KK Women's and Children's Hospital
SingHealth

# SPECIAL DELIVERY

NEWS FROM SINGAPORE'S ACADEMIC TERTIARY HOSPITAL FOR WOMEN AND CHILDREN

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## BABY JOY AFTER CERVICAL CANCER

*Woman successfully delivers healthy baby after fertility-sparing surgery to remove cervix due to cancer.*

**Radical abdominal trachelectomy patient, Ms Susan Zhao; her husband, Mr Emmanuel Chin; baby, Isaac Chin; and two of her doctors at KKH – Adjunct Professor George SH Yeo (right) and Dr Timothy Lim (far right).**

Thirty-year-old Ms Susan Zhao is believed to be the first patient in a restructured hospital in Singapore to have conceived and delivered a child after undergoing a radical abdominal trachelectomy (RAT) – a fertility-sparing surgical procedure for young patients with early stage cervical cancer.

RAT has been described as a successful fertility-sparing procedure in medical literature for more than a decade, with about 400 reported cases globally. In Singapore, KK Women's and Children's Hospital (KKH) is the main centre that carries out RAT. Since 2010, the hospital has successfully carried out RAT for eight patients diagnosed with early stage cervical cancer.

"While there is no one method that can guarantee successful conception and delivery, Ms Zhao's successful pregnancy and birth following RAT spells great hope for other young women affected by cervical cancer who wish to have children," says Dr Timothy Lim, Head and Senior Consultant, Department of Gynaecological Cancer, KKH, who performed Ms Zhao's surgery.



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## FIRST SUCCESSFUL BIRTH AFTER RADICAL ABDOMINAL TRACHELECTOMY

Ms Susan Zhao was diagnosed with early cervical cancer in 2011, after seeking medical evaluation while trying to conceive. Health screening results revealed the presence of human papillomavirus (HPV) at the neck of her womb – also known as the cervix.

Ms Zhao underwent a cone biopsy at KKH, where a cylindrical sample of cervical tissue was obtained and sent for laboratory testing. Test results confirmed the presence of early stage cervical cancer, and Ms Zhao was referred to the Gynaecological Cancer Centre at KKH for further assessment and management of her condition.

During discussions with her multidisciplinary care team, Ms Zhao expressed her desire for fertility preservation, as she wished to have a child.

Magnetic resonance imaging scans indicated that the cancer had not spread to Ms Zhao's lymph nodes. Thus the care team proceeded to remove the cancer while preserving her womb, through a fertility-sparing surgical technique known as radical abdominal trachelectomy, or RAT.

In 2012, a surgical team performed a RAT to remove Ms Zhao's cervix, together with surrounding connective tissue and the upper portion of the vagina. Post-surgery, she was closely monitored for a year, before being given a clean bill of health and encouraged to try to conceive.

Ms Zhao conceived naturally in 2013, but had a miscarriage when she was four months pregnant. After a six-month rest following her miscarriage, she became pregnant again. A cervical cerclage, also known as a cervical stitch, was placed during her second trimester of pregnancy, to support her severely shortened cervix.

In 2014, Ms Zhao delivered a healthy child by Caesarean section, and remains cancer-free.

Ms Zhao was attended by the following team of senior consultants: Dr Timothy Lim, Head and Senior Consultant; and Associate Professor Philip Yam, Senior Consultant, both from the Department of Gynaecological Cancer; and Adjunct Professor George SH Yeo, Chief of Obstetric, Head and Senior Consultant, Department of Maternal Fetal Medicine and Obstetric Ultrasound and Prenatal Diagnosis Unit, KKH.

## FERTILITY-SPARING INTERVENTION FOR CERVICAL CANCER

Cervical cancer is the fifth most common cancer in Singapore – approximately 200 to 250 women are diagnosed with cervical cancer every year. Almost half of these women are diagnosed in stage I, ten percent of whom are young women aged less than 35 years.

RAT is developed as a form of fertility-sparing surgery for young patients with early stage cervical cancer. The procedure involves the removal of the cervix, the surrounding parametrial tissue and the upper portion of the vagina, as well as the pelvic lymph nodes, but sparing the uterus and the ovaries.

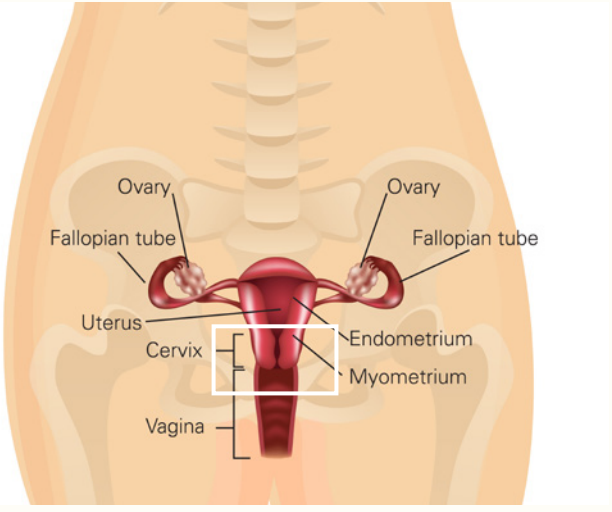
However, only about five to ten percent of women with cervical cancer are eligible for RAT. Factors considered conducive for RAT include:

- Patient should be less than 40 years
- Cancer should be at an early stage, i.e. stage IA2 - IB1
- No evidence of pelvic lymph node involvement or spread of cancer
- Tumour(s) should be smaller than two centimetres in diameter

The gynaecological oncology team at KKH manages about 150 patients with cervical cancer every year, accounting for about two-thirds of patients with cervical cancer in Singapore.

