

## **Assessing the cost of community-based genetic screening programmes: some challenges and a suggested framework**

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If we are to make sound judgements about whether genetic screening programmes should be implemented or expanded, like other forms of organised health services, the programmes need to be reliably and accurately costed. Robust cost analyses, moreover, are an essential ingredient in economic evaluations of alternative genetic screening policies. There are specific characteristics of many genetic screening programmes that make the straightforward application of conventional principles of costing more difficult. Firstly, we review standard principles of costing in economic evaluation and the costing of health programmes. Secondly, we apply these principles to two Australian examples: HaemScreen, a Victorian workplace-based genetic screening programme for hereditary haemochromatosis, and a Sydney school-based genetic carrier-screening programme for Tay-Sachs disease and cystic fibrosis. We then examine the challenges of costing such screening programmes, and develop some guidance for achieving high quality cost analyses of community-based genetic screening programmes.

## **Consanguinity and genetic referral**

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Consanguinity describes a relationship between two people who are related to each other because they share a common ancestor: Cultures including the Dravidian Hindus of South India continue to practice marriage between relatives, such as uncle-niece and first cousins, as a means of strengthening family ties and retaining property within the family. The Division of Human Genetics, St. John's Medical College has been a referral centre for karyotyping and counselling since 1976. Analysis of cause of referral and consanguinity from 3,028 patients' records referred from April 1996 to January 2004 revealed 1,658 individuals were couples (n=829) referred mainly for a bad obstetric history (BOH) or rarely for infertility, there also were 813 individuals with multiple congenital anomalies (MCA) with or without mental retardation (MR), 371 female patients with either primary or secondary amenorrhea, 104 male patients with either hypogonadism or male infertility, and 31 individuals with miscellaneous causes like ovarian tumor, leukemia etc. A total of 238 couples (476 individuals) with BOH were consanguineous, as were 268 individuals with MR/MCA, 122 female patients and 29 male patients with infertility were born to consanguineous couples and there were 14 individuals with a miscellaneous cause of referral. Cytogenetic analysis revealed a chromosomal abnormality in 395 individuals, of whom 78 were either born to a consanguineous couples or had been married to a relative and presented with BOH.

## **Consanguinity and chromosomal abnormality**

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During the 6 years of referral of patients for karyotyping to the Division of Human Genetics, 326 cases were confirmed to have chromosomal abnormality. Among these patients, a numerical abnormality was present in 240 cases (73.6%), a structural abnormality in 65 (19.9%) and polymorphic chromosomal variation in 21 cases (6.0%). Consanguinity was present in 61 cases (18.7%), which includes 43 with numerical abnormality (18%), 10 with structural abnormality (10%) and 8 with a chromosomal polymorphism (38.1%).  $\chi^2=0.05623$ . The effect of consanguinity on chromosomal abnormality was statistically non significant.

## **The spectrum of haemoglobinopathies in Central-East India**

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Haemoglobinopathies are the most common monogenic inherited disorders of erythrocytes. India is a home of several haemoglobin variants causing suffering to afflicted individuals and imposing genetic, economic and psychosocial burden on family members. The spectrum of haemoglobinopathies identified in 1,015 cases referred from different parts of Orissa in Central-East India are presented. The most common haemoglobinopathies observed were: sickle cell trait (29.8%), sickle cell disease (7.5%), sickle cell-b-thalassaemia (1.7%), b-thalassaemia trait (18.2%), thalassaemia major (5.3%), thalassaemia intermedia (0.9%), HbE trait (0.9%), HbE disease (0.3%), E-b-thalassaemia (0.7%), HbD trait (0.2%) and SD disease (0.2%). There was a preponderance of males and age at presentation varied from early childhood to adults in the sickle cell disorders, followed by b-thalassaemia trait, and thalassaemia major. From a community perspective, sickle cell disorders with a high level of fetal haemoglobin are common in the general castes (0.3-20.7%), scheduled castes (0-8.9%) and scheduled tribes (0-5.5%). Transfusion-dependent b-thalassaemia syndrome was prevalent in the Brahmin, Karan, Khandyat, Teli, etc. Haemoglobin E was detected in the Brahmin and Khandyat castes and haemoglobin D in the Chasa and Khandyat castes. Most cases originated in Anugul district, followed by Khurda, Nayagarh, Phulbani, Cuttack, Jajpur, Dhenkanal, Ganjam, Keonjhar, Mayurbhanj etc. The genetically heterogeneous population of Orissa harbours major haemoglobinopathies belonging to Coastal and Southwestern regions. This study provides a comprehensive database on the spectrum of haemoglobinopathies in Central-East India.

## **Securing a safe and sufficient blood supply**

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In any country, there is a cohort of patients with genetically determined disease who have a life-long dependence on the ready availability of safe and appropriate blood or blood components. They are the obligatory recipients of blood. In any country, developed or developing, there are logistic, technical and fiscal factors which influence this availability of supply; the differences between developing and developed countries exist only in degree. The most effective delivery of the best available product will occur when a number of principles are recognised, acknowledged, put in place and operate efficiently. They include national coordination (and integration) of the blood supply, governmental support in both legislative and financial matters, an equality of availability to all in need, a strong and competent technical infrastructure and a network of knowledgeable and competent health professionals. The current situation will be reviewed with examples, and suggestions offered for future action for the benefit of those most in need.

## **Molecular evidence for temporal stratification in Chinese genetic history**

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The joint application of different molecular marker systems, such as microsatellites, SNPs and mtDNA sequences, in concert with computationally intensive model-based techniques, is allowing the development of an increasingly complex picture of human genetic history. With >1,100 million Han and 55 officially recognized minority populations accounting for another 100+ million people, PR China represents an example of such complexity. For this study, DNA samples from the majority Han, seven official minorities in north, south, west and central China, the Hui, Miao, Yao, Tibetans, Bo'an, Dongxiang and Salar, and one unofficial minority, the Kuchong, were collected. The samples were analysed with autosomal, Y-chromosome and mtDNA markers that had differing mutation behaviours, and the resultant molecular data then compared with known historical, archaeological and demographic information. Strong evidence for the temporal stratification of human migration in China was established from the molecular data, spanning the first human migrations into East Asia to recent historical migrations along the Silk Road. Data on internal population structure can be added to this evidence using computationally intensive model-based techniques, thus allowing researchers to include the influence of factors such as endogamy when considering the effect of population stratification in future human genetic studies.

## Meeting the present and future challenges of genetic disease

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Despite the wealth of information made available by the Human Genome Project, genetic disease is still subject to widespread public misunderstanding and to the associated possibility of health- and employment-based discrimination. This presents a major educational challenge to all involved, whether health professionals or members of support groups, and applies equally in developed and low income countries. Many of the concerns expressed with regard to genetic disease reveal a basic lack of knowledge of population genetic structure. This in turn creates difficulties in assessing the prevalence and distribution patterns of specific disorders, and in providing appropriate clinical and counselling advice, whether in western multi-ethnic societies or more traditional populations characterized by longstanding ethnic, clan or religious divisions. Given the bioinformatics capacity now widely and inexpensively available, there should be no major impediment to the development of community, regional, national or even international databases and registers for genetic diseases, with rapid transfer of information between centres. Yet, even in developed countries, remarkably few comprehensive disease registers are operational and the numbers of affected persons often remain unrecorded. Without reliable disease prevalence data, diagnoses will continue to be made largely on an individual or family basis and the knowledge-, time- and cost-efficiencies possible through a Community Genetics/Public Health Genetics approach to case-finding will be squandered. In the face of continuing financial stringencies and restricted health budgets in virtually all countries, this is an area that merits urgent action.

### Prevalence of thalassaemia and haemoglobinopathies in Cambodian children

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Alpha-thalassaemia and HbE have been reported to occur at high frequency (80%) in children with hypochromic microcytic anaemia from Siem Reap. In addition, HbPS has been reported from this region. The study aims to document the prevalence of anaemia, a- and b- thalassaemia and other haemoglobinopathies in children presenting sequentially to the Angkor Hospital for Children. Two hundred and sixty children between 5 months and 16 years of age were assessed with full blood counts, films, ferritin levels, HPLC, a-globin multiplex PCR and b-globin PCR. 110 anaemic subjects were identified with 61 cases of microcytic anaemia. Six subjects were iron deficient. 163 children (63%) had a haemoglobinopathy. The high prevalence of HbE (29%) in the study population is consistent with previous reports. By comparison b-thalassaemia (0.7%) occurs at lower frequency than previously reported. Alpha-thalassaemia occurs at high frequency (35.4% of subjects), but a large majority of subjects (78%) have a single gene deletion, with double deletions occurring at low frequency (5%). HbPS occurs at low frequency whilst the frequency of triplicated a genes in the survey population is consistent with that described in other populations. Although haemoglobinopathies are common in Cambodian children, the majority of abnormalities (heterozygous HbE and -a3.7) are clinically insignificant. Only 2 cases with clinically severe haemoglobinopathy (HbH disease and Eb thalassaemia) were identified.

## **Hb H disease: time to screen?**

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Current strategies to reduce the incidence of thalassemia are focused on identification of genotypes in affected carriers that will give rise to severe disorders associated with excessive mortality or morbidity in the affected offspring, i.e., Cooley's anaemia and Hb hydrops fetalis. To date, there is little interest in screening for HbH at birth and in the general population as there is a perception that it is a mild disease and for the same reason, genetic counselling and prenatal diagnosis is also not offered for at-risk pregnancies. We believe it is timely to open a discussion on the screening of HbH disease based on the following:

HbH is an important public health problem in many part of Asia due to the high carrier frequencies of alpha gene deletions.

Clinical manifestations of Hb H disease can be very heterogeneous varying from mild in the deletional forms to severe in the nondeletional types. Besides anaemia, other complications include iron overload, gall stones, reduced growth and development in children and increase in complications during pregnancy.

Laboratory based screening tests are readily available.

An ethical approach to care for patients with genetic disorders requires an open discussion by the community including participation of the potential defective gene carriers. Discussion should focus on the pros and cons of genetic screening/testing for HbH in accordance to established standards of medical care and personal values and preferences.

