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Hong Kong Society of Medical Genetics

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Message from the Editor

One year has passed since the debut of the HKSMG Newsletter. Now we have come to the 4th issue, a little behind schedule though. I apologize for that because I am the editor of this issue. In this issue we have a scientific article, contributed by Dr. Brian Chung, on the topic of genetic and epigenetic factors of autism spectrum disorders, an increasingly recognized problem in Hong Kong which is also a common reason for referral to the genetic counselling clinic. There is also a brief report on the AGM held on 30 May. Last but not least, there is a section to introduce our new members. On behalf of the Society, I welcome them all.

Ivan Lo

Chairman & Editor

Scientific Article

Genetic and Epigenetic Factors Contributing to Autism Spectrum Disorders

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Abstract
Autism spectrum disorders represent a group of developmental disorders with strong genetic predisposition, including numerous monogenic disorders and chromosomal abnormalities. More recently the etiology of autism spectrum disorders has expanded to include genomic copy number variants and epigenetic factors. This article will briefly review our current understanding of the genetic and epigenetic factors contributing to autism spectrum disorders as well as the direction of current and future research studies, using a case scenario.

Andy was a 3 y.o. boy referred for genetic evaluation because of his diagnosis of autism spectrum disorder. In addition there was a history of use of assisted reproductive technology (ART) prior to his conception, involving a cycle of ovulation stimulation, followed by in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). His parents wished to obtain information regarding the possibility of a connection between ART and autism.

Autistic spectrum disorder

Autism is a neuro-developmental disorder that is typically apparent by age 3 years. It is characterized by impaired communication, impaired reciprocal social interaction skills, and by repetitive behaviors and restricted interests. Autism spectrum disorder (ASD) is a broader umbrella term which includes autism as well as less severe conditions such as Asperger syndrome and Pervasive Developmental Disorder-not otherwise specified (PDD-NOS).

The most recent estimate of the prevalence of autism is 3 to 6 per 1000 when all forms of ASD are included. ASD occurs 4 times more commonly in males than in females.

Assisted reproductive technology

Assisted reproductive technology (ART) involves handling eggs, sperm, or both outside the human body. ART includes in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI), fresh or frozen/thawed embryo transfer, IVF with donor oocytes, and intrauterine insemination either with ovarian stimulation using hormonal medications such as clomiphene or in unstimulated cycles (IUI).

Since the birth of the 1st child was born after conception with IVF in 1978, Over 1 million babies have been born after ART. At present 1-3% of children born in developed countries are conceived through ART [1]. In Canada, recent figures from 2006 showed that annually there were about 12,000 treatment cycles involving ART and at least 2974 cycles resulted in a live birth [2] (from the Canadian ART Registry, www.cfasonline.ca).

Genetics of autistic spectrum disorders: what is known?

Autism is a complex disease with a strong genetic component. Twin studies show a concordance of 60-92% for monozygotic twins and 0-10% for dizygotic pairs, depending on phenotypic definitions [3-5]. Identifying the genes is not an easy task. There are approximately 30,000 genes in the 23 chromosomes that make up the human genome. Roughly 4,000 of these genes are expressed in the brain. Many genes have been implicated in the etiology of autism, defining it as an etiologically heterogeneous disorder.

Despite a strong genetic load, the search for susceptibility genes for autism has generated mixed and sometimes controversial results. This could be due to many factors. One is that the disease may be caused by a combination of many common genetic variations, each providing a small contribution to disease susceptibility. Secondly, there is strong phenotypic heterogeneity that may confound the efforts directed at identifying the genetic factors involved in the disease. Therefore, accurate delineation of the clinical phenotype and demonstrating associated genetic, epigenetic or environmental factors contributing to autism becomes the major task in autism genetic research.