## REGULAR SCREENING AIDS EARLY DETECTION OF CANCER

The pap smear test helps to detect abnormal cell changes in the cervix early, and allow for more effective treatment and intervention against cervical cancer. Women aged 25 years and above who have had sex, or who are sexually active, are strongly recommended to undergo a pap smear test every three years.




**The intent of RAT is to resect the cervix, upper 1–2 cm of the vagina, parametrium, and paracolpos (region indicated by a white square) but sparing the uterine corpus.**

# TACKLING THALASSAEMIA

*Confronting Singapore's most common genetic disease*

*Tan Guek Peng, Senior Statistical Officer, National Thalassaemia Registry*
*Associate Professor Law Hai Yang, Chief Scientific Officer, Genetics Service, KK Women's and Children's Hospital; Deputy Director, National Thalassaemia Registry*

Thalassaemia is the most common genetic disease in Singapore – about 4.5 percent of the population are carriers of this blood disorder. The disease is also highly prevalent in Southeast Asia.

An autosomal recessive disorder, thalassaemia is passed from parent to child, and affects both males and females. The disease is triggered by a defective globin gene which disrupts the production of haemoglobin – the oxygen-carrying protein – in red blood cells.

Affected individuals either express symptoms of the disorder (thalassaemia major), or remain largely asymptomatic but carry the causative gene (thalassaemia minor).

Individuals with thalassaemia major or intermedia are anaemic, and may experience fatigue, growth failure, shortness of breath and jaundice. Individuals with thalassaemia minor may not show any symptoms apart from mild anaemia, and their blood cells will appear unusually small and pale.

## TYPES OF THALASSAEMIA IN SINGAPORE

Three types of thalassaemia-related conditions prevail in the Singapore population – alpha (α)-thalassaemia (3%), beta (ß)-thalassaemia (0.9%) and Haemoglobin E (HbE) trait (0.55%).

### α-thalassaemia major

Also known as Bart's hydrops fetalis, α-thalassaemia major is incompatible with life; babies with α-thalassaemia major are usually stillborn, or pass on a few hours after birth. The condition can also cause severe toxaemic complications, such as pre-eclampsia, which can endanger the mother during pregnancy.

While no comprehensive treatment or cure currently exists for α-thalassaemia major, in recent years, intrauterine blood transfusions followed by lifelong blood transfusions have been used as a possible treatment in some countries. This has met with limited success, and surviving patients may have serious neonatal complications and congenital anomalies.

### ß-thalassaemia major

A child with ß-thalassaemia major is healthy at birth, but usually develops anaemia within a year, and requires lifelong blood transfusions.

Frequent blood transfusions can result in the accumulation of excessive levels of iron in the body; patients would require oral or subcutaneous chelating agents to help remove excess iron in their bodies.

Currently, the main treatment for ß- thalassaemia major is haematopoietic stem cell transplantation (HSCT). This is only possible when a suitable human leukocyte antigen-matched donor is found.

With the holistic management of thalassaemia involving regular medical reviews, safe blood transfusions and effective chelating agents, most patients with ß-thalassaemia major can live into adulthood, marry and have children.

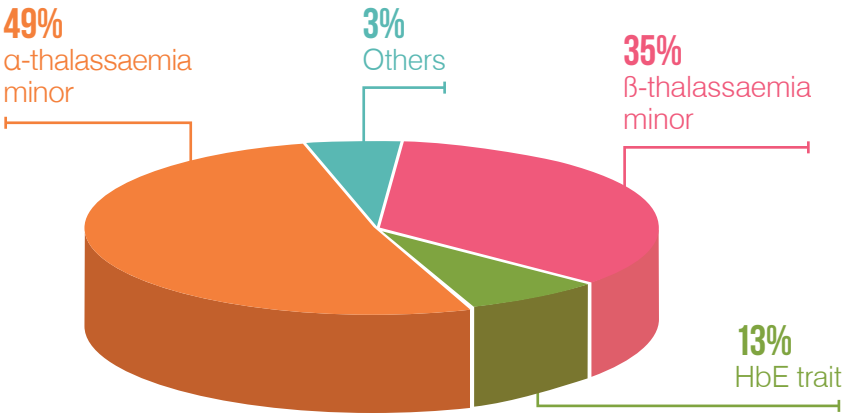
### HbE trait

Individuals with HbE traits carry one abnormal haemoglobin gene and one normal ß-globin gene. They are usually asymptomatic. However, if an individual with HbE trait has a partner with ß-thalassaemia minor, the couple will have a 25 percent risk of having a child with HbE-ß thalassaemia.

Similar to ß-thalassaemia major, a child with HbE-ß thalassaemia may develop severe anaemia requiring regular blood transfusions. The main treatment for HbE-ß thalassaemia also remains HSCT.