## **Haemoglobinopathies in Cocos Islanders**

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An investigation was conducted into the prevalence and types of haemoglobinopathies in residents of Cocos Island, a group of islands under Australian governance 3,000km NW of Perth, with a population of 630 Cocos Malays and Europeans. From 1998-2004, blood samples were received from 44 Cocos Islanders for haemoglobinopathy investigations, with FBC, film, HbH preparation, HPLC, Hb electrophoresis and DNA analysis performed. Thirty-five individuals (79.5%) had a haemoglobinopathy. The most common genetic defect was the aa/--FIL, a 30-34kb deletion involving the a1, a2 and zeta genes, present in 20 individuals. Heterozygotes had Hb 84-139g/L, MCV 62-77fL and 44% had positive HbH bodies. Ten individuals had -a3.7 and 2 aa/--SEA. There were seven HbH disease, six -a3.7/--FIL and one -a4.2/--FIL, and nine b-thalassaemias, one b-thalassaemia major and eight traits. Genotyping showed six of seven individuals to have the 45kb b0-Filipino deletion, with high HbA2 levels (6.0-7.8%), HbF 1.0-4.9%, haemoglobin 98-135g/L and MCV 63-68fL. No compound heterozygotes or variant haemoglobins were detected. The data show that haemoglobinopathies are prevalent in the Cocos

Islands, with bFIL and aa/--FIL the most common genetic lesions. These are significant mutations leading to a high risk of b-thalassaemia major and HbBarts hydrops fetalis. The incidence of the latter may be minimised by early fetal loss, due to absence of zeta chains with aa/--FIL. There is therefore a need for screening and preconceptual genetic counselling in this population with a restricted gene pool.

### **New strategies for DNA diagnosis and preimplantation single cell analysis of fragile X mental retardation syndrome**

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Fragile X syndrome is the most common inherited mental retardation disorder, and is caused primarily by hyperexpansion and hypermethylation of a polymorphic CGG trinucleotide repeat in the 5' untranslated region of the fragile X mental retardation-1 (FMR1) gene. Numerous diagnostic methods have been developed to detect this mutation, the most common being Southern blot and PCR analyses. The major disadvantage of Southern analysis is its difficulty in distinguishing between large normal and small premutation alleles, while standard PCR cannot detect large premutation and full mutation alleles.

We have developed an alternative approach for fragile X syndrome testing based on methylation-specific PCR that reliably discriminates between normal, premutation, and full mutation affected males and females. After sodium bisulfite treatment, one PCR reaction detects all nonmethylated allele sizes (normal and premutation), while two PCR reactions are used to classify the methylated allele(s) (normal, premutation, and full mutation). Using this triple ms-PCR strategy, we accurately classified the fragile X status in all 44 male and 45 female DNA samples that were tested.

At present, however, it is not possible to detect large premutation and full mutation expansions from the limiting DNA of a single cell. We will discuss two indirect diagnostic strategies that can be applied to preimplantation genetic diagnosis (PGD) of fragile X syndrome. The first involves detection of the normal maternal CGG repeat allele in male embryos, or of the normal maternal and paternal CGG repeat alleles in female embryos. The second involves utilizing a panel of linked polymorphic markers flanking the mutation site to track the mutant allele. We have analyzed this panel of markers in our local population to determine their informativeness, and these assays should enable PGD to be offered to a majority of couples at risk of transmitting this disorder to their offspring.

### **Alpha-haemoglobinopathies**

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Mutations of the a-globin genes are among the most common in man. Many of these mutations, both deletional and non-deletional, cause down-regulation or abolishment of a-globin chain production, i.e., a-thalassaemias. Other missense mutations can result in highly unstable haemoglobins, haemolytic anemias or a-thalassaemias. Still other uncommon mutations can bring about decreased oxygen saturation in blood, and cyanosis. Expression of a-globin genes begins during embryogenesis and persists throughout fetal and adult life. Serious a-globin gene

mutations can have deleterious effect upon affected fetuses during intra-uterine life, even death. Haemoglobin Barts hydrops fetalis, often found in Southeast Asian populations is one such an example. A recent review of HbH disease indicates that it might not necessarily be a benign condition as previously thought. In addition, triplication and even quadruplication of  $\alpha$ -globin genes may impact upon the phenotypes of  $\beta$ -thalassaemia. There are two  $\alpha$ -globin gene loci, and mutation affecting only one  $\alpha$ -globin gene usually does not have clinically discernible manifestations. Coupled with the lack of readily available and reliable laboratory screening tests for  $\alpha$ -globin gene mutations, these abnormalities have generally been neglected, in comparison to  $\beta$ -haemoglobinopathies. This presentation will review new knowledge on  $\alpha$ -globin gene expression, mutational diagnostics, and clinical relevance.

## **17 year trends in the prevalence of Down syndrome and maternal age in Victoria**

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The changing demographics of women giving birth and the greater use of prenatal screening and/or diagnosis have contributed to changes in the prevalence of Down syndrome (DS). Data extracted from two population databases – the Victorian Birth Defects Register and the Prenatal Diagnosis Database – have been examined to document trends in total and livebirth prevalence of DS from 1986 to 2002. Against a relatively stable birth rate, the total number of DS notifications has increased from 115 in 1986 to 195 in 2002 reflecting the greater number of early diagnoses of fetuses, and increasing maternal age. The expected decline in the number of babies born with DS due to increasing use of prenatal testing is not evident, with only a slight decrease in numbers over 17 years. However, the maternal age distribution for babies born with DS has changed significantly, with the proportion of women under 35 years of age decreasing from 75% in 1986 to 54% in 2002 ( $\chi^2$  for trend = 19.4,  $p < 0.001$ ). The relatively greater contribution to the livebirth prevalence of DS by older women in later as compared to earlier years may be due to the greater number of older women becoming pregnant, a lower proportion having diagnostic testing, and choices about termination following prenatal diagnosis. These results demonstrate the usefulness, and limitations, of population-based databases in assessing the impact of the changing demographics of pregnant women and the ever-changing pattern of use of prenatal testing.

## **Nature or nurture: Talent Identification of 13 – 22 year-old male and female cyclists in regional Queensland**

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Competitive track and road cycling are physiologically demanding sports, requiring enormous demands from the aerobic and anaerobic energy pathways as well as leg power. The successful performance of cyclists can be related to the volume and intensity of training. The purpose of this study was to establish if a 12-week specific cycling training program was adequate to change the

physical and physiological characteristics of novice individuals who were Talent Identified (TID) through the National Talent Identification Search Program (NTSP). A TID group (n = 7, age = 16 ± 2 yr, height 171 ± 1 cm, mass = 62 ± 8 kg, skinfold = 70 ± 30 mm, BMI = 21 ± 2 m<sup>2</sup>, FSA 0.38 ± 0 m<sup>2</sup>) and a Control group (n = 7, age = 17 ± yr, height 170 ± 1 cm, mass 64 ± 11 kg, skinfold = 76 ± 37 mm, BMI = 21 ± 4 m<sup>2</sup>, FSA 0.37 ± 0 m<sup>2</sup>) were matched for physical and physiological characteristics. The Control group had no cycling training program. Following the 12-week training program, the TID group decreased their skinfold reading and FSA by 14% and 5%, respectively. The Control group decreased skinfold reading by 9%. Both the TID and Control groups increased their post-test physiological characteristics during cycling specific laboratory tests, i.e., a 10-second bike power test (TID = 19% vs Controls 8%, respectively), a maximal oxygen consumption test (TID = 10% vs Controls 4%, respectively), a power output at individual anaerobic threshold (TID = 13% vs Controls 2%, respectively) and an averaged work output for a 30-minute bike test (TID = 18% vs Controls = 21%, respectively). The results of this study may provide an opportunity for further research into the genetic backgrounds of these individuals and/or the future of Talent Identification in Australia for novice individuals in the pursuit of athletic excellence.

### **Consanguinity and population health among the Irish Travellers**

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The Travellers are a distinct ethnic group making up approximately 1% of the Irish population. They are commercial/industrial nomads characterized by a specific set of customs, a private vocabulary and endogamy as preferential mating behaviour. Despite a variety of myths regarding their origins, analyses of classical marker data suggest that the Travellers are an isolate derived from the Irish population. As a marginalized group within society, the health status of Travellers is poor with elevated infant mortality and reduced life expectancy. In recent years consanguinity has become an issue for Travellers, due in part to a Roman Catholic episcopal ban on Traveller cousin marriages in certain areas. This resulted from the perception of a high incidence of metabolic disorders in the population due to consanguinity. Recent studies have demonstrated that transferase-deficient galactosaemia is the only metabolic disorder present in the Traveller population at significantly elevated incidence (overall carrier frequency of 1 in 11). Haplotype analysis of the predominant Q188R GALT mutant allele suggests that it has reached this frequency as a result of founder effect coupled with rapid population expansion. A national strategy has been approved recently by Irish Government for the provision of community genetics services to the Traveller community.

## HLA associations of Asian Indian patients with seronegative spondyloarthropathies

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Northern and southern Indian populations are likely to differ in terms of genetic make up. HLA typing of 300 healthy blood bank donors, 189 B27-positive and 130 B27-negative patients with seronegative spondyloarthropathies was done with a microlymphocytotoxicity technique using a sera set from One Lambda (Terasaki Third HLA (72) Well Tray) in our tertiary care teaching hospital in south India. Of the 189 B27-positive patients, only 20 (10%) are from southern India and the rest are from the north. Of our 85 south Indian healthy controls, only 1 (1.1%) was B27-positive, in contrast to the 10 (4.6%) who were B27-positive out of the 215 north Indian controls. Of the 24 significant positive and negative HLA associations (data not shown) detected by Chi square test using SPSS programme, HLA A32 was observed in B27-positive patients with spondyloarthropathy when compared with B27-negative patients (9.5% vs 3.1% p=0.02). HLA B38 was similarly associated with B27-negative patients with spondyloarthropathy as compared to both B27-positive patients (3.8% vs 0.5%, p=0.04), and healthy controls (4 vs 0.7 %, p=0.03). HLAs B13, B75/77, B15/57 and B62/40 were all less common in patients with spondyloarthropathy, irrespective of their B27 status.

## Prevalence of genetic risk factors for venous thrombosis in patients with Budd Chiari Syndrome and Portal Vein Thrombosis: a study from north India

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Budd Chiari Syndrome (BCS), characterized by hepatic vein thrombosis, and portal vein thrombosis (PVT) are frequently encountered in India. Both lead to haemostatic abnormalities, which may be due to primary and secondary deficiency of natural anticoagulants synthesized by the liver, protein C (PC), protein S (PS) and antithrombin III (AT). Point mutations in coagulation factors like Factor V Leiden (FVL), Prothrombin G20210A and MTHFR 677 C-T have been associated with venous thrombosis. These factors were studied with BCS and PVT. DNA analysis for FVL, PT G20210A and MTHFR 677 C-T by PCR-RFLP was carried out.