From the perspective of clinical geneticists, about 10% are associated with a genetic syndrome (e.g. fragile X syndrome and tuberous sclerosis complex). Another 5-7% are associated with a cytogenetically visible chromosome abnormality. And inborn errors of metabolism probably are found in less than 5% of children with ASD. Until a few years ago, the remaining affected individuals were presumed to have multi-factorial forms of ASD. More recently, microarray testing has shown that de novo copy number variations (CNVs) occur in 7-10% of ASD patients and that some of these children have a syndromic appearance. A practice guideline has been developed by the American College of Medical Genetics to recommend genetic evaluation of children with ASDs [6]. A template on the clinical genetic diagnostic evaluation of ASDs is extracted and shown in Table 1.

Table 1. Template for the clinical genetic diagnostic evaluation of autism spectrum disorders

Pre-evaluation

- Confirmation of diagnosis of autism by trained professional using objective criteria and tools
- Sensory screening (complete audiogram)
- Electroencephalogram – if clinical suspicion of seizures
- Cognitive testing
- Verify results of newborn screening
  - [High-resolution chromosomal analysis and Fragile X studies may be performed before referral]

First tier

- Initial evaluation to identify known syndromes or associated conditions
  - Examination with special attention to dysmorphic features
    - Should include Woods lamp evaluation
- If specific diagnosis is suspected, proceed with targeted testing
  - Rubella titers – if clinical indicators present
  - "Standard" metabolic screening – if clinical indicators present and if suspected condition was not assessed *by* newborn screening
    - Urine mucopolysaccharides and organic acids
    - Serum lactate, amino acids, ammonia, and acyl-carnitine profile
- High-resolution chromosomal analysis - if not already performed
- DNA for Fragile X – if not already performed

Second tier

- Fibroblast karyotype if leukocyte karyotype is normal and clonal pigmentary abnormalities are noted
- Comparative genomic hybridization (chromosomal microarray)*
- *MECP2* gene testing (females only)
- *PTEN* gene testing (if the head circumference is 2.5 SD greater than the mean)

Third tier

- Brain magnetic resonance imaging
- Serum and urine uric acid
  - If elevated, Hypoxanthine-guanine phosphoribosyl transferase *(HgPRT)* and Phosphoribosylpyrophosphate *(PRPP)* synthetase superactivity testing
  - If low, purine/pyrimidine panel (uracil excretion, xanthine, hypoxanthine)

Extracted from Schaefer GB and Mendelsohn NJ. Genetics evaluation for the etiologic diagnosis of autism spectrum disorders. Genet Med 2008;10:4-12.
**Advances in microarray technology will likely elevate aCGH to a first tier study in the near future.*

Assisted reproductive technology: Is there a link between ART and autism spectrum disorders? Current evidence

With children conceived through ART now forming a significant subgroup of the population, there are concerns about lack of information about the long-term outcomes especially the neurodevelopmental outcome.

In the joint guideline "Pregnancy Outcomes After Assisted Reproductive Technology" issued by the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the Canadian Fertility and Andrology Society (CFAS) in 2006 [7], published data on the long-term outcome of children conceived by ART was evaluated. In 2- and 5-year follow-up studies, there did not appear to be any differences in psychomotor, cognitive, intellectual, or psychological development between IVF, IVF-ICSI, and spontaneously conceived children.

As for Autistic spectrum disorders specifically, a recent systematic review [8] has summarized 8 studies published from 1996 to 2008. The findings were inconsistent and did not point to either an increased or decreased risk of ASD in children born following ART.

Therefore in the joint SOGC-CFAS guideline, it was suggested that further epidemiologic and basic science research is needed to help determine the etiology and extent of the risks to children with respect to the long-term growth and development following ART.

Recurrence of ASD in siblings/future pregnancies

For individuals with known cause of autism after investigations, risk of recurrence is dependent on the specific primary diagnosis. For idiopathic autism, i.e. autism with no identifiable cause, the risk of recurrence to siblings is 4% for autism and an additional 4-6% risk for milder conditions, including language, social, and psychiatric disorders.

