Medical genetics around the world

Journal of Medical Genetics 1988, **25**, 253–257

Medical genetics in China

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Medical genetics blossomed in Western Europe and North America in the years after the second world war. The momentum of this development has remained strong and is felt in every branch of medicine.

In China, Russian influence held sway in the early days after the liberation. In genetics, the so-called Michurin-Lysenko school dominated the field and classical Mendelian genetics was criticised as capitalistic and idealistic. The break with the Russians in the mid 1950s brought new vitality to the Mendel-Morgan school. Medical genetics from the western world thus gained a foothold in China. In 1962, the first cytogenetics group in China was started by Wu Min in the pathology department of the former Institute of Experimental Medicine in Beijing. In 1963, the first medical genetics division, headed by the author, was set up in the Department of Medicine of the Peking Union Medical College (PUMC) Hospital by Professor Zhang Shiao-quan, then head of the department. Work in this field also began in Shanghai in the Department of Biology of the Fudan University and the Department of Pediatrics of the Sixth People's Hospital in Shanghai. Unfortunately, the political turmoil in the mid 1960s interrupted scientific activities throughout the country. It was not until the end of this disaster that medical genetics regained its ground. It has since developed rapidly, especially after the founding of the Chinese Genetics Society and its Human and Medical Genetics Section in 1978 and 1979 respectively. In what follows, a concise description will be given of the historical development and the present state of affairs of several of the subspecialties of medical genetics in this country.

Cytogenetics

The first cytogenetic report from this country was

that of Wu Min, published in 1961.¹ It dealt with the cloning of normal and malignant human cells and studies on their chromosome complement. The normal karyotype of Chinese was described in articles published in 1962² and 1966.³ After this, investigations on chromosomal aberration syndromes,⁴ chromosomal anomalies in cancer⁵ and leukaemia,⁶ and cytogenetic effects of radiation⁷ followed, only to be interrupted by the political chaos that started in 1966. Work was resumed with vigour when order was re-established. Because of the relative simplicity of the procedures for karyotype analysis, cytogenetics groups mushroomed in many parts of the country in a relatively short period of time.

Surveys among newborns for incidence of chromosomal aberrations have been carried out. In a typical series of 3415 newborns, the incidence was found to be 0.73%,⁸ which is similar to that reported elsewhere. Screening was also carried out among the mentally retarded in different populations for the fragile X syndrome.⁹ This revealed, after correcting for those refusing to be examined, a population incidence of 5.8/10 000 males, which is somewhat lower than that reported from other parts of the world. Among 1260 patients diagnosed as having genetic diseases seen in a six year period at the Pediatric Genetics Clinic in PUMC Hospital, 8.5% were found to have chromosomal abnormalities.¹⁰ At the top of the list are Down's syndrome, Turner's syndrome, and Klinefelter's syndrome. This is in accord with findings in other clinics.

In the wake of developments in the west, various banding techniques, prenatal diagnosis of chromosomal disorders, sister chromatid exchange, cytogenetic effects of chemicals and radiations, fragile sites, and high resolution banding became topics of interest. Worthy of note are the construction of the ideogram of high resolution banded human chromosomes in the Chinese,^{11 12} work on fragile sites,¹³ chromosomal instability in relation to

cancer and cancer susceptibility,^{14 15} a case of homologous 14q14q Robertsonian translocation,¹⁶ and a marker chromosome in patients with nasopharyngeal carcinoma.^{17 18} In particular, chorionic biopsy for fetal sexing was first introduced by Han in this country.¹⁹ It is now being used the world over for prenatal diagnosis in the first trimester. Recently, the mechanism of expression of the common fragile site at 3p14 was studied. The results support the conclusion that DNA repair inhibition plays an important role in the expression of FRA3B.^{19a}

Recently, molecular techniques have been applied in combination with chromosomal banding to the mapping of genes directly onto chromosomes. Cheng *et al.*²⁰ have used the *in situ* hybridisation method to map the α interferon gene and the yellow mutation gene²¹ of the mouse to chromosome 4C3→C6 and chromosome 2H1 respectively. This will certainly be the precursor of microcytogenetics in this country.