	Total	Hetero	Homo	Normal	Prevalence %	OR (95% CI)
Factor V Leiden						
Controls	316	10	-	306	3.16	
BCS	164	8	1	155	5.5	1.78 (0.71-4.46)
PVT	162	7	-	155	4.3	1.38 (0.52-3.70)
PT G20210A						
Controls	134	-	-	-	Nil	
BCS	76	-	-	-	Nil	
PVT	92	-	-	-	Nil	
MTHFR 677 C-T						
Controls	204	45	1	155	22.5	
BCS	74	17	-	57	22.9	1.00 (0.53-1.89)
PVT	59	18	-	41	30.5	1.48 (0.78-2.82)

Screening for AT, PC and PS was by functional assays, with 5/79 (6.3%) and 1/81 (1.2%) cases of AT deficiency found in BCS and PVT; 36/80 (45%) and 30/81 (37%) of PC deficiency found in BCS and PVT, and 30/60 (50%) and 23/83 (27.7%) of PS deficiency found in BCS and PVT respectively. Since PC and PS deficiencies are high in both conditions, the possibility of secondary deficiencies due to hepatocellular damage is high. Only FVL appears to have an increased prevalence in the cases. PT G20210A is not found in our population, by comparison with Caucasians.

### **Haematological malignancies in children with Down syndrome: a study from north India**

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Down syndrome (DS) is the commonest postnatally viable chromosomal anomaly having an incidence of 1:920 live births in India. These children have 10-20 fold increased risk of developing acute leukaemias. Transient myeloproliferative disorder (TMD) / congenital leukemia uniquely occurs with DS and most neonates show spontaneous regression. A retrospective analysis of our records in the Department of Hematology revealed 12 cases of DS presenting as acute leukemia in 11 yrs. The age of presentation of leukemia was birth-10 yrs and M:F was 2:1. The clinical spectrum of presentation ranged from neonatal jaundice, fever, bleeding manifestations and hepatosplenomegaly. At presentation, using peripheral blood findings (blast count of 56-96%), bone marrow examination, cytochemistry and immunophenotyping the cases could be classified as six cases of acute leukaemia (NOS), four cases of megakaryoblastic leukaemia (AML-M7), one case each of acute myeloid leukaemia (AML-M2) and acute lymphoblastic leukaemia (ALL-L1). Follow-up was available for seven cases and in five of them the leukaemia regressed spontaneously (TMD). One case died on follow-up. The cases of ALL-L1 and AML-M2 were 10 yrs and 7 yrs respectively and both responded to chemotherapy. All children who presented as AML-M7 were <1 yr of age.

### **A Community Genetics approach to screening for mental retardation in India: a model for developing countries**

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Some 0.55 million people living in semi-urban and slum populations were screened for mental retardation by trained primary health centre (PHC) doctors, nurses and community health volunteers (CHVs). The staff were provided with prior training on the detection, prevention and diagnosis of mental retardation, prenatal diagnosis, and reproductive responsibilities. Field visits were employed to confirm diagnosed developmental disabilities, and demographic data incorporating social maps of 10 PHCs were prepared. Cases detected by PHC staff with high-risk genetic factors were referred to CREMERE for cytogenetic and metabolic investigations, thus

linking the study population and the Referral Centre. A genetic team interacted with the patient and family members for genetic counselling. Data analyses confirmed mental retardation in 511 of 525 cases reported, reflecting the positive impact of training on the CHVs. Potentially preventable environmental factors, such as birth asphyxia, infections, and low birth weight were found in 251 cases (49%), 137 (27%) of which had additional genetic factors. Genetic causes were found in 186 (36%) individuals, the most common being Down syndrome. The study illustrates the urgent need for the integration of genetic screening into the public health services in India.

### **Screening of high-risk neonates and infants in India for IEM by GC/MS**

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Most inborn errors of metabolism (IEM) cause severe pathological sequelae, such as mental retardation, sudden infantile death or other irreversible conditions. The present study reports experience gained by CREMERE in the simultaneous, accurate chemical diagnosis of some 101 IEM by GC/MS using specific urinary metabolite markers. Of 1218 high-risk children screened, with clinical features including seizures, vomiting, poor feeding, metabolic acidosis, lethargy, mental and/or motor delay, 242 (20%) were diagnosed with a metabolic disorder. Amino and organic acidopathies accounted for 47% of these disorders, with MMA (n=19), MSUD (n=8), Glutaric aciduria types I & II (n=11), Propionic acidemia (n=8), OTC (n=5), Urea Cycle Disorders (n=7), FDPD (n=8), Galactosaemia (n=7), and Canavan disease (n=6) the most common. In NICU babies the prevalence of disorders was 78/299 (26%). Overall, low birth weight (34%), convulsions (33%), premature birth (27%), acidosis, refusal to feed (13%) and respiratory distress (13%) were recorded, with consanguinity, a history of mental retardation and the death of earlier sibs other high-risk genetic factors. With over 28 million annual births nationally, the data offer important information to health policy makers on the value of early detection and therapeutic management of critically ill neonates in India. They also emphasize the need for newborn screening as a Preventive Public Health Program

### **Genetic benefits of consanguinity: computer simulation of the effect of inbreeding on a-thalassaemia genotype frequencies**

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There is a recognized overlap between the geographical distribution of malaria and a-thalassaemia. There also is an unrecognized overlap between the geographical distribution of consanguineous marriages and a-thalassaemia. To evaluate the possible effect of inbreeding on selection of a-thalassaemia genotypes and population growth, a computer program was designed to simulate population reproduction under the selective survival pressure of malaria. The computer program was written in FuterBasic for Macintosh. The main input parameters were the coefficient of inbreeding ( $F=0-0.125$ ), probability of survival for different genotypes (sensitivity analysis was conducted for values in the 0.4-0.9 range), initial rates of genotypes, and initial effective population size. For each set of parameters, 100 runs were executed and genotype frequencies and growth rates were determined. The results indicate that the loss of a single a-

thalassaemia mutation due to drift is lower in more inbred populations and this effect is stronger in initially smaller populations. The growth rates of consanguineous populations were faster, and consanguineous populations reached twice the size of non-consanguineous populations after a variable but relatively small number of generations. The study suggests that consanguinity is genetically beneficial by increasing the chances of an a-thalassaemia gene 'taking off' and spreading through the population under the selective pressure of malaria. By extension, inbreeding benefits people by helping the emergence and spread of co-dominant and recessive mutations that increase fitness.

### **Cousin marriage and the nineteenth-century novel**

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Three currents of opinion concerning cousin marriage ran through the nineteenth-century and early twentieth century novel. Prior to 1862, marrying a cousin was portrayed as conventional practice, primarily leading to financial security and often dull domesticity. During the decade following 1862, when Charles Darwin had appeared to condemn inbreeding in his book, *Fertilization of Orchids*<sup>1</sup>, thereby igniting the debate about the possible dangers of consanguinity, novels reflected a degree of uncertainty and ambivalence towards marrying within the family. Some marital matches between cousins went ahead; others did not. Those that did not succeed seemed to involve a cousin partner whose respectable credentials were called into question. Far from being seen as safe, yoking oneself in matrimony with a cousin could lead to a life imperilled either by moral ambiguity or financial insecurity. From the early 1870s into the Edwardian period, despite medical and scientific opinion being divided on the issue, romances between cousins in fiction were inevitably thwarted by some tragic impediment and, perhaps because they were considered to be a forbidden fruit, were far more passionate than similar relationships represented a century earlier.

<sup>1</sup>Darwin C. *On the Various Contrivances by which British and Foreign Orchids are Fertilized by Insects, and on the Good Effects of Intercrossing*. London: John Murray, 1862.

### **Databases in the study of population genetic structure: the Demographic DataBase in Umeå, Sweden**

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The DDB contains the life histories of individuals and their families, based on the parish record books of the Swedish Lutheran church, with data covering the 18th and 19th centuries to a maximum depth of ten generations. The DDB databases (<http://www.ddb.umu.se>) are designed for research across a broad range of fields, and the information is readily accessible to researchers. A current study is based on consanguineous marriage in the Skellefteå region of northern Sweden. First cousin marriage was banned by the Lutheran church until 1680, and then was subject to royal approval until 1844. Between 1720 and 1899 there were 14,639 marriages in the study region. By constructing extended family pedigrees from the parish books and complementary data sources, it has been shown that 20.8% of marriages were between

consanguineous couples, ranging from first cousins ( $F=0.0625$ ) to sixth cousins once removed ( $F=0.000006$ ). The frequency and types of consanguineous marriages changed through time in apparent response to both religious and civil legislation, with first cousin unions increasing in number and prevalence during the course of the 19th century. To date, investigations have concentrated on the effects of consanguinity on spousal fertility, and offspring mortality. Future work aims to examine the relationship between consanguineous marriage and specific disease genes present at high frequency in the local population.

### **The GRAIDS trial: Genetic Risk Assessment on the Internet and Decision Support for primary care**

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Innovative methods are required to integrate genetic medicine into primary care and support the appropriate application of genetic research in clinical practice. Previous experimental studies have shown that computer support can improve the management of familial cancer by general practitioners. An on-going study is presented that progresses this work to a cluster-randomised trial in primary care, with 45 general practices in Eastern England recruited and randomised. Comparison practices attend an educational session and receive clinical guidelines about familial breast and colorectal cancer. In the intervention practices a lead clinician attends a training session covering basic cancer genetics and use of the GRAIDS software. The GRAIDS software is a simple pedigree-drawing program that implements clinical guidelines for familial breast and colorectal cancer. It also presents individualised information about breast cancer risk in a range of numerical and graphical formats, to support consultations with women whose risk is not raised sufficiently to warrant referral for genetic testing or mammography. Outcome measures include frequency of software use, practitioners' attitudes towards the software, total number of referrals to secondary care about familial cancer and the proportion that meet regional referral criteria, and a patient-centred measure of informed decision making. We will present the development of the intervention, the design of the trial, preliminary findings, and demonstrate the GRAIDS software. The family history will become an increasingly important tool in primary care to assess genetic risk. The GRAIDS software is a generic tool for pedigree production and risk assessment. The trial evaluates an approach to support high quality advice about cancer genetics in primary care which could be applied more broadly as our understanding of complex disease genetics increases.

