the number of coding genes - one gene may affect expression of many other genes, for example, in Duchenne muscular dystrophy, a dystrophin gene mutation downregulates 327 other genes but upregulates 77 genes. In an apparent successful gene therapy for severe combined immunodeficiency (SCID) patients, insertional mutagenesis caused activation of an adjacent oncogene, resulting the patients to die later from T-cell acute lymphoblastic leukaemia. Immunological reactions and toxicity continue to be a serious problem, and targeted delivery of the normal gene copy to all affected tissues, including brain and heart had largely been limited.

The failure of gene therapy has forced genetic research to re-focus on the basic issues – the multiple gene effects and the association of specific variations with clinical phenotypes. This has resulted in many new fields of research - epigenetics, micro ribonucleic acids (microRNAs), copy number variations (CNVs) and so on, and coupled with new technologies such as genome-wide association studies (GWAS), microarray analyses and low cost sequencing technology, personal genomics emerged (7).

Yet, the gap between these new discoveries and clinical utility remains huge. Emerging data from recent research showed the public perception towards non-specific genomics-informed personalised medicine has rather been muted. For the clinical genetics community, this

is not surprising. Personal genomics (PG) tests provide targeted genetic risk profiles for specific conditions. The tests may include studies on linked or causative single nucleotide polymorphisms, functional assays, and genome sequencing and the clinical utility and validity of PG must be validated before available for personalised medicine (10). Patients, families and society want to continue to be the stakeholders, and retaining ownership of their genetic heritage while obtaining accurate diagnosis for their ailments. Personalised treatment will need to combine the classical medicine - clinical history taking with detailed family medical history, careful physical examination and appropriate diagnostic tests, with genetic counselling and genetic tests, where applicable (8).

In the face of the above transformation, what directions should be taken by the healthcare system in a developing country such as Malaysia? How do low and middle-income countries benefit from this genomics revolution and personalised medicine in view of the high cost of technology? The World Health Organization advocated the role of medical genetics and genetic counselling in the control and prevention of non-communicable diseases such as genetic conditions and birth defects (3, 4). To start on this journey, each country will need to study the epidemiology of its inherited disorders and to under the genotype-phenotype of these conditions before medical intervention using these new developments can be instituted. The following are examples of research on birth defects and genetic conditions in Malaysia that led to new insights on conditions that hitherto not been well documented in Malaysia. This enabled preventive and curative options to be utilised to reduce the impact of genetic diseases (11, 12).

### ***From Paediatrics to Genetic Counselling and beyond***

A review of Malaysian health statistics showed the number cause of death in children less than 5 years of age is no longer malnutrition or infectious diseases – it is chromosomal disorders and congenital malformations. In addition, learning difficulties and mental handicap have emerged as pressing medical problems. Adult-onset genetic disorders such as hereditary cancers have become an important target for genetic counselling and early disease detection (13, 14).

It is well-known that prevention of genetic diseases may be achieved through empowering individuals with information on their genetic risks and enabling them to make informed choices about their reproductive options. Genetic counselling is non-directive. It is a process whereby counsellors inform patients about their genetic diseases; discuss whether an inherited disorder is a certainty or just a remote possibility for their future offspring; help families make informed decision about reproductive options; and help patients cope with their grief and finally accepting their conditions (15). Accurate genetic counselling requires population-based epidemiology data as well as careful

genotype-phenotype description of various diseases found in the relevant population. Some of these issues have been studied in detail in Malaysia. Arising from these findings, some important milestones have been achieved.

### **Birth defects**

Birth defects are the leading cause of paediatric disability and mortality in developed and developing countries (3). Most Malaysian data on birth defects come from hospital-based studies (13). Information from these studies may be biased as reported data from tertiary referral hospitals are derived from admission of infants with severe birth defects. Data on minor birth defects are not available as they may not be diagnosed. The epidemiology of birth defects from population-based studies is lacking. One of the first such studies which was jointly undertaken by the University of Malaya and Ministry of Health, focused on the epidemiology of major birth defects in Kinta district, Perak (12). Using a population-based birth defect register, major birth defects were studied in 17,720 births. For the first time, the birth prevalence of major birth defects was found to be 1 in 70. With 600,000 births a year, nearly 9,000 newborns are expected to be born with major birth defects in Malaysia each year. The exact syndromic diagnosis of the babies with multiple birth defects could not be identified in 22.5% of these babies. This finding may have implications for the allocation of healthcare resources for corrective surgery, medical treatment, early rehabilitation and intervention programs in Malaysia for this group of patients (12).