**PROPORTION OF THALASSAEMIA TYPES REGISTERED WITH THE NATIONAL THALASSAEMIA REGISTRY, SINGAPORE**

Source: The National Thalassaemia Registry 2014

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# HELP FOR FAMILIES WITH THALASSAEMIA

In 1992, the National Thalassaemia Registry (NTR) was established by the Ministry of Health, Singapore, with the aim to register all individuals with thalassaemia, and offer genetic counselling and screening for affected families.

### Screening

Routine screening tests at the NTR include full blood count (FBC), haemoglobin (Hb), electrophoresis and DNA analysis tests where necessary. For individuals with α-thalassaemia, further molecular testing is necessary to define the specific subtype of α-thalassaemia. This information is critical in calculating the risk of having a child with the severe types of α-thalassaemia.

### Counselling

Screening enables the registry to identify individuals who are thalassaemia carriers, and couples at high risk of having children with thalassaemia major. The NTR also provides at-risk couples access to appropriate genetic counselling and education on reproductive options, to empower them to make informed decisions about family planning and prenatal diagnostic testing.

### Registration

More than two decades since its establishment, the NTR has registered more than 38,000 individuals with thalassaemia from more than 21,000 families. Further screening to determine thalassaemia types has been carried out for more than 34,000 individuals from affected families.

This comprehensive and proactive approach has seen an overwhelming decrease in the incidence of thalassaemia major in Singapore. The number of births of individuals with thalassaemia major has also declined – from 10 to 20 cases per year in the early 1970s, to zero to one case per year since 2005.

# SCREENING AND COUNSELLING FOR THALASSAEMIA

Individuals with no known family history of thalassaemia should visit a polyclinic or family doctor for screening. Individuals with a family history of thalassaemia, or doctors who wish to refer consenting patients to the NTR for screening, may contact the NTR at **+65 6394 1865/1866** or email **Nat.Thal.Reg@kkh.com.sg**.

# TOP 6 THALASSSAEMIA MYTHS

**Myth** **Thalassaemia skips generations and will not affect every generation**

Truth Thalassaemia can affect every generation.

**Myth** **Thalassaemia only affects certain ethnic groups**

Truth While thalassaemia is prevalent in all three major ethnic groups in Singapore, certain types of thalassaemia are more common in certain ethnic groups.

For example, ß-thalassaemia and $\alpha^0$-thalassaemia (caused by a two-gene deletion) are more common in the Chinese population, while $\alpha^+$-thalassaemia (caused by a single gene deletion) is more common in the Indian population. HbE trait is more common in the Malay population.

**Myth** **Individuals with thalassaemia minor cannot donate blood**

Truth Thalassaemia minors are discouraged from donating blood as most have low levels of haemoglobin. However, they can donate blood if their haemoglobin levels are normal.

They can also donate blood products such as platelets and blood plasma. Thalassaemia is not transmissible through blood donation.

**Myth** **Individuals with thalassaemia require a special diet and iron supplements**

Truth Individuals with thalassaemia do not require iron supplements unless they also have an iron deficiency. They do not require a special diet and should maintain a healthy lifestyle, as recommended for all individuals.

**Myth** **Thalassaemia is contagious**

Truth Thalassaemia is genetically inherited, i.e. can only be passed down from a parent to a child. It is not contagious and is not transmitted by body fluids or germs.

**Myth** **Children with thalassaemia minor will develop thalassaemia major when they get older**

Truth The child will stay a thalassaemia minor throughout their lifetime.

# WHAT ARE THE CHANCES OF A CHILD INHERITING THALASSAEMIA?

**Thalassaemia is an autosomal recessive disorder. It is passed down from parent to child, and can affect both males and females.**

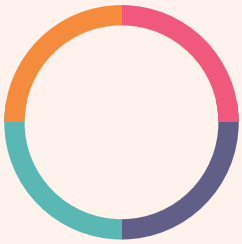
- thalassaemia minor
- thalassaemia major
- does not have thalassaemia
- thalassaemia intermedia
- HbE trait

**If only one parent is a carrier of thalassaemia:**

Child has **50 percent** chance of having thalassaemia minor

Child has **50 percent** chance of not having thalassaemia

**If both parents are carriers of different types of thalassamia (ß and HbE trait):**



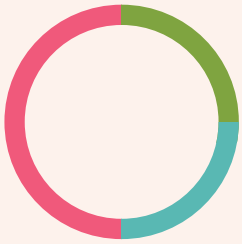
Child has **25 percent** chance of having thalassaemia intermedia

Child has **25 percent** chance of having ß-thalassaemia minor

Child has **25 percent** chance of having HbE trait

Child has **25 percent** chance of not having thalassaemia or HbE

**If both parents are carriers of the same type of thalassaemia:**

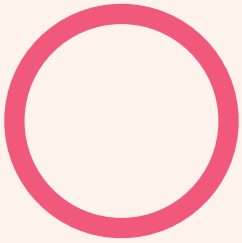


Child has **25 percent** chance of having thalassaemia major

Child has **50 percent** chance of having thalassaemia minor

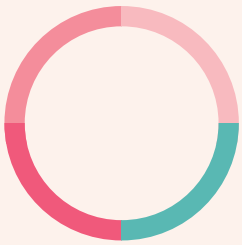
Child has **25 percent** chance of not having thalassaemia