## **A community profile of $\alpha$ -thalassaemia in Western Australia**

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Over the last 50 years there has been substantial migration to Australia. Initially migrants came from Europe, but over the last 30 years significant numbers have originated in SouthEast Asia and more recently SubSaharan Africa. Because of the changed migration pattern it is believed that  $\alpha$ -thalassaemia mutations have been introduced. This paper reports the results of a one-year study of the prevalence of  $\alpha$ -thalassaemia in Western Australia. Testing for  $\alpha$ -thalassaemia was performed on 920 blood samples referred from doctors or pathology laboratories in Western Australia as part of the investigation for a haemoglobinopathy. Molecular testing was performed on extracted DNA for single and double  $\alpha$ -globin gene deletions and mutations by PCR. An  $\alpha$ -globin gene abnormality was detected in 35.4% (326/920) of samples. There were 177 cases (50.6%) with a single gene deletion  $\alpha^+$ -thalassaemia, most commonly  $-\alpha 3.7\text{kb}$ , and 102 cases (31.2%) with double  $\alpha$ -gene deletions ( $\alpha^0$ -thalassaemia), most commonly  $--\text{SEA}$ , including 7 cases of HbH disease compound heterozygotes, were also detected. These findings amount to 1.7 new cases of  $\alpha$ -thalassaemia per 10,000 population in the 12-month period and demonstrate that  $\alpha$ -thalassaemia is an increasingly common disorder in the Western Australian population. This has implications for genetic counselling and health screening of at-risk populations.

## **Race, genetics and medicine: the role of genetic studies of population**

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Recent analyses of some 400 microsatellite DNA markers sampled from worldwide human populations allow us to depict the migration patterns and ancestry of modern humans. I will discuss how many markers and the sample size necessary to make these inferences. How these findings relate to recent debates on race and medicine will be addressed. One particular population of historical interest, residing in Israel, will be discussed in detail. I will conclude with a discussion of genetic relationships among Mycobacterium tuberculosis in patients from San Francisco and how these are related to medical research and human migration.

## **Prevention of thalassaemia and haemoglobinopathies in remote and isolated communities: the Maldives experience**

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The Maldives comprises 1,192 islands covering a land mass that is under 1% of the total geographical territory. The population of 280,000 is dispersed over 200 isolated communities, with an average of 1,000 people per community. Recent progress in health terms includes a reduction of the IMR from 62 in 1992 to 14 in 2003, and 95% child immunization. The problem of thalassaemia remained hidden as the Government focused on communicable diseases. However, interaction with the community by the NGO Society for Health Education (SHE) recognised the urgency in addressing the problem. In 1992, SHE established a national thalassaemia prevalence rate of 18.1% and launched a nation-wide awareness and population screening programme, visiting each island every five years and targeting 12 to 35 year olds. Screening results indicated a high incidence of  $\alpha$ -thalassaemia (28%) and identified islands with more than one haemoglobinopathy. There are few thalassaemia mutations – 75% bear IVS 1nt5 G-C and three types account for 98% of cases, ensuring the cost-effectiveness of PND. Outcomes include screening of more than a quarter of the population, the establishment of a Government National Thalassaemia Centre, a curriculum for thalassaemia, the legal requirement for screening, legalising PND and MTP, and the commencement of PND services. Programme successes include effective advocacy, resource mobilisation, motivation for screening, voluntary blood donation, and thalassaemia becoming a household word.

## **Genotype-phenotype interactions in $\beta$ -thalassaemia**

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$\beta$ -thalassaemia/HbE is clinically very heterogeneous in severity. A previous study showed that haemoglobin levels varied from 3-13g/dl (mean  $7.7 \pm 1.55$  g/dl). Major modifying factors in the mild cases were coinheritance of mild  $\beta$ -thalassaemia gene, coinheritance of  $\alpha$ -thalassaemia and increased production of HbF. We are conducting a prospective study into modifying genetic factors in  $\beta$ -thalassaemia/HbE patients. They were divided into 267 mild, 337 intermediate and 323 severe cases using strict scoring criteria, which include age of onset, age at first transfusion, requirement of blood transfusion, condition of the spleen and growth development. Results from the first 927 patients showed that the most common  $\beta$ -thalassaemia mutation is the 4 bp-deletion in codons 41/42 (42.1%). In mild cases the mutation in the -28 ATA (A->G) causing a mild  $\beta$ -thalassaemia and co-inheritance of  $\alpha$ -thalassaemia gene were found at prevalences of 1.9% and 26.6%. With the exclusion of these two genetic factors, absolute HbF was found to be higher in the mild cases in comparison to the intermediate and severe cases,  $3.1 \pm 1.14$  vs  $2.2 \pm 0.93$  vs  $1.8 \pm 0.6$  g/dl, respectively. The presence of the homozygous XmnI polymorphic site at the position -158 of the Gg-globin gene, which was previously found to be associated with increased HbF production and milder anemia, was found in only 7% of the mild cases in this study. Other single nucleotide polymorphisms in the BP1 and BP1 receptor, alpha-haemoglobin stabilizing

proteins (AHSP) and HFE genes in the three groups were not different. A further genomewide search for SNPs is underway, to identify other genetic factors that may contribute to the severity of the disease.

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### **Increased prevalence of non malignant life threatening conditions in a multi-cultural UK Child Development Centre**

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There have been a few estimates of the prevalence of non-malignant, life threatening conditions in English children. A report in 1987 estimated 26-27 such children in an average United Kingdom health district. Lenton and colleagues in 2001 reported 123 such children in Bath, giving a prevalence of 1.2/1000.

Recent studies have noted an increased prevalence in Bradford of conditions such as cerebral palsy, deafness, microcephaly, neurodegenerative disorders and visual impairment. Large numbers of autosomal recessive disorders occur in our Pakistani community, although individually each condition is still uncommon.

To ascertain the significance of these genetic disorders as part of the spectrum of serious childhood disability and illness we are undertaking a study to identify all local children with a non-malignant life threatening condition. We will report initial results of this ongoing study, focussing on children with disabilities attending Bradford's Child Development Centre. Fifty-eight of the Bath children had a neurodevelopmental disorder, classified as CNS abnormality, CNS degeneration, neuromuscular degeneration or 'syndromes'. For these categories, our prevalence is more than doubled. There are significant increases in autosomal recessive disorders, particularly for CNS and neuromuscular degeneration. The higher prevalence in the Pakistani population will be discussed.

### **Alpha thalassaemia in Malaysia: diagnosis and management**

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Alpha thalassaemia (a-thal) is the most common form of thalassaemia in Malaysia. The a-thal defect occurs in 2 phenotypes,  $\alpha$  thal 1 ( $\alpha^0$ ) and  $\alpha$  thal 2 ( $\alpha^+$ ). The  $\alpha$ -thal syndromes are carrier or trait, a thal intermedia or Hb H disease or thal intermedia disease and Hb Barts hydrops fetalis or a thal major. Carriers of  $\alpha$  thal 1 and  $\alpha$  thal 2 are asymptomatic where the presumptive diagnosis is by exclusion of a beta thalassaemia trait. DNA studies are required to confirm findings. The estimated prevalence of  $\alpha$  thal 1 in Malaysian-Chinese is 4.5% and in Malays 0.2%. In the Malays, the estimated prevalence of  $\alpha$  thal 2 is 15-23%. The rightward deletion ( $-\alpha^3.7$ ) is more common than than leftward deletion ( $-\alpha^4.2$ ). Co-inheritance of  $\alpha$  thal 1 and  $\alpha$  thal 2 defects results in Hb H disease. The most common non deletional a-thal is Hb Constant Spring. Hb H disease with the non deletional combination is more severe than the deletional type. Patients with Hb H disease

are asymptomatic requiring blood transfusions during pregnancy, in fulminant infection and when receiving oxidant drug therapy. Equal numbers of deletional and non deletional Hb H disease are seen. Hb H disease may also result from inheritance of Hb Q and  $\alpha$  thal 1 (Hb Q-H disease). Hb Bart's hydrops fetalis is the result of the coinheritance of two  $\alpha$  thal 1 ( $\alpha^0$ ) gene determinants. The most common  $\alpha$  thal 1 determinant in Malaysian Chinese is the -SEA defect which deletes 17.5-20 kb of the  $\alpha$  globin gene complex leaving the  $\alpha^1$  globin gene intact. The molecular basis of Hb Barts hydrops fetalis is -SEA/--SEA and include the possibilities of -SEA/--THAI and -SEA/--FIL. The co-inheritance of a thal in  $\beta$  thal syndromes ameliorates the clinical condition by reducing the chain imbalance.

## **Haemoglobinopathies in the population of Christmas Island**

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Christmas Island is a remote Australian territory 2400 km north of Perth. Health care is administered from Perth. The population mix is predominantly Chinese, with some Malay, Indian and European. Haemoglobinopathies are common amongst these ethnic groups; accordingly, a study to determine the significance of haemoglobinopathies in the Christmas Island population was undertaken. 364 individuals (adults and children) were tested, which represented approximately 15% of the Island's population (n=2200) at the time. All subjects were assessed by full blood count, a globin multiplex PCR, and PCR testing for Hb Constant Spring. Microcytic patients (MCV <80) were further investigated by BioRad Variant HPLC and serum ferritin was determined. Where present, b-thalassaemia mutations were characterised by PCR. Thirty four subjects (9.3%) were microcytic and of these 5 were iron deficient. The remainder were heterozygous for a haemoglobinopathy, giving an incidence of haemoglobinopathies in Christmas Islanders of 9.1%. Of the 8 subjects heterozygous for b-thalassaemia, at least 5 different mutations are represented, indicating diverse and heterogeneous origins for the population.

## **Effective external Quality Assurance for haemoglobinopathies**

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Quality Assurance is vital for reliable clinical testing, particularly when investigating patients for a genetic defect such as a haemoglobinopathy. Internal quality control measures daily accuracy and precision, while an external quality assurance programme offers a different but important evaluation. It measures the ability of different laboratories (and methods) to produce similar results and obtain the same diagnosis for a given specimen. The Royal College of Pathologists (Australia and New Zealand) provides such a Quality Assurance Programme and its application to Haemoglobinopathies will be presented.