Biochemical genetics

Biochemical genetics is more sophisticated and difficult to grasp. Progress in this area was also hampered by the difficulty in obtaining the necessary reagents and equipment, most of which have to be imported. As a consequence, only institutions in the larger cities, such as Beijing, Shanghai, and Guangzhou, have been able to carry out work in this area. Genetic services with regard to inborn errors of metabolism are, therefore, limited to a few large institutions in these cities.

For obvious reasons, work in this area started with the haemoglobinopathies and glucose 6 phosphate dehydrogenase deficiency. Mass screenings for the haemoglobinopathies were started in 1980.^{22 23} Abnormal haemoglobins were found to be widely distributed throughout the country and in various ethnic groups, though more prevalent in the south. Simultaneously, studies at the molecular level to determine the amino acid substitution in Hb variants were begun by Liang and Lo^{24 25} at the Institute of Basic Medical Sciences (IBMS) in Beijing and Zeng and Huang²⁶ in Shanghai. About 65 types of abnormal haemoglobins were identified, 16 of which are new.²⁷ Hb S was not detected and Hb E was the most prevalent. The thalassaemias are more or less confined to provinces in south and south-western China and are rare to the north of the Yangtze River²⁷; this is also the case for glucose 6 phosphate dehydrogenase deficiency.²⁸ Several new variants of G6PD have been identified by Du²⁹ in Guangzhou, based on their electrophoretic mobility, K_m G6P, percentage utilisation of 2-deoxy-G6P and deamino-NADP, heat stability, and optimum pH.

Surveys of phenylketonuria among newborns revealed an incidence of about 1/15 000³⁰ which is similar to that in Caucasians. It is a pity that China is still unable to produce a low phenylalanine diet in large enough quantities for adequate therapy for most affected babies.

Studies on the lysosomal storage diseases have been in progress at the IBMS since 1982 and also in Shanghai. The number of patients with this group of diseases seen at PUMC Hospital was second only to those with aminoacidopathies among the inborn errors of metabolism.¹⁰ Assays for the lysosomal enzymes in serum, skin fibroblasts, amniocytes, and chorionic villi have established the normal values for Chinese. Cases with GM1³¹ and GM2 gangliosidosis,³² mucopolipidosis III,³³ the various mucopolysaccharidoses,^{34 35} Niemann-Pick disease,³⁶ and Gaucher disease³⁷ have been diagnosed and the prenatal diagnosis of some of them accomplished. Cases with methylmalonic aciduria³⁸ and maple syrup urine disease³⁹ have also been reported, the diagnosis being confirmed by gas chromatographic analysis for the abnormal organic acids involved.

Large scale population studies of the various polymorphic systems in different ethnic groups showed several interesting features. The Rh(-) rate was very low, less than 1%,⁴⁰ with the exception of the minority races in Xinjiang Province in north-west China. As for α_1 antitrypsin, no deficient alleles, PiZ or PiS,⁴¹ have been found. Only recently, an infant with the genotype M₁S who died of hepatitis was reported from Shanghai.⁴² Lactase deficiency was widespread⁴⁰ with the exception of the Kazakhs and Uygurs who are traditional herders in Xinjiang. The deficient type of aldehyde dehydrogenase was quite prevalent among the Han race⁴⁰ (the majority race in China), a fact that may be related to the relatively low incidence of alcoholism among Chinese.

Molecular genetics

The success of DNA analysis in prenatal diagnosis and its great potential in medical genetics has had a major impact on Chinese researchers. Work on gene diagnosis started in 1982 both at the IBMS in Beijing and in Shanghai. It started with the thalassaemias and has extended to other genetic diseases, such as phenylketonuria, haemophilia, etc.

The α thalassaemias were studied first. Workers at the IBMS investigated the α gene organisation in 54 cases of Hb H disease.⁴³ Nearly 50% of them were found to be of the non-deletion type. A similar study was done in Shanghai with comparable results.^{43a} It is evident that, in contrast to the α thalassaemias seen in south-east Asia where α gene

deletion plays a major role, both α gene deletion and defective α genes are important in the pathogenesis of α thalassaemia in China. Bart's hydrops fetalis has been successfully diagnosed both in Beijing and Shanghai.^{44 45}