Based on the Kinta district study above, the major organ systems involved in the isolated birth defects were cardiovascular (13.8%), cleft lip and palate (11.9%), clubfeet (9.1%), central nervous system (CNS) (including neural tube defects) (7.9%) and musculoskeletal system (5.5%) (8). Among the cohort of babies with major birth defects, the mortality rate was 25.2% during the perinatal period. Various risk factors were identified in the study that predisposed mothers to having a newborn with birth defects. The consanguinity rate of 2.4% was twice that of the control population. Only 15% of major defects were detected antenatally. It is concluded that a birth defects register is needed to monitor these developments and future interventional trials such as fortification of food with folic acid and genetic counselling for at-risk families are needed to reduce birth defects in Malaysia. Subsequently, the Malaysia National Neonatal Registry was established and birth defects surveillance system was implemented (16).

Another separate study on undescended testes in newborns was done in which 1,002 consecutive Malaysian male newborns were examined and 4.8% were found to have undescended testes (UDT). The rate and laterality of the UDT were associated with lower birth weight and prematurity, respectively. Boys with UDT were also more likely to have other congenital abnormalities of the external genitalia, the commonest being hydrocele. Although

76.5% of UDT achieved full spontaneous descent by 1 year of age, 1.1% of all infants whose testes remained undescended required regular long-term follow-up with surgical referral and correction at an appropriate time. This finding highlighted the importance of careful postnatal and follow-up examination of these male infants with UDT to prevent future complications (17).

### **Beta thalassaemia**

One of the major life-threatening genetic conditions in Malaysian children is beta thalassaemia major. It is one of the commonest genetic disorders in South-East Asia. Hitherto, all the molecular genetics studies of this condition were done in patients from the Peninsular Malaysia. Yet, the state of Sabah had one of the highest numbers of patients with beta thalassaemia major but the spectrum of beta-globin gene mutations in the various ethnic sub-populations on the island of Borneo was relatively unknown. The first genetic study on the KadazanDusun children from Sabah with a severe beta-thalassaemia major phenotype, was done using a combination of Southern analysis, polymerase chain reaction analysis and direct sequencing. For the first time, it was found that the affected children were homozygous for a large deletion, which has a 5' breakpoint at position -4279 from the cap site of the beta-globin gene (HBB) with the 3' breakpoint located in a L1 family of repetitive sequences at an unknown distance from the beta-globin gene. This report showed evidence of a founder mutation - homozygosity of the deletion, caused a severe phenotype. This finding also provided the first information on the molecular epidemiology of beta-thalassaemia in Sabah. Since the publication of this report, many similar reports from other parts of South-east Asia had emerged, including studies from Indonesia and the Philippines. This argues that this deletion may be the most common deletion of the beta globin gene, and therefore has implications for the population genetics, counselling and preventative strategies for beta-thalassaemia major for nearly 300 million individuals in South-East Asia and world communities with large SEA migrants (18).

Taking the next step forward, the control of beta-thalassaemia major requires a multi-disciplinary approach that includes population screening, genetic counselling, prenatal diagnosis and the option of termination of affected pregnancies. The molecular characterisation of the spectrum of beta-globin gene mutations in each of the affected ethnic groups in Malaysia was necessary to achieve this aim. Using a cost-effective, 2-step molecular diagnostic strategy consisting of amplification refractory mutation system (ARMS) to identify the 8 most common mutations followed by other DNA-based diagnostic techniques, a total of 98.3% of beta-thalassaemia alleles were characterised. A 100% success rate was achieved in studying the Kadazan-Dusun community. The strategy to identify beta-globin gene mutations in Malaysians with beta-thalassaemia was proposed based on the findings above (19).

### ***Distal renal tubular acidosis and hereditary elliptocytosis***

In the area of genetic syndromes in Malaysia, the first case report of distal renal tubular acidosis (RTA) and hereditary elliptocytosis (now known as South-east Asia ovalocytosis) was reported in a Malay family with 3 children having both elliptocytosis and distal RTA. The simultaneous occurrence of these two distinct genetic conditions was intriguing and it was postulated then that the mechanism may be due to covariations in the same family, a contiguous gene syndrome or dual function of a single gene. The report emphasised the importance of excluding a renal tubular defect in any child who presents with elliptocytosis and failure to thrive in Malaysia. Following this report, a large number of publications describing this similar syndrome were reported, culminating in the discovery that mutations of *SLC4A1*, in either its cytoplasmic or its membrane portion, may cause abnormalities in red cell morphology or interference with proton secretion by the renal collecting duct, giving rise to distal RTA (20). Subsequently, in one of the biggest studies on this condition, it was hypothesised that these changes in the red cell metabolism caused by these mutations might protect against malaria. This landmark paper was made possible with the participation of multiple centres in South-East Asia, including Malaysia (21).

### ***Al-Gazali syndrome***

From a Bidayuh family in Sarawak, two siblings from a consanguineous family with multiple skeletal abnormalities, anterior segment anomalies of the eye and early lethality were reported. These features are consistent with a syndrome first described by Al-Gazali and we provide further delineation of the syndrome. This second report provided evidence to support the proposed new Al-Gazali syndrome (22).