## **Prevalence of haemochromatosis gene mutations in Cambodian children**

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More than 30 mutations of the HFE gene result in hereditary haemochromatosis, the commonest being homozygous C282Y and the second most common the H63D mutation. The prevalence of these mutations varies between populations. We assessed the prevalence of HFE mutations in 260 Cambodian children as part of a study of iron status and haemoglobinopathies. C282Y and H63D HFE mutations were assessed by PCR. There were no cases with the C282Y mutation, 19 H63D heterozygotes (6.4% frequency) and no H63D homozygotes. Twelve of the 19 (63.1%) H63D heterozygotes had an elevated ferritin, and 5 (41.7%) had a co-existent haemoglobinopathy. Of the children without the H63D mutation, 51.8% had an elevated ferritin, 51.2% of whom had a haemoglobinopathy. HFE mutations were rare in the Cambodian children, with 6.4% having H63D and no C282Y. No definite conclusions can be drawn as to the impact of H63D on the iron burden of children due to the small numbers. The ferritin in H63D heterozygotes was not influenced by co-inheritance of a haemoglobinopathy. Since H63D mutations have only a moderate effect on iron accumulation, it is not clear whether this mutation will affect the long-term iron status and the development of iron overload, particularly in persons with  $\alpha$ -thalassaemia.

## **The Western Australian Family Connections Genealogical Database**

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Understanding the inheritance of complex disease requires the combination of both genealogical information and health data at a population level. The Western Australian Family Connections Genealogical Database was recently established to address this need. Information from birth, death and marriage registrations is used to electronically link Western Australian residents into family tree structures. The initial focus is to create genealogical links from registrations recorded electronically since 1974. Linkages are made at the Data Linkage Unit which is situated at the Department of Health. It is also responsible for performing data linkages between population databases that contain health-related data for Western Australian residents. Strict international best practice measures allow linkage of sensitive information and permit genealogical data to be available for research purposes while protecting the identities of individuals. Through the Data Linkage Unit, health information for individuals who are genealogically connected to case subjects can be sought from the population databases that contain such data. The Western Australian Family Connections Genealogical Database will be an invaluable support tool for researching disease inheritance patterns at the population level. It is a unique resource which is made possible by the data linkage expertise and population databases that are maintained in Western Australia.

## **Intellectual disability among Indigenous Australians**

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The health and wellbeing of indigenous peoples is a significant global problem. Information on intellectual disability (ID) in the Aboriginal population of Western Australia was obtained from records maintained since 1953 by the Disability Services Commission, supplemented by linkage with data from other state databases on morbidity and mortality. Indigenous Australians form 3.5% of the state population, but comprised 7.4% (n = 734) of all people registered for ID services. Their level of ID was borderline or mild in 40.7% of cases, moderate in 19.9%, and severe or profound in 12.1%, but unspecified in 27.2% cases. Median survival was 55.1 years for males and 64.0 years for females, with a mean age at death of 19.6 years. A genetic aetiology was indicated in 131 cases (17.8%), including 32 people with Down syndrome. Leading causes of death in the study cohort were respiratory diseases, circulatory system disease, and accidents. The study provides a comprehensive overview of Indigenous Australians registering for ID services, but more specific information on geographical location, burden of disability and specific client profiles is needed. The data also illustrate the important role of well-maintained population databases in the detailed monitoring of health and wellbeing.

## **The Four Ages of Down syndrome**

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Down syndrome affects approximately 1 per 750-1,000 live births and is the most common known genetic form of intellectual disability. The typical picture evoked of a person with Down syndrome (DS) is usually of a young, happy, contented child, who is a much-loved family member. While detailed information on the clinical effects of DS is readily available, it is largely concentrated on events in the first decade of life. What often remains unstated is that life expectancy in individuals with DS has increased from approximately 15 to 60 years of age during the last fifty years. A change of this nature requires a major re-appraisal in our thinking, with greater focus on the medical and social needs of people with DS and their families across their entire lifespan. It has been assumed that, with improved medical technologies, younger Down syndrome cohorts will experience healthier lives than in previous generations. However, the health issues associated with the disorder are largely genetically encoded and their onset is usually age-associated. Four life stages of Down syndrome can be defined – prenatal, neonatal/early childhood, adulthood, and senescence – all of which exhibit specific comorbidities. To maintain a high quality of life for people with DS, these conditions need to be recognised and managed appropriately.

## **Genetic disorders in a paediatric teaching hospital, Cambodia**

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Angkor Hospital for Children serves as the provincial paediatric department for Siem Reap, Cambodia and also receives many children from outlying provinces. Cambodia is one of the poorest countries in Asia. The population can be divided into ethnic groups, such as Khmer Krom and Sino-Khmer, and intra-family marriage is common. The patient population is mainly drawn from rural communities without electricity or clean water, and there is 48% female illiteracy. The most common cause of childhood morbidity and mortality is infectious disease. Many of these patients have co-existing, previously undiagnosed, inherited haemoglobin disorders contributing to their morbidity, and data from an earlier survey of 300 out-patients in Angkor Hospital for Children showed that 58% had genetic haemoglobin disorders, including thalassaemia, G6PD deficiency and haemoglobin E. Rare haemoglobin variants and haemophilia have also been found. However, essential treatments for thalassaemia and haemophilia are currently unavailable in Cambodia. Multifactorial conditions, for example, congenital heart disease and cleft palate, are common and rare genetic diseases, such as congenital methaemoglobinaemia, incontinentia pigmenti, Seckel's dwarfism and ichthyosis are seen. Chromosomal syndromes also present regularly but, in the absence of chromosomal analysis, diagnoses cannot always be made, and appropriate genetic counselling cannot be given.

## **Beckwith-Wiedemann syndrome and IVF: a population-based, case-control study**

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We report the results of the first case-control study, done using population-based data sets, to test an association between IVF and Beckwith-Wiedemann syndrome (BWS). BWS is characterised by pre- and/or postnatal overgrowth, macroglossia, abdominal wall defects and sometimes other abnormalities including embryonal tumours. Cases diagnosed in Victoria between 1983 and 2003 were identified from the records of Genetic Health Services Victoria (the sole provider of Clinical Genetics services in Victoria), and the Molecular Oncology Laboratory, Royal Children's Hospital, Melbourne (the only Victorian laboratory offering molecular diagnostic testing for BWS). Four controls per case were randomly selected from births recorded routinely at the Perinatal Data Collection Unit, matched on baby birth date, and maternal age within one year. The overall prevalence of BWS was 37/1,316,382 livebirths or 1 in 35,578. Manual record linkage was used to see if the 37 cases and 148 controls were in the IVF databases held by the service providers. Ethics approvals were obtained from all sites. Four cases (10.81%) and one control (0.67%) were identified as IVF babies, Odds Ratio 17.82, Fishers Exact p value = 0.006. It is now clear that children conceived through IVF are at increased risk of BWS. We can quantify the absolute risk in our population because of the availability of population-based datasets.

## **Genotype-phenotype relationships in thalassaemia: predicting clinical severity by molecular testing**

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Beta-thalassaemia is characterised by a wide spectrum of phenotypic severity, the fundamental defect being an imbalance of  $\alpha$ - and  $\beta$ -like globin chains. The main underlying factors are (1) inheritance of mild  $\beta$ -thalassaemia alleles, (2) inherent ability to produce high levels of HbF, (3)  $\alpha$ -thalassaemia or extra copies of  $\alpha$ -genes, and (4) “unusual”  $\beta$ -thalassaemia alleles, e.g., dominant  $\beta$ -thalassaemia. An understanding of the mechanisms by which  $\beta$ -thalassaemia defects downregulate gene expression provides valuable insights into genotype-phenotype relationships. In transcription, deletions removing the LCR silence a structurally intact  $\beta$ -gene, while  $\beta$ -promoter defects also reduce transcription. In RNA processing, the important roles of splice junctions and aberrant splicing demonstrate a consistent relationship between the amounts of normally spliced mRNA and phenotypic severity. Premature termination codons (PTCs) disrupt mRNA stability and cause early interruption of translation. A relationship between the two mechanisms may explain why PTCs in 5' exons produce recessive  $\beta^0$ -thalassaemia, while those in exon 3 result in dominant thalassaemia. Increased expression of gamma-globin improves the  $\alpha/\beta$ -like imbalance and reduces phenotypic severity. Both cis- and trans-acting factors are implicated, although the identities of the latter (localised to chromosomes 6q, Xp, 8q) are undetermined. Alpha-thalassaemia and extra  $\alpha$ -genes modulate the  $\alpha/\beta$  imbalance. While  $\alpha$ -haemoglobin stabilising protein was found to prevent  $\alpha$ -globin precipitation, no clinical impact has been detected in  $\beta$ -thalassaemia/HbE. Multiple non-globin factors are also being evaluated in the complications of  $\beta$ -thalassaemia, e.g. HFE and hepcidin in iron accumulation.

## **The role of Genetic Support Groups in the development of Genetics Services in Victoria**

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Genetic Support Groups possess very powerful information, both biological and social. Clinical genetics services and researchers in genetics have traditionally drawn upon this information in a researcher-subject relationship, where the support group members are lesser partners in that relationship. In recent years there has been a move towards more collaborative relationships where the knowledge and power of the support group is recognised, respected and utilised. This has occurred in the context of reduced isolation of people due to electronic communication, and a strong movement of consumer participation in other health sectors. This talk will illustrate some examples where Genetic Support Groups have positively influenced the development of genetics services and research and demonstrate the power of both information and knowledge that is found in consumer organisations.

## **The effect of religious, cultural and social identity on population genetics**

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Knowledge of historical demography and contemporary social stratification can be valuable in understanding disease patterns including genetic disorders especially in communities that have a high prevalence of endogamous and/or consanguineous marriages. This paper provides a background to the religious, historical and socio-cultural factors that have helped define the bounds of endogamy for Muslims in undivided India and more specifically since the creation of Pakistan. The preference for endogamous marriages is based on the clan-oriented nature of the society, which values and actively seeks similarities in social group identity comprising several factors including religious, sectarian, ethnic, tribal/clan affiliation. Religious affiliation is itself multi-layered and includes other religious considerations other than being Muslim such as sectarian identity (e.g., Shia or Sunni etc.) and religious orientation within the sect (Isnashari, Ismaili, Ahmed etc.). Both ethnic affiliation (e.g., Sindhi, Baloch, Punjabi etc.) and membership of specific biraderi or zat/quom are additional integral components of social identity. Thus within the bounds of endogamy defined by above parameters, close consanguineous unions are preferential due to congruence of key features of group and individual-level background factors.