**If only one parent has thalassaemia major and the other does not have thalassaemia:**



Child has **100 percent** chance of having thalassaemia minor

**If both parents are carriers of different types of thalassaemia (α and ß):**



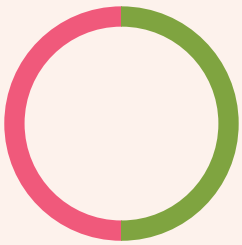
Child has **25 percent** chance of having both α- and ß-thalassaemia minor

Child has **25 percent** chance of having α-thalassaemia minor

Child has **25 percent** chance of having ß-thalassaemia minor

Child has **25 percent** chance of not having thalassaemia

**If one parent has thalassaemia major, and the other has thalassaemia minor:**



Child has **50 percent** chance of having thalassaemia minor

Child has **50 percent** chance of having thalassaemia major


Assoc Prof Law Hai Yang received her D Phil from Oxford University in Human Genetics. In addition to her roles at KKH and the NTR, Assoc Prof Law is also Academic Vice Chair, Research, for the SingHealth-Duke NUS Paediatric Academic Clinical Program.

Assoc Prof Law's research interests include understanding the prevalence and spectrum of mutations causing common genetic diseases in the local population, and developing and evaluating carrier and diagnostic tests for these conditions; as well as investigating the genetic basis of developmental delay, intellectual disability and congenital anomalies.

Ms Tan Guek Peng graduated with a Bachelor of Science in Animal Biology from National University of Singapore, and pursued a Master of Science in Haemoglobinopathy from University College London. Her research interests include studying the prevalence of thalassaemia and other genetic diseases.

# PIONEERING GLOBAL VACCINE SAFETY

*KKH partners WHO in global epidemiological surveillance study*

*Report by Editorial Team*

**To pioneer safer care in global vaccine delivery, KK Women's and Children's Hospital (KKH) is collaborating with World Health Organization (WHO) on an investigation into the relationship between measles-containing vaccines and two associated adverse events following immunisation (AEFI) – immune thrombocytopenic purpura and aseptic meningitis.**

This study into a widely-recommended vaccine type and two known associated AEFI aims to provide proof of concept for the world's first global hospital-based active surveillance network for vaccine safety.

The WHO Global Vaccine Safety Multi-Country Collaboration (WHO GVS-MCC) is dedicated to the epidemiological study of the association between vaccines, and rare, serious and complex adverse events following immunisation (AEFI).

The collaborative network comprises 49 sentinel sites for the surveillance of AEFI from 16 countries over six world regions. KKH, Singapore's sentinel site for Inpatient Surveillance of Post Immunisation Reactions (INSPIRE), is the sole Southeast Asian member of the network.

"Active surveillance for potential AEFI is a vital arm of any large-scale vaccination programme," says Associate Professor Thoon Koh Cheng, Head and Senior Consultant, Department of Paediatrics, Infectious Disease Service, KKH, who is also Primary Investigator for the INSPIRE active surveillance programme.

"It helps to minimise potential risks associated with the introduction of future vaccines, and risks that may arise with existing vaccines due to factors such as changes in manufacture, storage or delivery."

With cross-border vaccine-preventable disease transmission becoming all too common, a very high vaccine coverage is necessary for existing vaccines to maximise vaccine effectiveness and facilitate timely global response to pandemics. This requires high public confidence and hence the need for rigorous vaccine safety surveillance.

"Joining forces with fellow sentinel sites around the world enables us to pioneer safer care in vaccine safety and immunisation practices not only for our country, but also for our neighbours and regions around the world," adds Assoc Prof Thoon, who also sits on the National Antimicrobial Taskforce, and the Expert Committee on Immunisation advising the Ministry of Health, Singapore.

## BETTERING WORLD HEALTH

The WHO GVS-MCC aims to bolster countries' ability to monitor and protect public health by strengthening the development of their existing vaccine safety surveillance protocols. Benefits of this international vaccine safety monitoring infrastructure include:

- More rapid and epidemiologically valid evaluation of vaccine safety, particularly with regard to vaccines when they are first made available (e.g. dengue vaccine), and new vaccines that require swift deployment during mass outbreaks (e.g. pandemic avian influenza vaccines).
- Large-scale multi-country collaborative epidemiological studies involving millions of patient numbers, which can help to confirm extremely rare AEFI that may not be detected in pre- or even post-licensure vaccine safety assessments in a single-population study.
- Closer monitoring of associations between events and relevant vaccines, to strengthen public safety and confidence and facilitate swift response to vaccine safety concerns.

Immunisation is one of the world's most successful and cost-effective health interventions, preventing debilitating illness, disability and death. In Singapore, the National Childhood Immunisation Programme, introduced in 1962, has since virtually eliminated the childhood incidence of diphtheria, neonatal tetanus, poliomyelitis and congenital rubella. By the same token, vaccine safety concerns can affect all countries.