### ***Duchenne muscular dystrophy***

Another area of research is on Malaysian children with learning or physical disabilities. A clinical, molecular genetics and functional assessment was performed in a group of Malaysian boys with Duchenne muscular dystrophy (DMD). The study successfully delineated the demographic characteristics, electrophysiological and molecular genetics analyses and reported the outcome of 21 Malaysian males diagnosed with DMD over a period of 10 years. Molecular genetic analysis showed that dystrophin gene deletions were found in 11 of 16 patients (69%). Chief concerns were the delay in diagnosis and only 43% had satisfactory school performances. The majority were classified as having severe to total dependency levels, based on the modified Barthel Index for activities of daily living assessment. DMD is associated with significant medical and social needs for a developing country such as Malaysia. This study resulted in a change of diagnostic approach, where molecular genetic testing is performed

before muscle biopsy as latter procedure was invasive. Earlier referral, genetic counselling, and provision of support and rehabilitative services were the main priorities identified for children with DMD (23).

### ***Rett syndrome***

A study on Malaysian girls with Rett syndrome (RS) - a severe neurodevelopmental disorder characterised by normal neurological development followed by progressive developmental regression - was done using denaturing high-performance liquid chromatography (DHPLC) to detect mutations in the *MECP2* gene. Mutations in the *MECP2* gene were detected in 65% of RS patients. On the basis of this study, a suitable algorithm for clinical and molecular genetic assessment was proposed for Malaysian girls with RS (24).

### ***Inborn errors of metabolism***

One major area of interest in medical genetics is the study of inborn errors of metabolism (IEM). Issues pertaining to the diagnosis and management of IEM in Malaysia include low awareness of atypical and variable presentations in IEMs leading to delayed diagnosis or treatment, absence of reliable population data on IEMs and involvement of multiple siblings in the same family due to consanguinity. The importance of careful reporting of family history and genetic counselling needs to be emphasized. Selected testing of ill infants and children for IEM yielded a positive 2% (264/13,500) results for IEMs in Malaysia. Out of the 264 patients, the spectrum of IEMs in Malaysia included organic acidurias (n=98), aminoacidopathies (n=78), urea cycle defects (n=54), neurotransmitter conditions (n=12) and lysosomal disorders, mainly mucopolysaccharidosis (n=14). Confirmatory studies of IEMs are an important aspect of management of IEMs. There is a need for more metabolic specialists and funding for diagnosis and treatment of IEMs in Malaysia. Long-term care issues and cost-effectiveness of IEM therapy, supportive and preventive aspects will need further studies in Malaysia (25, 26).

### ***Congenital disorder of glycosylation***

A number of first reports of IEM were made in Malaysian children. The first report of congenital disorder of glycosylation (CDG) was identified in a Malaysian infant female at 2 days of life with CDG type Ia. The diagnosis was suspected on the basis of dysmorphic features supported by neuroimaging studies showing cerebellar hypoplasia and presence of coagulopathy, hypothyroidism and severe pericardial effusion. The patient died at 7 months of life. The diagnosis was supported by abnormal serum transferrin isoform pattern. Enzyme testing of peripheral leukocytes showed decreased level of phosphomannomutase (PMM) activity and a normal level of phosphomannose isomerase activity, indicating a diagnosis of CDG type Ia.

Mutation study of the PMM2 gene showed the patient was heterozygous for both the common p.R141H (c.422T>A) mutation and a novel sequence change in exon 7, c.618C>A, that was confirmed to be pathogenic. To the best of our knowledge, this is the first report of CDG in the Malay population. Prenatal diagnosis was successfully performed in subsequent pregnancies for this family (27).

### ***Citrin deficiency***

Another emerging IEM in Asia was first reported in two Malaysian siblings with neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD). This was first reported in a six-month-old Chinese girl who presented with prolonged cholestasis and was investigated for biliary atresia. Urine metabolic screen showed the presence of urinary-reducing sugars, and she was treated with a lactose-free formula. NICCD was suspected based on the clinical history, examination and presence of urinary citrulline. Mutation study of the SLC25A13 gene showed the compound heterozygotes, 851del4 and IVS16ins3kb, which confirmed the diagnosis of NICCD in the patient and her three-year-old female sibling, who also had unexplained neonatal cholestasis. Long-term dietary advice, medical surveillance and genetic counselling were provided to the family. The diagnosis of NICCD should be considered in infants with unexplained prolonged jaundice. DNA-based genetic testing of the SLC25A13 gene may be performed to confirm the diagnosis retrospectively. An awareness of this condition may help in early diagnosis using appropriate metabolic and biochemical investigations, thus avoiding invasive investigations such as liver biopsy in infants with neonatal cholestasis caused by NICCD (28). Many other publications on NICCD in Asia and Malaysia were published after this condition was reported (29).