## **Prevention and management of thalassaemia in a low resource setting**

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Sri Lanka, a developing country with a land mass of 65,000 sq. km. and a population of 18 million, has a per capita income of 856US\$ and a per capita health expenditure of 25 US\$. It provides health and education free to its people. Facing the double burden of diseases in a low resource setting, Sri Lanka has a major challenge in managing its emerging non-communicable diseases. Although the thalassaemia case-load is not so heavy, the annual expenditure incurred for these patients is 5% of the total health budget. Sri Lanka has identified its projected future social burden if this disease is left unchecked, and has focused attention on prevention while improving quality of care. Over the years, curative and preventive efforts have gathered momentum resulting in an organized programme for thalassaemia control, well supported by individuals, interested parties, professional bodies, NGOs, other sectors, and the community at large. Awareness creation, with multisectoral involvement especially involving the media, education and health, along with screening and counselling, has provided a good impetus to the preventive programme. Case detection has been improved through an infrastructure established with assistance rendered by national and international donors and well-wishers. Although the cost of treating these patients is high, the government has committed itself to providing free care to all patients. Access to free care, made possible through the network of equitably distributed specialized care institutions, has improved the quality of case management and the prognosis of patients, thereby making a marked difference in the quality of life of people with thalassaemia. Community involvement is a hallmark, both in prevention and in the provision of care. With the wealth of experience already gained, the Government of Sri Lanka is in the process of establishing a National Programme for the ongoing support of individuals with thalassaemia.

## **Short on the outside but tall within**

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The presentation will tour the website, launching the book on Turner's syndrome (TS) to the wider world of parents, families, teachers and health professionals. Genetic counsellors at a delicate interface between families and the medical profession need to know of this work. Produced by a General Medical Practitioner, and consumer of health services, the focus is on information and empowerment of individuals affected by Turner's syndrome. The combined personal and professional understanding of the challenges adds depth to the themes explored. The resultant tapestry of personal narrative, shows the similarity yet diversity of people's attitudes and experiences and is a rich resource for health professionals. For health professionals, listening to people's experience and perceptions, allows better understanding of the difficulties they face. It also allows services to be developed to best meet the needs of consumers. For teachers, recognition of a child's potential, with appropriate expectations and educational scaffolding may transform a student's ability to achieve. For parents, key issues are support, advocacy, and cultivation of self-esteem and resilience. A treasury of people's life experiences, this unique work explores the social and emotional impact on individuals and families affected by Turner's syndrome. Pertinent issues of self-esteem, relationships and fertility, are relevant to all people with a genetic condition, not only those with TS.

## **The importance of Genetic Support Groups and the challenge of providing care in adulthood for those with genetic conditions**

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The role of Genetic Support Groups (GSGs) is largely unknown or little understood outside those individuals with genetic conditions or predispositions, their families, friends, and others who work within the sector. Nevertheless, GSGs make an enormous contribution to these individuals and their families. Increasing community awareness of this work is a significant challenge and efforts to raise awareness as to the role of GSGs are ongoing. Identifying and providing commentary on issues is a part of increasing this awareness. Peak bodies representing GSGs in Australia and New Zealand have formed the Australasian Genetic Alliance (AGA) which is supporting efforts to better respond to the needs of GSGs and their members. An emerging concern relates to primary care. Improved medical intervention and better health care has had a positive outcome in increasing life expectancy into middle or late adulthood for many people with previously life-limiting genetic conditions. Primary care needs for this group are likely to become a serious concern. There has been some thought that advances in genetic technology may result in fewer children being born with genetic conditions, to date this is not generally seen to be the case.

## **Vision for the future: development of a universal Regional Screening Service in West Yorkshire**

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Thalassaemia is one of the major serious inherited disorders. It has an increasing impact on individuals and families, population groups, both indigenous and immigrant, and community health resources. In the UK, 80% of affected babies are currently born to South Asian families. Local systems have been in place for 17 years in high prevalence (predominantly urban) areas and have provided selective haemoglobinopathy screening, timely antenatal testing, testing of partners, identification, counselling and pre-natal testing of at-risk couples, with testing of neonates/infants. Now the National Health Service plan demands integrated antenatal with universal neonatal haemoglobinopathy screening. In conjunction with the Health Care Commissioners regional network, we intend to provide a central screening laboratory for the expanded geographical area, IT networking, education/training resource, evaluation processes and development of the clinical service for affected individuals. This is based on the current process components, which include: booking bloods, partner testing, specialised haematology laboratory. At-risk pregnancy(s) are referred to a prenatal diagnosis clinic, genetic counselling is available. Invasive tests can be performed with samples being sent to the DNA laboratory for analysis. The complex process of the identification and management of carriers, at-risk couples and affected individuals in the context of universal screening will be illustrated.

### **Public health surveillance of genetic disorders**

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The discipline of public health genetics has been increasing in importance in the past few years, with governments needing to address such policy questions as the use of genetic tests as screening tools. Fundamental to the discipline of public health policy development is public health surveillance. This is well developed in a co-ordinated national approach in the field of communicable diseases, where timely response is critical, and for diseases such as cancer. Public health surveillance for genetic disorders has been accomplished in the most comprehensive fashion in the field of birth defects. As part of the growing co-ordinated involvement by government in national policy development, further development of national surveillance is required. Recent policy questions such as appropriate policies on screening for haemochromatosis, thalassaemia, cystic fibrosis and congenital adrenal hyperplasia, should be subject to a rigorous policy analysis process based on surveillance and research data.

## **A preliminary criminal DNA program in PR China**

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A preliminary Chinese Criminal DNA Database has been constructed by the analysis of samples from 2,500 offenders in custody in Shanghai, southeast China. Thirteen autosomal tetranucleotide STRs widely used in forensic identification were selected for the DNA profiling, together with the X-Y homologous gene Amelogenin for sex determination. Only one of the 13 autosomal loci showed significant deviation from Hardy-Weinberg equilibrium in the individuals genotyped. The cumulative discrimination power and power of exclusion of the 13 loci were greater than 0.999999999 and 0.9999888 respectively, giving an average match probability of  $5.5 \times 10^{-15}$  for the population. Allelic distributions at the vWA, TH01, D13S317 and D16S539 loci differed from African-Americans and U.S. Caucasians, and more detailed population data at these four loci may be needed to ensure their applicability for forensic purposes in Chinese populations. Previously unreported alleles were detected at several loci, some at relatively high frequencies, suggesting the need for their inclusion in the reference allelic ladder to meet the practical standard of forensic profiling in certain Chinese ethnic sub-populations. The preliminary DNA database provides base-line information applicable to the construction of a National Index System for criminal DNA profiling in PR China.

## **Health, education and genetic care of people with oculocutaneous albinism in Venda, South Africa**

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The frequency of the genetic condition oculocutaneous albinism (OCA) is almost ten times higher among the Venda people in northern South Africa than the world average, with an incidence of 1 in 1970 determined from hospital birth statistics. The Venda allow alliances between close relatives and practice a polygamous system of marriage. A community studied showed a very high frequency in one clan where OCA is found in the chief's family. OCA is a major cause of visual impairment in the region; most affected children attend special schools. Sun protection is a key aspect of the health education programme in this tropical region. The hypopigmentary phenotype associated with OCA in black population groups is distinctive; misconceptions and myths abound in local communities, with beliefs that albinism is linked to evil or supernatural forces. Genetic nurses at rural hospitals provide genetic and health care information and facilitate the social integration of families affected by albinism. Information pamphlets in the local language, workshops and focus groups, talks on local radio and articles in newspapers all serve to increase awareness and disseminate accurate information to help dispel misconceptions.

## Genetic modifiers of the b-thalassaemia phenotype in Chinese patients

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The clinical phenotype of b-thalassaemia syndrome is largely determined by the nature and severity of the b-thalassaemia allele, interacting a-thalassaemia mutations, and genetic determinants of enhanced g-globin chain production. In Chinese patients, homozygosity for b<sup>0</sup>/b<sup>0</sup>-thalassaemia is associated with b-thalassaemia major phenotype apart from rare exceptions. Compound heterozygous b<sup>0</sup>/b<sup>+</sup>-thalassaemia shows considerable phenotypic heterogeneity. Approximately two-thirds of patients behave as b-thalassaemia major and the remaining one-third behaving as b-thalassaemia intermedia. The genotypic finding of b<sup>0</sup>/b<sup>+</sup>-thalassaemia without other alleviating factor therefore cannot be used to predict b-thalassaemia intermedia phenotype in our patients. Homozygosity for b<sup>+</sup>-thalassaemia, i.e. homozygous nt-28 (A@G) is associated with b-thalassaemia intermedia phenotype. Likewise, compound heterozygosity for b<sup>0</sup>/b<sup>++</sup>-thalassaemia is predictive of b-thalassaemia intermedia phenotype. Since subjects harbouring these alleles are haematologically silent, they are not identifiable by current thalassaemia screening strategies and require molecular diagnostics for detection. Interactions between a- and b-thalassaemia occur at our locality due to high prevalence of both conditions. The (--SEA) a-thalassaemia (SEA) deletion ameliorates the clinical phenotype of b<sup>0</sup>/b<sup>+</sup>-thalassaemia but not necessarily b<sup>0</sup>/b<sup>0</sup>-thalassaemia. Two other interactions, HbH disease co-inherited with heterozygous b-thalassaemia, and triplicated a-globin genes co-inherited with heterozygous b-thalassaemia, necessitate the use of genotyping in arriving at a definitive diagnosis and explaining the inheritance in affected families. The latter genotype is found only among b-thalassaemia intermedia patients and is associated with a mild clinical phenotype. Possible genetic modification of disease complications, such as the hyperbilirubinaemia, iron overload and osteoporosis will also be discussed. The documentation of phenotypic diversity despite identical genotype, e.g., in compound heterozygous b<sup>0</sup>/b<sup>+</sup>-thalassaemia as well as HbE/b-thalassaemia, testifies to the presence of modifying factors, genetic or otherwise, that remain to be identified. It is envisaged that observations derived from genotype-phenotype correlation in genetic counselling to couples at risk of offspring affected by more severe forms of b-thalassaemia, but also in prognostication and guiding management decisions in the clinical setting.

This study is supported by the Research Grants Council and Children's Thalassaemia Foundation of Hong Kong

## **Uniparental markers, human migrations and histories**

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The human evolution literature has been dominated by single-locus studies of both the mtDNA and the Y chromosome. These uniparental markers have been used extensively to reconstruct human lineages, infer population expansions and trace ancient migration routes. However, the role of these markers in understanding human history is largely confined to testing hypotheses formulated using data derived from other disciplines such as archaeology, palaeontology and linguistics. Although these markers have been used to infer mass migration events, the increasing number of newly identified single nucleotide variants in both the mtDNA and Y chromosome has permitted high-resolution haplotyping. This can reveal novel and unexpected regional population differentiations. I will describe some specific examples of the use of uniparental markers to understand population movements and histories in both in Europe and Asia. I will also describe the inherent limitations of these single-loci studies and the need to avoid over-interpretation and over-simplification of the genetic data.