For families with two or more affected children, the recurrence risk approaches 35%. Male siblings (brothers) of an individual with idiopathic autism have a 7% risk for autism and an additional 7% risk for milder autism spectrum disorders. Female siblings (sisters) of an individual with idiopathic autism have a 1% risk for autism. The risk for a milder autism spectrum disorder is unknown [9].

There is no specific data with regards to the recurrence risk of autism or ASDs in siblings for children born with ART and diagnosed to have autism/ASDs.

Epigenetics of autistic spectrum disorders: a new research question

Epigenetics refers to modification of genetic information not encoded in the DNA sequence. Epigenetic modification can change gene expression patterns without a change in primary nucleotide sequence. Changes in gene expression often occur in response to epigenetic changes such as DNA methylation, chromatin conformation (methylation, acetylation), and expression of non-coding RNAs. Epigenetic regulation of gene expression is an important but poorly understood component of normal development and homeostasis. Disruption of normal epigenetic states in various genomic regions cause congenital malformation syndromes associated with (I) growth dysregulation e.g. Beckwith-Wiedemann syndrome (overgrowth [10]), Silver-Russell syndrome (intra-uterine growth retardation [11]), and (II) neurobehavioural features e.g. Angelman syndrome and Rett syndrome [12]. Further, epigenetic regulation has received considerable attention with the recent demonstration that assisted reproductive technologies (ART) may significantly increase the rate of epimutation and the incidence of Beckwith-Wiedemann syndrome and Angelman syndrome.

Different research groups are investigating whether epimutations play a role in causing autism spectrum disorders. Current research suggests that early embryonic factors can change epigenetic packaging. One environmental factor being studied is assisted reproduction. The hypothesis is, assisted reproductive techniques (ART) such as ovulation stimulation, in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) may expose gametes and early embryos to different environmental factors that have an effect on epigenetic packaging.

Epigenetics opens a new area of research focus in autism. It could provide the "missing link" between the genome and environmental influences on autism.

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Report on the AGM Mini-symposium

The 10th AGM of the Society was successfully held on 30 May 2009, following marvelous talks on the genetics of neurodegenerative disorders given by Prof. Larry Baum and Prof. Pak Sham, respectively. The HKSMG Book Prize was presented to two students from The Hong Kong Polytechnic University for their outstanding performance in the medical genetics course. That evening was concluded with a very nice dinner at the Dragon Place Restaurant. Here I sincerely thank the speakers and all the members who have attended the meeting. For those members who could not attend the meeting, a glimpse of the content of these talks can be obtained from the following abstracts.

Introduction to Genetics of Brain Diseases

Larry Baum

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Abstract

Genetics contribute to different diseases to varying degrees. The three most important brain diseases, in terms of loss of the most disability adjusted life years (DALYs), are stroke (~5%), depression (~3%), and Alzheimer's (~1%). Stroke leads to 10% of deaths and is projected to become the single largest cause of mortality. Family and twin studies suggest a major genetic contribution to stroke: about 2/3 - 3/4. Most strokes are not caused by a single mutation, but variations in many genes, plus environmental factors, combine to affect stroke. Depression increases risk of death by suicide. About half of depression risk is heritable. Polymorphisms in serotonin and dopamine systems contribute to depression. The biggest risk factor for Alzheimer's disease is old age, but relatives of patients also display greater incidence. The apolipoprotein E ε4 allele is the largest genetic contributor.

Genome-Wide Association Studies and Genetic Risk Prediction in Dementia

Pak C Sham, Hon-Cheong So

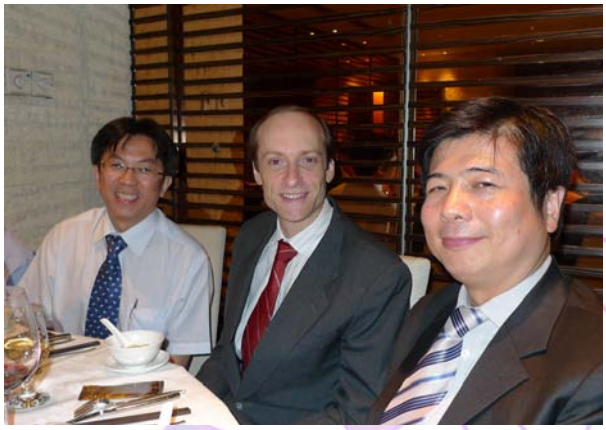
Department of Psychiatry and Genome Research Centre, The University of Hong Kong