"The WHO GVS-MCC helps hospitals around the world, us included, to better evaluate vaccine safety concerns in our populations, and collectively work to ensure that vaccines used globally are safe," says Assoc Prof Thoon. "However, vaccine safety begins with one simple step. If a parent or patient reports an adverse event following immunisation, healthcare providers are strongly encouraged to report the event to Health Sciences Authority (HSA)."

Led by Assoc Prof Thoon Koh Cheng, the INSPIRE programme is a partnership with HSA that monitors vaccines to maximise the safety of childhood and women's obstetric vaccines in Singapore. The investigative team also includes Assoc Prof Chong Chia Yin, Senior Consultant; and Dr Natalie Tan, Consultant, Department of Paediatrics, Infectious Disease Service, KKH.

## CASE STUDY: LYMPHADENITIS FOLLOWING ADMINISTRATION OF BCG VACCINE

### Situation

In Singapore, the Bacillus Calmette-Guéri (BCG) vaccine is routinely given to newborns as part of the National Childhood Immunisation Schedule. From 2009 to 2012, hospital-based active surveillance of AEFI detected an increase in cases of regional lymphadenitis associated with the BCG vaccine, with a three-fold spike in 2011*.

### Assessment

Investigations identified the likely cause of the spike in suppurative lymphadenitis cases to be multifactorial. One factor was batch-related, arising from manufacturing issues encountered by the manufacturer. Administration technique was another factor – investigators noted that administration technique could have played an important role in minimising BCG-associated complications, such as suppurative lymphadentitis.

While administration location (deltoid vs. gluteal) did not appear to increase the risk of lymphadenitis, gluteal administration was associated with a slightly higher risk of vaccination site infections and abscesses (presumably due to the greater difficulty in caring for a potential wound that may be frequently soiled by faeces).

### Recommendation

The HSA issued an advisory to healthcare professionals on the consideration of intradermal administrative technique when administering the BCG vaccine. The advisory also reminded healthcare professionals to inform parents of possible suppurative lymphadenitis following vaccination, so that early treatment could be sought.

* The overall rate and pattern of BCG vaccine-associated AEFI remained comparable to the frequency of occurrence in other countries, as well as the expected frequency of occurrence published by the vaccine manufacturer.

## WHEN PATIENTS ASK: 'ARE VACCINES SAFE?'

PRACTICE TIPS FOR GENERAL PRACTITIONERS

*Assoc Prof Thoon Koh Cheng, Head and Senior Consultant, Infectious Disease Service, KKH*

### Are vaccines safe?

Licensed vaccines are safe. In Singapore, vaccines are subject to very stringent review, primarily because they are used in healthy persons, unlike drugs that are usually used to treat disease. This includes undergoing extensive trials with thousands to tens of thousands of volunteers, often far exceeding any trial involving a therapeutic medication.

### Is my child at risk of adverse events after immunisation?

As with all pharmaceuticals, vaccines can be associated with certain adverse events following immunisation (AEFI).

Some AEFI can be due to issues with production, storage and delivery, administration errors, or from the vaccine contents. Yet others may be due to the person receiving the vaccine (e.g. fainting). These are well-documented in literature, and should be made known to patients and/or their parents before immunisation.

Common AEFI include: fever, irritability, redness and pain at the injection site. These are usually minor and self-limiting. Uncommon, but more serious AEFI include: high fever, fits, rash, and other even rarer vaccine-specific events such as Guillian-Barré Syndrome.

### How is vaccine safety monitored?

HSA is the national regulatory authority that monitors vaccine safety. KKH partners HSA as Singapore's vaccine safety sentinel site to conduct active surveillance for the detection and investigation of AEFI.

Appropriate verification is then conducted to investigate possible vaccine-AEFI associations, and relevant findings are reported to HSA and the Ministry of Health to inform national policy.

# KKH LAUNCHES NEW DNA DIAGNOSTIC TEST

*Southeast Asia's first accredited chromosomal microarray analysis laboratory*

*Report by Editorial Team*

KK Women's and Children's Hospital (KKH) has launched Southeast Asia's first accredited chromosomal microarray analysis (CMA) diagnostic test, to aid the diagnosis of genetic disorders in babies and children.

Chromosomal microarray analysis (CMA), a DNA-based method of genetic investigation, helps to identify clinically significant chromosome anomalies that are too small to be detected by conventional chromosome analysis – also known as karyotyping.

"With an expected diagnostic yield of about 20 percent, compared with 3.7 to 9.5 percent for conventional karyotyping, CMA is expected to provide an underlying genetic diagnosis in a greater proportion of patients," says Dr Angeline Lai, Head and Senior Consultant, Genetics Service, KKH, who leads the CMA diagnostic service.

"This benefits patients as it ends the diagnostic odyssey, preventing further unnecessary investigations. It also provides information about possible complications, allowing appropriate monitoring and early management, and facilitates the provision of accurate information about recurrence risks in future pregnancies, and the reproductive choices available."

## WHAT ARE CHROMOSOME ANOMALIES?

Chromosome anomalies include deletions, duplications and other alterations in whole or parts of chromosomes.

Either inherited or occurring spontaneously, chromosome anomalies are estimated to be present in one in 150 babies, and are implicated in 25 percent of all miscarriages and stillbirths, and 50 to 60 percent of miscarriages in the first trimester.