## **The London IDEAS Translation Project**

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The London IDEAS Translation Project aims to develop meaningful and accessible patient information about genetics for London's linguistically diverse communities, and ultimately to improve patient access to genetic services. London is the most linguistically diverse capital of the world, inhabited by over 45% of Britain's minority ethnic populations. Therefore, although this project is a local initiative, material generated will have global applications. Resources are available to translate up to 27 patient information leaflets in 12 languages, and there is limited provision for providing this information in audio formats. This five-year collaborative project is between The North-West Thames Regional Genetic Service and the Genetic Interest Group. To date, leaflets have been written in accessible English with uniform style, and a panel of clinicians has verified their content and accuracy. A "best practice" model for translating patient information has been developed, which includes steps of validation and community consultation. With this model, the first four languages have been translated. Language needs have been assessed by surveys and a conference of interested parties from around the UK. Translated leaflets will be made freely available (alongside the English version) to clinics over the Internet.

## **Strategies for the prevention of hereditary diseases in a highly consanguineous population**

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Autosomal recessive hereditary diseases are relatively common in the Saudi population. The consanguinity rate is in excess of 50% and remains strongly embedded within Saudi culture. The impact of this practice is recognized and is being addressed. Early detection and treatment of diseases can reduce mortality and minimize morbidity. This is the basis of successful neonatal screening for inborn errors of metabolism where treatment or modification of lifestyle can modulate disease. Ultimately, understanding the genetics of these diseases will provide opportunities for prevention. In addition options such as pre-natal screening and pre-implantation genetic diagnosis (PGD) can be used to reduce the incidence of live births with inherited diseases. However, prenatal diagnosis and associated intervention is unacceptable to wide sections of all societies and the application of PGD is restricted to relatively few individuals. Carrier detection and genetic counseling programs have been very successful in reducing incidence of inherited disorders. These programs are most successful when they are sensitive to the cultural backgrounds of populations in which they are applied. In Saudi society, premarital screening to identify carrier status and the provision of appropriate counselling has huge potential to PREVENT inherited disease at the population level.

## **Molecular characterization of G6PD deficiency in India**

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G6PD deficiency was first reported from India more than 30 years ago and some 13 variants have been characterized biochemically. However, the spectrum of mutations causing G6PD deficiency have not been elucidated. We have studied 182 unrelated G6PD-deficient males (78 referred with different clinical manifestations and 104 diagnosed during a population survey) to characterize the causative mutations in India. G6PD Mediterranean (563 C>T) was the commonest mutation (56.0%), followed by G6PD Kerala-Kalyan (949 G>A) (21.5%), and G6PD Orissa (131 C>G) (12.0%). G6PD Mediterranean, which was associated with the 1311 C and 1311 T polymorphism, had a more widespread distribution, a significantly lower red cell enzyme activity and more severe clinical manifestations than G6PD Kerala Kalyan and G6PD Orissa. G6PD Chatham (1003 G>A) with undetected red cell enzyme activity and G6PD Insuli (989 G>A) with normal G6PD activity were very rare in the Indian population. This study indicates that most of the G6PD mutations in Indians are located in exons 6 and 7 of the gene, in close proximity to the G6P binding site.

## **Spectrum of chromosome abnormalities and increased chromosome instability in myelodysplastic syndromes from India**

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Myelodysplastic syndrome (MDS) represents a group of clonal haematological disorders characterized by progressive cytopenia and reflecting defects in erythroid, myeloid and megakaryocytic maturation. The incidence of MDS is higher in the older age group. No previous studies on MDS have been available from India. We have studied cytogenetic and other aetiological factors in 80 patients with MDS. The mean age of the MDS patients was 42.05±0.4 years and more than 50% of patients were below 45 years of age. The cytogenetic study using GTG-banding revealed 37.5% clonal chromosomal abnormalities. We have also carried out a chromosome breakage study in MDS patients from peripheral blood cultures induced with mitomycin C, which showed a significantly ( $p < 0.001$ ) higher frequency of chromosomal breakage compared to age- and sex-matched controls. In our series the majority of patients were from an urban area and 41.3% were exposed to industrial pollutants. The results suggest that exposure to pollutants has a role in their chromosomal instability.

## **InterRett: the application of bioinformatics to international Rett syndrome research**

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Funded by the International Rett Syndrome Association, InterRett – IRSA Rett Phenotype Database is a unique international project which brings together child neurologists, geneticists, pediatricians, researchers and families of affected children. Its principal aim is to increase the clinical understanding of Rett syndrome throughout the world and in particular with large case numbers, determine any correlations between the phenotypic characteristics and the resulting genotype. Since the establishment of the database in January 2003, InterRett has registered 228 cases from 21 countries around the world. Family questionnaire data have now already been submitted on 147 cases and clinician data on 77 cases. Collated de-identified data collected from families and clinicians have been incorporated into a searchable online database which allows simple and complex interrogation of the clinical phenotype information to take place. InterRett will also serve as a clearing house for data to encourage collaboration with researchers from around the world. Current negotiations are in place with several countries for data contributions in excess of 1000 cases. The resulting online database will be an invaluable resource for understanding the nature and management of Rett syndrome as well as providing a model for other rare childhood disorders.

## **Implementation of HaemScreen, a workplace-based genetic screening program for hemochromatosis**

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There is debate as to whether community genetic screening for the mutation(s) causing hereditary haemochromatosis should be implemented, due to issues including disease penetrance, health economic outcomes and concerns about community acceptance. Haemochromatosis is a common, preventable iron overload disease, due in over 90% of cases to C282Y homozygosity in the HFE gene. We have therefore piloted C282Y screening to assess understanding of genetic information and screening acceptability in the workplace setting. In this program, HaemScreen, education was by oral or video presentation in a group setting. C282Y status was assessed by PCR and melt-curve analysis on DNA obtained by cheek brush sampling. Of eligible participants, 5.8% (1.5–15.8%) attended information and screening sessions, of whom 97.7% (5571 individuals) chose to be tested. Twenty-two C282Y (1:253) homozygotes were identified and offered clinical follow-up. There were 638 heterozygotes (1:8.7). The determinants for participation have been analysed in terms of the principles outlined in the Health Belief Model. Widespread screening for hereditary haemochromatosis is readily accepted in a workplace setting and a one-to-many education program is effective. The level of participation varies greatly and the advertising and session logistics should be adapted to the specific features of each workplace.

## **Educational challenges and outcomes of workplace genetic screening for haemochromatosis**

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The aim of education in any screening program is to allow participants to make an informed choice about screening. We piloted genetic screening for hereditary haemochromatosis (HH), a common, preventable iron-overload disease, and assessed understanding of genetic education via a self-administered questionnaire for 5,532 of the 5,775 participants. In this program, HaemScreen, education was by oral or video presentation in a group setting. Participants gained good understanding of the underlying cause of HH (85.6% correct) and how it can be prevented and treated (89.9%), but a poorer understanding of disease penetrance (50.3%) and genetic heterogeneity (64.0%). For three of the four knowledge measures, verbal and video presentation gave similar knowledge measures, but continuous loop video, viewed at participants' leisure, gave poorer knowledge outcomes. There was also a significant improvement in knowledge measures with increasing educational attainment ( $p < 0.001$ ). Clinical concepts were better understood by women than men (odds-ratio 1.7,  $p < 0.001$ ) whilst the reverse was true for genetic concepts (OR 0.73,  $p < 0.001$ ). Younger people understood the genetic concepts more than older

(OR 0.47,  $p < 0.001$  for  $>55$  years compared with  $<25$  years). We have demonstrated that one-to-many education is effective in this setting and that video presentation is as effective as verbal.

### **Genetic studies in the Old Order Amish**

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The Old Order Amish communities in the United States were founded by Swiss Mennonites, who fled religious persecution because of their belief in adult baptism. It is estimated that there were in the order of 8000 individuals who originally came to the United States in the early 1700s. Although the original communities were established in Pennsylvania there are now also Amish communities in Ohio, Indiana and other areas in the United States. They remain genetically isolated by their religious beliefs and have been the source of many genetic studies since Victor McKusick started his research on Ellis van Crevald syndrome in 1962. As a genetic isolate the Amish offer a number of distinct advantages to researchers in addition to their isolation. There is a great wealth of genealogical records, which can identify relationship, and there is also a high standard of medical care.

### **IDEA (Intellectual Disability Exploring Answers): a population-based database for intellectual disability in Western Australia**

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Since 1953 a database for intellectual disability (ID) has been maintained in WA by the Disability Services Commission (DSC) and its predecessors. In 2002 DSC agreed to ongoing transfer of data to the Telethon Institute for Child Health Research, and provided funds to maintain and improve the existing data and widen the sources of ascertainment. The IDEA database resulted and ID (IQ $<70$ ) is now ascertained from DSC, the Department of Education and Training and direct reporting to IDEA. The network of potentially linkable Western Australian databases that collect basic demographic information plus data on specific disabilities has been utilised in conjunction with the IDEA database to investigate various aspects of intellectual disability. Prevalence in school-aged children is 14.3 per thousand; greater in males (prevalence ratio 1.6); and in children of Aboriginal mothers (prevalence ratio 2.3). One third of children with an intellectual disability have a birth defect and Down syndrome is the single most common cause accounting for approximately 10% of cases. No underlying cause was identified in 62% of cases with evidence of a medical examination. Children identified only through educational sources rarely had a diagnostic label. Social disadvantage was shown to increase the risk of intellectual disability in the group with no identified biomedical cause particularly where the level of disability was mild-moderate.

## **Magnetic resonance imaging (MRI) measurement of cardiac iron concentrations: assessing the spatial variation of the putative iron marker R2\* in the myocardium of transfusion dependent $\beta$ -thalassaemia subjects.**

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Although the quantification of hepatic iron concentrations with MRI has been established in a number of studies through the measurement of an MRI parameter R21,2, similar measurements for myocardial iron using a parameter, R2\* remain under investigation3,4. Many complications such as cardiac motion and magnetic susceptibility artefacts are issues that need to be addressed. In this study a group of transfusion dependent  $\beta$ -thalassaemia patients managed with sub-cutaneous desferioxamine (n = 17) were scanned with two different relaxometry techniques to generate R2\* images of the heart and both R2 and R2\* images of the liver. The results show an inhomogeneous distribution of R2\* values throughout the left ventricle and also within the septum – a region generally considered free of artefact5. R2\* enhancement was seen in locations consistent with previous studies5, suggesting that such enhancement is due to magnetic susceptibility artefacts caused by the major cardiac vessels. It is yet to be determined whether the spatial variations of R2\* within the septum are related to spatial variations in tissue iron concentration or other physical phenomena such as tissue motion or magnetic susceptibility artefact. A reasonable correlation (R2 = 0.74) was seen between R2\* and R2 of liver tissue. However, no correlation was observed when the average R2\* in the septum was compared to liver R2 or R2\* (R2 = 0.02 and 0.11 respectively), consistent with previous observations3,4.