Abstract

Dementia affects approximately 6% of the population of Hong Kong above the age of 70 years, with 2/3 of cases being Late-Onset Alzheimer's Disease (LOAD). Dementia generally, and LOAD in particular, have a substantial genetic component in aetiology; with heritability estimates of 43% and 74%, respectively. The best established genetic susceptibility locus for LOAD is the *APOE* gene, where the ε4 allele is associated with increased risk (pooled OR 3.68) and the ε2 allele with decreased risk (pooled OR 0.64), relative to the ε3 allele. As for many other complex disorders, the genetic study of LOAD has progressed to systematic genome-wide association scans using high-throughput genotyping technologies capable to assaying up to 1 million single nucleotide polymorphisms (SNPs) and providing through linkage disequilibrium (LD) coverage of over 90% of all common single base-pair variants in the human genome. To date 8 genome-wide association studies (GWAS) have been conducted on LOAD, which have led to the identification of a number of novel susceptibility genes, although these have generally much smaller effect size than *APOE*. Even when taken together, all the susceptibility genes detected to date explain only a small proportion of the overall genetic component of LOAD. This has a direct bearing on the potential use of these known genetic variants for risk prediction of LOAD.

Book Prize presentation

AGM Dinner



New Members

CHAN See Ka Scarlet

Affiliation:

- Department of Ophthalmology, Prince of Wales Hospital, Shatin, Hong Kong

CHING Kuk Lai

Affiliation:

- PDC Lab, Tsan Yuk Hospital, Hong Kong

CHUEN Ka Yee

Affiliation:

- Dept of Obstetrics & Gynaecology, University of Hong Kong

Area of interest:

- Cytogenetics, stem cell research

HE Guo-Wei

Affiliations:

- Research Professor of Surgery, CUHK; Senior Cardiac Surgeon, TICH Hospital, Tianjin, China; Director, Cardiovascular Research, St. Vincent Heart Institute, Portland, OR, USA; and Clinical Professor of Surgery, OHSU, USA.

Area of interest:

- Multivariate analysis of clinical outcome of cardiac surgery; 2. Regulation of coronary circulation (endothelium, nitric oxide, ion channels and molecular biology); 3. Coronary bypass grafting vessels – biology, pharmacology, and long-term patency; 4. Myocardial protection; 5. Genetic study of cardiovascular diseases (congenital, coronary, exec…) by using GWAS and other genetic methods.

LEI Tan Monica

Affiliation:

- Paediatric Department, Hospital Conde S. Januário, Macau

LI Martin

Affiliation:

- Department of Medicine & Therapeutics, Prince of Wales Hospital, Shatin, Hong Kong

Area of interest:

- Genetics of autoimmune diseases and osteoporosis

YANG Qin

Affiliations:

- Research Assistant Professor, Department of Surgery, The Chinese University of Hong Kong.

Area of interest:

- Regulation of coronary circulation (endothelium-smooth muscle interaction, ion channels, and molecular biology); 2. Myocardial protection; 3. Prenatal exposure on the development of cardiovascular system; 4. Genetic study of cardiovascular diseases.

Scientific Activities

2009 International Conference on Personalized Medicine

Date: 19-20 September 2009

Venue: Auditorium and Conference Hall, Phase 2, Hong Kong Science Park

Organizer: Division of Clinical Pharmacology, Department of Medicine and Therapeutics, Faculty of Medicine, CUHK

Website: www.pharmacy.cuhk.edu.hk/news/pm/php

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