### ***Adult-onset cancer***

In adult-onset genetic conditions such as hereditary breast and ovarian cancer syndromes, genetic counseling (GC) and genetic testing are vital risk management strategies. Hitherto, cancer genetic testing amongst Asians has been described only in developed and high-income Asian countries. A long-term collaborative study between University of Malaya (breast surgeons, clinical geneticist) and CARIF (Cancer Research Initiative Foundation) studied the uptake and acceptance of GC and genetic testing services in Malaysian BRCA carriers in a middle-income country. A total of 363 patients were tested by full sequencing and large rearrangement analysis of both BRCA1 and BRCA2 genes in the Malaysian Breast Cancer (MyBrCa) Genetic Study. Of these, 13.5% were found to carry deleterious mutations. GC pre- and post- result disclosures were provided and these groups of patients and their families were studied. GC and genetic testing were accepted by 82% of Malaysian patients at high risk for HBOC syndromes. Only 78% of index patients informed their families of their risks and 11% of relatives came

forward when offered free counseling and testing. Even when GC and genetic testing were provided at no cost, there remained significant societal and regulatory barriers to effective cancer genetic services. There is a need for regulatory protection against genetic discrimination. Further studies are needed in the area of increasing awareness about the potential benefits of GC and genetic testing in this region (30).

The lessons learnt from these examples above showed the importance of astute clinical observation, careful documentation and diagnosis, genetic counselling before performing any genetic testing and the importance of multi-institutional collaboration. While these examples emanated from childhood disorders, it was clear there was a wider implication for the family and society - ranging from improved understanding of the basic pathophysiology of the conditions to psychosocial, reproductive, ethical and public health issues and their short and long-term ramifications. There is still much to do in providing an acceptable level of care for patients with hereditary conditions in Malaysia.

### ***Pitfalls, challenges and opportunities***

While genetic testing and mutation analyses are increasingly used in medicine, it is crucial that clinicians are aware of their pitfalls and limitations. Genetic testing should be preceded by genetic counselling. There are ethical concerns that mutation studies should not be performed in children or minors unless there are important medical consequences. Many genetic tests are often done on a research basis and are not meant for diagnostic purposes. In addition, a 'negative' molecular result does not exclude a diagnosis. Conversely, a novel DNA variant or polymorphism may be mistakenly regarded as pathogenic by medical staff not familiar with genetics. Biotechnology is rapidly evolving and the sensitivity of the various methodologies of mutation detections may vary with different techniques (31, 32).

On the other hand, the medical genetics community encourages the use of family medical history as a 'front-line' screening tool for genetic disorders. The Center for Disease Control (CDC) Office of Genomics and Disease Prevention in collaboration with National Institutes of Health, USA embarked on a public health initiative to use family history information to assess risk for common diseases and to influence early detection and prevention strategies in 2002 (Family History Public Health Initiative). The American Society of Human Genetics has declared family medical history the 'gold standard' for assessing disease risk. Genes alone do not act in a vacuum and family health history is a better predictor than personal genomics testing. By using an easy to follow "Family History Tool" to assess risk classification for each individual, it is feasible to stratify public health and personalised recommendations for each family. Therefore family doctors and public health practitioners have their roles to play in reducing genetic disorders in the community (33).

The ethical, legal, social and religious implications of 'New Genetics' and 'Personal Genomics' must be carefully evaluated and debated. The Ministry of Health of Malaysia announced plans to screen the population for thalassaemic trait as part of the Thalassaemia Control program. While this is a laudable move, there are a number of considerations that must be taken into account before population screening can be done. For example, will genetic counselling be provided to the population? Which age groups will be screened? Will prenatal diagnosis and termination of pregnancy for affected fetuses be allowed in government hospitals if two thalassaemic carriers decided to start their family? The setting up of genetic support groups such as Malaysian Rare Disorders Society and others are crucial to give a voice for families and patients, to advocate and to allow clinicians to act in the best interest of the patients (34-36).

In conclusion, it is recommended that both suitable curative and preventive aspects be utilised to reduce the impact of genetic diseases in the era of personalised medicine (3, 36). More clinical research into genetic conditions is required in Malaysia. Genetic counselling should remain the mainstay of all genetic services and empowering at-risk families and individuals should be a priority, even in the age of personal genomics and individualised medicine.

The text was presented in an inaugural lecture by Professor Dr Thong Meow Keong in the Faculty of Medicine, University of Malaya on 15th July 2011.

### Acknowledgement

I acknowledge all the contributions and assistance from my mentors, collaborators, colleagues, students, friends and family members who have contributed to my personal growth and the road to discovery that enabled this Inaugural Lecture to take place. This is dedicated to all of you and our children.

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