They are the underlying cause in a substantial proportion of conditions that present at birth or during childhood. These include multiple congenital anomalies (MCA), developmental delay and/or intellectual disability (DD/ID), and autism spectrum disorder (ASD).

The American College of Medical Genetics recommends CMA as first-tier genetic testing for patients with these disorders.

## DECODING THE GENETIC CAUSE OF CHILDHOOD DISORDERS

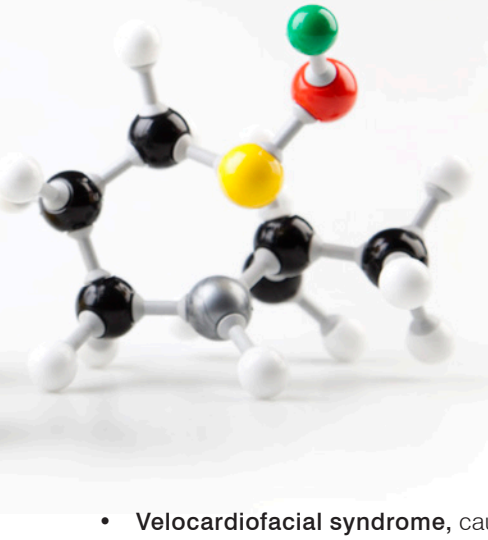
Since its launch in February 2014, the hospital has performed CMA diagnostic testing for 143 patients comprising mainly babies and children. Twenty-nine (20%) were identified to have copy number variants – deletions and duplications of chromosomal segments – that were pathogenic (known to cause disease) or likely pathogenic.

These led to the eventual diagnosis of 24 genetic syndromes, most common of which were Angelman/Prader-Willi syndrome (4), Velocardiofacial syndrome (2) and 1p36 microdeletion syndrome (2).

- Microdeletions of chromosome 15 at bands q11.2q13 cause Angelman syndrome or Prader-Willi syndrome, depending on whether the deletion occurs on the maternal or paternal copy of chromosome 15.

  **Angelman syndrome** is characterised by developmental delay or intellectual disability, unsteady gait, frequent laughter/smiling and seizures.

  **Prader-Willi syndrome** in babies is characterised by low muscle tone (hypotonia), distinct facial features, feeding difficulties and developmental delay. Older children with Prader-Willi syndrome may have excessive appetites, leading to obesity if uncontrolled.



- **Velocardiofacial syndrome,** caused by a microdeletion at chromosome 22q11.2, is characterised by a combination of medical problems that vary from child to child. More common characteristics include cleft or other problems in the palate, heart defects, problems fighting infection and speech and feeding problems.
- **1p36 microdeletion syndrome** in babies is characterised by low muscle tone, seizures, developmental delay and brain or heart abnormalities.

To enable patients to make an informed choice about testing, information about CMA is provided to patients and their families, and their consent is obtained prior to the test being performed.

Pre-test counselling informs patients about the benefits and limitations of CMA testing, as well as the possibility of obtaining a result of uncertain clinical significance.

Where testing yields an abnormal result, genetic counselling is recommended to explain the findings and any diagnosis made, as well as to plan appropriate intervention and management.

## CASE STUDY: CMA DIAGNOSIS OF 15Q24 MICRODELETION SYNDROME IN AN ADOLESCENT FEMALE

Patient P was first seen by the Genetics Service at KKH in 2004, at the age of two. She presented with failure to thrive, hypotonia, global developmental delay and non-specific dysmorphic features.

Investigations carried out included blood tests to analyse her muscle enzymes, computed tomography of the brain and conventional karyotyping – all of which yielded normal results. Patient P's family had no history of congenital disorders, and her only other sibling was well. The patient was referred for early intervention to support her developmental needs, and the family subsequently discontinued follow-up visits to the hospital.

In 2014, patient P presented to the hospital with acute abdominal pain and vomiting. Investigations revealed a severe hiatal hernia – protrusion of the upper stomach through the diaphragm – for which she subsequently underwent surgical repair. During patient P's hospitalisation, her parents reported that she had been receiving special education and progressing in her development. At 12 years of age, she was able to carry out self-care tasks independently and communicate in sentences.

With informed parental consent, patient P underwent CMA, and results revealed a pathogenic loss of 3.96 Mb at 15q24.1q24.3. This is consistent with a diagnosis of 15q24 microdeletion syndrome –in which a small piece of chromosome 15 is deleted in each cell.

Through CMA, the hospital care team was able to make an accurate genetic diagnosis for patient P, and provide genetic counselling to her family on specific recurrence risks and reproductive choices.

### About 15q24 microdeletion syndrome

15q24 microdeletion syndrome is characterised by dysmorphic facial features, developmental delay, hypotonia, digital and genital abnormalities, and diaphragmatic hernia – most of which were present in patient P. Reported cases of the syndrome have all arisen as spontaneous microdeletions, and the recurrence risk for parents is expected to be low.

The CMA diagnostic service is a joint collaboration between several hospital services at KKH: the SAC-SINGLAS*-accredited Cytogenetics Laboratory (Department of Pathology and Laboratory Medicine) and DNA Diagnostic and Research Laboratory; the Genetics Service (Department of Paediatrics); and KK Research Laboratory.