Using seven gene or DNA probes and 11 restriction sites, the RFLP haplotypes in the β globin gene cluster in 15 families with β thalassaemia from Guangdong Province were determined.⁴⁶ Thirty β^T chromosomes were found to be associated with seven haplotypes, three of which were new, suggesting that the β^T genes they carry are probably new. About 55% of the haplotypes were of the β gene framework III Asian. A similar study was done in Shanghai and 10 new haplotypes were found among 50 β^T chromosomes.^{46a} In order to discover the common β^T genes in south China, it is necessary to clone and sequence β^T genes. Two β^T genes from Guangdong were cloned and sequenced,^{47 48} one of which was due to a point mutation in the TATA box and was a new one in the Chinese. Such data will undoubtedly contribute to the successful use of the oligonucleotide probe method and to the improvement of the success rate of prenatal gene diagnosis of the β thalassaemias, which has already been accomplished by the indirect linkage analysis method.^{49 50} Recently, investigators in Shanghai have succeeded in using the oligonucleotide probe method to diagnose β thalassaemia prenatally.^{50a 50b} Work is in progress to develop new methods of gene diagnosis, such as biotin labelling of gene probes and the amplification of target DNA sequences by polymerase chain reaction.

Recently, successful prenatal gene diagnoses of haemophilia A⁵¹ and B⁵² and phenylketonuria⁵³ have been reported. It is to be expected that with the acquisition of more gene probes more and more genetic diseases will be amenable to prenatal diagnosis and carrier detection. However, because of the difficulty and expense in obtaining ³²P labelled dNTPs and restriction enzymes, such work will probably be limited to a few institutions in the larger cities.

Clinical genetics

In the past, genetic diseases were seen by paediatricians and internists. With the surge of enthusiasm in medical genetics after the cultural revolution, medical genetics departments or divisions were set up in many of the large hospitals over the country, especially those affiliated to major medical schools. However, only a limited number of medical schools are offering courses in medical genetics and clinical genetics has not yet reached the status of a medical specialty. Dysmorphology became a distinct branch

of clinical genetics years ago in the advanced countries, yet it remains to be initiated in China.

Even though many hospitals in the larger cities have genetics clinics, the level of expertise varies a great deal. Qualified and experienced genetic counsellors are relatively few. Only a few hospitals in Beijing, Shanghai, and Guangzhou can do enzyme assays, though many are able to perform karyotype analysis. Gene diagnosis is limited to one or two institutions in Beijing and Shanghai. It is evident that much needs to be done to upgrade clinical genetics in this country. However, it will not be long before this situation changes because of the increased emphasis placed on the prevention of genetic diseases by the Ministry of Public Health.

Research in clinical genetics has not received enough attention. Worthy of note is a group in Shanghai which has collected a large amount of data on inherited eye diseases from reports throughout the country, providing comprehensive coverage of this topic.^{53a} A classical genetic study on congenital deaf mutism in a district of Shanghai was carried out by the same group.^{53b} Relatively few centres are engaged in the study of multifactorial disorders. A mass survey of 11 congenital malformations, as recommended by the International Clearing House for Congenital Malformations of Newborns, was carried out between 1984 and 1986 in Sichuan Province.⁵⁴ Among the more serious malformations, the incidence of hydrocephalus is high compared with figures from other parts of the world. The incidence of neural tube defects was much higher in north China than in the south⁵⁵ and a nationwide survey is presently under way. A group in Shanghai has been studying the recurrence risk of a series of multifactorial diseases.⁵⁶ However, no report on the pathogenetic mechanism of any of the multifactorial disorders has appeared.

The future

With the serious population situation in China, prevention of genetic diseases has become an urgent problem. The seventh five year plan, starting from 1986, of the Ministry of Public Health has included genetic medicine on the top priority list. More and more funds will be allocated to genetic services and genetic research in the years ahead. Plans to organise a genetic counselling network are being drawn up and steps have been taken to set up several national centres for referrals in different regions of the country. These centres will also be responsible for the supervision of activities of this network as well as the training of personnel. It is expected that these measures will substantially reduce the incidence of many genetic diseases in the

long run. The founding of the Chinese Society of Medical Genetics last year will also contribute to the furtherance of efforts to control genetic diseases in China as well as to academic exchange and international collaboration. The future of medical genetics in China has never been so bright.

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