### ORDER A CMA DIAGNOSTIC TEST

Paediatricians, neurologists and geneticists who wish to order CMA testing for their patients can contact KKH's DNA Diagnostic and Research Laboratory (DDRL) at **+65 6394 1395/6** for information about sending samples.

### REFER A PATIENT FOR ASSESSMENT

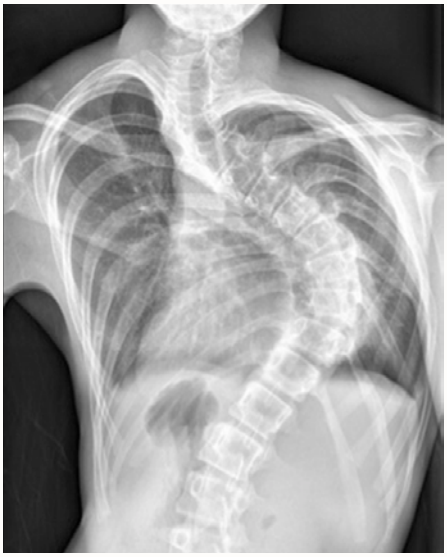
Doctors can also refer patients to the Genetics Service at KKH for assessment, by contacting the hospital at **+65 6294 4050**.

* Singapore Accreditation Council Singapore Laboratory Accreditation Scheme (SAC-SINGLAS)

# STAYING AHEAD OF THE CURVE

*Research reveals five percent of children with scoliosis delay seeking treatment*

*Cheri Chan, Undergraduate, Nanyang Technological University*
*Associate Professor Kevin Lim, Senior Consultant, Department of Orthopaedic Surgery and Chairman, Division of Surgery, KK Women's and Children's Hospital*



**X-Ray of a patient with severe AIS, with a spinal curve of 90 degrees.**

Scoliosis is an unnatural curvature of the spine that is common in children. The condition has an incidence rate of two percent in Singapore, and is most often seen in healthy children and adolescents aged ten years or more. While scoliosis is believed to be multifactorial, the condition has no obvious cause in a majority of cases, giving rise to the term adolescent idiopathic scoliosis (AIS).

The severity of AIS is categorised by degree of spinal asymmetry, as measured by the Cobb angle. Categories include: mild (less than 25 degrees), moderate (25 to 40 degrees) and severe (greater than 40 degrees). Management is dependent on the patient's age, stage of development and degree of spinal asymmetry; treatment modalities include observation, bracing and surgery.

Since 1982, nationwide screening for the early detection of AIS in children has been carried out in schools. As the condition presents during puberty, girls undergo screening from 11 to 14 years, and boys undergo screening from 14 to 15 years. Children identified to be at risk for AIS are then referred for tertiary evaluation.

## STUDY FINDS PATIENTS DELAY SEEKING TREATMENT

From 2007 to 2008, the Department of Orthopaedic Surgery at KK Women's and Children's Hospital (KKH) observed an unusually high number of patients with AIS presenting with severe scoliosis on their first visit. In most cases, this late presentation necessitated surgical intervention as the only viable treatment option.

A study* was commissioned to investigate the occurrence of late presentation in patients with AIS – 'late' being defined as scoliosis with a Cobb angle of 40 degrees or more. The study also aimed to explore the possibility of a time delay in seeking tertiary evaluation, and probable factors for the delay.

The researchers reviewed data from 1,176 children with AIS who sought tertiary evaluation at KKH from 2007 to 2011. They found that 65 (5.5%) patients presented with scoliosis at a Cobb angle of 40 degrees or more on their first visit. Of this group of patients, 48 (73.85%) agreed to an interviewer-administered survey.

Half of the survey respondents admitted either delaying seeking tertiary evaluation for more than a month after initial referral, or failing to attend school health service appointments.

Top three reasons for the delay in seeking tertiary evaluation included:

1. Did not think that scoliosis was a problem
2. Too busy
3. Did not know it was scoliosis

Of the survey respondents, 27 percent tried an alternate form of treatment, such as traditional massage or chiropractic therapy, prior to seeking tertiary evaluation. More than half of the survey respondents had no knowledge of AIS prior to their diagnosis. Even amongst respondents with some prior knowledge of AIS, understanding of the condition was poor.

All survey respondents eventually sought tertiary evaluation upon visible worsening of the scoliosis, or repeated advice by medical professionals and family.

## PATIENT EDUCATION CRUCIAL TO COMBAT INDIFFERENCE

In a study by Rogala et al in 1985, the occurrence rate of patients with AIS who had scoliosis at a Cobb angle of 40 degrees or more on initial presentation was 0.1 percent. In comparison, the occurrence rate of 5.5 percent observed in the KKH study is significantly higher.

The findings of the KKH study suggest that this high occurrence rate could be due to indifference caused by lack of knowledge about AIS. The condition does not present with pain, and in its early stages, any cosmetic deformity is often very subtle and may not be visibly apparent. These factors could further contribute to patients underestimating the potential severity of the condition, and thus delaying seeking tertiary evaluation and treatment.

In general, mild scoliosis can be observed, and moderate scoliosis (25 to 40 degrees) may benefit from spinal bracing to reduce the likelihood that the condition will progress to the stage where surgery is required.

However, spinal bracing is only suitable for children whose skeletal systems are still immature, and in whom the risk of progression is greatest. Girls attain skeletal maturity at 14 to 15 years, while boys do so at 16 to 17 years.

For patients with severe scoliosis (greater than 40-45 degrees) whose skeletal systems have matured, surgical intervention is often the only viable treatment option. The most common surgical treatment for AIS is spinal fusion, where two or more spinal vertebrae are surgically fused together, immobilising part of the spine.

In the event that intervention is not sought for severe scoliosis, the spinal curvature will continue to progress in adulthood. This places the patient at increased risk of developing back pain, worsening physical deformity and impacted lung function in some cases.

## EARLY EVALUATION RECOMMENDED FOR BEST OUTCOMES

Early detection and timely spinal bracing with good compliance have proven to be successful in controlling the progression of scoliosis; ultimately reducing the likelihood of the patient being required to undergo surgery. Crucial to this is timely tertiary evaluation for children who have been positively screened for scoliosis or those in whom scoliosis is suspected.

Greater patient education and awareness, and timely tertiary evaluation are critical to arrest the high occurrence rate of late presentation of patients with AIS and help patients achieve optimal outcomes. Primary health care providers are strongly encouraged to:

- Maintain a healthy index of suspicion for scoliosis, especially for adolescent patients
- Educate patients and caregivers on the potential severity of the condition
- Encourage patients and caregivers to seek prompt tertiary evaluation, to reduce the likelihood of the patient requiring surgical intervention.

* The study was led by Dr Joel Lee and Dr Derrick Lam, under the supervision of Assoc Prof Kevin Lim. During the study, Dr Lee and Dr Lam were fourth year medical students at the Yong Loo Lin School of Medicine, and are now both residents with the Department of Orthopaedic Surgery, KKH.

A paper outlining the study findings, entitled 'Late presentation in adolescent idiopathic scoliosis: who, why and how often?' was published in the January 2014 issue of Journal of Pediatric Orthopaedics B.

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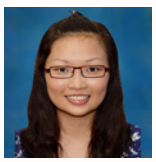

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Associate Professor Kevin Lim underwent subspecialty training in paediatric orthopaedics at The Hospital for Sick Children in Toronto, Canada and at The Starship Children's Hospital in Auckland, New Zealand. His subspecialty interests include scoliosis, clubfoot, cerebral palsy, and fractures in children.

In addition to his roles at KKH, Assoc Prof Lim is Board Chairman and volunteer doctor at the Cerebral Palsy Alliance Singapore. He also serves as Academic Deputy Chair for the SingHealth-Duke NUS Surgery Academic Clinical Program, and Board Member for the Chapter of Orthopaedic Surgeons, College of Surgeons, Academy of Medicine, Singapore.

# CHANGING THE LIVES OF MANY

*New anaesthesia study enhances post-surgical experience for women*

"Even if I cannot do great things, I can do small things in a great way," says Dr Farida Ithnin, Principal Investigator of a research study to improve pain relief for women after abdominal hysterectomy (surgical removal of the womb).

A Senior Consultant with the Department of Women's Anaesthesia at KK Women's and Children's Hospital (KKH), Dr Ithnin is investigating the use of low-dose S-ketamine to enhance post-operative pain relief for patients.

Abdominal hysterectomy is commonly performed to manage complications due to abnormal growths in the womb. The surgery is associated with significant pain, requiring strong pain relief medication such as morphine.

"Through translational research, we are empowered to turn medical discoveries into practical applications that make a difference in the lives of many."

**Dr Farida Ithnin**
Senior Consultant
Department of Women's Anaesthesia, KKH

"In high doses, morphine can be associated with shallow breathing, drowsiness, nausea and vomiting," says Dr Ithnin.

"By investigating a combined treatment involving morphine and S-ketamine, we hope to enhance the quality of pain relief patients experience while further minimising associated side effects."

More than a thousand women undergo abdominal hysterectomy at KKH every year.

"Through translational research, we are empowered to turn medical discoveries into practical applications that make a difference in the lives of many," says Dr Ithnin. "This is the future of medicine."

## GIVE TO SUPPORT WOMEN AND CHILD HEALTH

The KKH Health Endowment Fund (KKHHEF) supports research investigations such as Dr Farida Ithnin's, to advance better diagnoses, treatments and cures for women and children.

**Make a gift to the KKHHEF, or volunteer at KKH to support women's and children's health.**

The KKHHEF also provides financial support for medical treatment to patients in need at KKH, and funds education and disease prevention programmes.

For more information, please contact Christine at **+65 6394 2329** or email **development@kkh.com.sg**.

Scan this code with your smart phone to find out more

Paediatric Surgery Forum

## GP Forum for Paediatric Health 2015

Date : 23 May 2015 (Saturday)
Time : 1.00pm to 5.00pm
Fee : $10 per pax (includes lunch and tea refreshment)
Venue : KKH Auditorium, Training Centre, Level 1, Women's Tower

For more details, please call **6394-8746** (Monday to Friday, 8.30am to 5.30pm) or log on to **www.kkh.com.sg/events**

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