1. St. Pierre TG, Clark PR, Chua-anusorn W, Fleming AJ, Jeffrey GP, Olynyk JK, Pootrakul P, Robins E, Lindeman R. Blood. 2004; in press.
2. Clark PR, Chua-anusorn W, St Pierre TG. Magnetic Resonance in Medicine. 2003; 49: 572-575
3. Wood JC, Tyszka JM, Carson S, Nelson MD, Coates TD. Blood. 2004; 103: 1934-1936
4. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, Firmin DN, Wonke B, Porter J, Walker JM, Pennell DJ. European Heart Journal. 2001; 22: 2171-2179
5. Reeder SB, Faranesh AZ, Boxerman JL, McVeigh ER. Magnetic Resonance in Medicine. 1998; 39: 988-998

## **The incidence of a-thalassaemia in an Indigenous Australian Community**

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Thalassaemia has been reported to occur in indigenous Australians in northern Australia. The incidence and types vary between studies. Yenichsomanus (1986) and Tsintsof (1990) reported the -a3.7 kb thalassaemia single gene deletion in 27% and 6.9 % (respectively) of aboriginals from several communities. We undertook a population study of indigenous Australians with no racial admixture, from one community in the Kimberley of Western Australia. Peripheral blood from 185 subjects was collected following ethical approval, DNA extracted and tested for a-globin gene abnormalities by PCR. 36 samples (19.4%) were positive for the -a3.7 kb deletion, and all were heterozygous for this deletion. Subtype testing using Apa1 restriction enzyme showed 21 (58.3%) type II, with the remaining 15 types I or III. This differed from the Tsintsof

study in which type I was most common (>90%). No cases had the -a4.2 kb deletion or triplicated a-globin genes. Indigenous Australians are the only population in the Pacific region in which all three -a3.7 subtypes have been identified. It has been proposed that types I and II are South-East Asian variants, and therefore, may have been imported into the indigenous population. Type III may be from the Papua New Guinea population which originated in Melanesia.

### **Building the capacity of General Practitioners in cancer and genetics**

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The rapid expansion of genetic knowledge and technologies from the Human Genome Project has major implications for the role of General Practitioners in genetic medicine. With genetics becoming increasingly implicated in the aetiology of cancers, there is a rising demand for cancer genetic information and advice, which is increasingly becoming the domain of primary health care providers, particularly General Practitioners (GPs). The Family Cancer Program has been successfully upskilling Victorian GPs in cancer and genetics since the launch of the Victorian Family Cancer Genetics Service in March 2000. The education initiative has been building the capacity of the GP workforce in cancer and genetics through curriculum and resource development, and the delivery of interactive workshops; in 2003 approximately 6% of Victorian GPs participated in one of the 16 familial cancer workshops hosted by Victorian Divisions of General Practice. Research investigating GP referral patterns and accuracy is currently underway, with promising preliminary results. To complement the educative strategies, national and international strategic partnerships have been developed in advocating for increased GP access to high quality cancer genetics education.

### **Genetics education in a culturally diverse population: lessons learnt, future directions**

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The challenge of providing genetics education services to a culturally diverse population such as that of the people of NSW is not new. The Centre for Genetics Education, based in Sydney NSW, serves a population rich in many diverse languages and cultures and has done so since 1987. During this time, the make-up and the information and communication needs of the community have changed. In response to these changes, the content and format of genetics education resources have evolved. The methodology employed in guiding the modifications in the development and dissemination of resources will be discussed including:

1. The importance of involving individuals from cultural groups
2. The importance of involving cultural leaders
3. Overcoming language barriers without risking misinterpretation
4. Maintaining culturally appropriate terminology in often complicated, personal concepts

Evaluations of the process of developing culturally specific educational resources have shown that there can be stages of concern that have led to the development of appropriate protocols and policies that govern the practice of the Centre. Specific resources with “before” and “after” examples will illustrate the concepts discussed.

### **Lack of HFE mutations in patients of hereditary haemochromatosis and healthy controls from Tamil Nadu, South India**

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Hereditary hemochromatosis (HH) is caused most commonly by homozygous C282Y mutation in the HFE gene in the Caucasian population. Another mutation associated with HH is H63D. Very little is known about the distribution of these mutations in the South Indian population. We analyzed the two mutations in five patients who were diagnosed to have HH by clinical and biochemical parameters at the Christian Medical College and Hospital Vellore and in 45 healthy controls. DNA was extracted from five HH patients and 45 healthy controls using standard protocols. PCR was carried out for exons 2 and 4 and RFLP analysis was done using restriction enzymes, SnaBI and NdeII (MboI) for C282Y and H63D mutations respectively. The C282Y mutation was not detected in the healthy controls and in the HH patients. None of the HH patients showed the H63D mutation however one of the controls tested was heterozygous for H63D allele. The common HFE mutations described in the European population are absent in HH patients of South India. The cause of HH may be other mutations in the HFE gene or in other known or unknown genes of iron metabolism. Sequencing for the HFE gene in HH patients is underway.

### **Genomics and the role of Genetic Support Groups: an international perspective**

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The rights and dignity of individuals with disabilities attributable to genetics are recognised and honoured mostly in the developed world. Genetic Support Groups (GSGs) in these countries sensitised their public and Governments about the special needs of such individuals, which led to the enactment of specific regulations. They also played a proactive role in promoting genomics research in specific diseases, either by prompting their Governments or by raising resources themselves. However, in the majority of developing countries the struggle is still going on to ensure basic dignity for affected individuals. Prevailing prejudices in these countries ensure that a severely afflicted individual is confined within the house, or is simply allowed to die at birth, or is abandoned in a desolate place for nature to take its course. When female infanticide and feticide have been so difficult to eradicate, because of their social acceptance in developing countries, protection of the rights of genetically-ill individuals is an uphill task for GSGs. International Alliances of GSGs which played a prominent role in deciphering the riddle of genetic diseases have a crucial responsibility here. Genetics and genetically-ill individuals both can gain significantly if such Alliances from the developed world join hands with scientists from developing countries where the genetic load is maximal.

## **Possible role of Blood Transfusion Service (BTS) doctors in the prevention of thalassaemia, the most common inherited disorder in Indonesia**

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Thalassaemia, particularly  $\beta$ -thalassaemia is among the most prevalent genetic disorders in Indonesia. Its carriers were widely distributed in the country with frequency ranges from zero to almost 10% in various populations so far studied. It was predicted that without proper systematic preventive measures, it would become a potential health problem with significant impact in blood transfusion practice due to the large blood requirement. The existence of professional organizations in genetics and schools of medicine with their teaching hospitals did not seem to have adequate effect to prevent the increasing number of thalassaemia cases. Genetic services were only available in very limited centres, while public education in genetic issues was hardly available. In addition, professional organizations such as the Indonesian Society of Human Genetics and the Indonesian Society of Clinical Genetics had been idle for the last few years. In medical practice, thalassaemia cases could only be diagnosed in research centres or teaching hospitals with adequate facilities and well trained personnel which were mostly located in the provincial capital. Therefore, many thalassaemia cases were left undiagnosed and probably also untreated properly. The need of blood and blood products for thalassaemia patients was acknowledged by medical and paramedical staff in the Blood Transfusion Service (BTS). With more than 100 BTSs throughout the country, all serve more than a million units of blood per year. Despite their role in providing blood and having somewhat direct communication with the patients' relatives and community, BTS doctors had not been involved in any activities related to the prevention of thalassaemia. In fact, mobile units to collect blood in the community would be an ideal means for public education. Collaboration among professional organizations, schools of medicine, the BTS and district hospital should be encouraged to set up joint activities in the prevention of the disorder. Professional organizations and schools of medicine would provide training materials and expertise, the BTS should provide its medical and paramedical staff as the trainees, while the district hospital had to improve its laboratory facilities for genetic services. Following the training, the BTS staff were expected to have enough knowledge and skills to educate the people and provide counselling, while the district hospital would improve its ability to screen thalassaemia carriers. Above all, the Department of Health should be responsible for taking the initiative and making this programme applicable. Such comprehensive activities would hopefully reduce thalassaemia cases in the future.

## **Computerized calculation of the roll-off points in Kaplan-Meier population survival curves**

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Kaplan-Meier curvilinear analysis is a useful and well-used tool for plotting population survival estimates against analysis time. A practical consequence of this method is that the researcher must make a subjective estimate of the curve roll-off separating different age groups within one cohort. A computer program has been written to minimize the subjectivity and to mathematically calculate the roll-off point by evaluating the intersection point between two regression lines fitted to each "arm" of the curve. The program, written in interpretive BASIC can be run on multiple platforms and accepts data in standard spreadsheet form from a variety of programs. The experimenter selects two zones on the Kaplan-Meier graph based on minimal regression

coefficients. The program calculates the intersection point and presents the answer in years. A further version of this program is in development to provide a more user-friendly visual interface. Data are presented showing computerized vs manual analysis of Kaplan-Meier survival estimates for several population cohorts.

## **The Human Genome Project and population health**

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One of the ultimate aims of the Human Genome Project (HGP) is to enhance human welfare. While the HGP has achieved its major milestone of determining the DNA sequence of the human genome, it is far from being completed. This will not have happened until the DNA sequence is fully annotated, the functions of all genes and their interactions with each other and the environment are known, the significance of all genome variation for health and disease is understood, each community is comfortable with the applications of genomics to health and welfare, and no individual is discriminated against on the basis of genome variation. The understanding of our genome and those of our pathogens and parasites should lead to new ways of combatting infectious and parasitic diseases. The identification of disease susceptibility genes and the mechanisms by which they operate opens the way to potentially delay the onset and then specifically treat many of the common diseases of adulthood that result in morbidity and premature death. The use of pharmacogenomics offers the means to develop and use new, cheaper drugs that should have fewer side effects and be better targeted to individuals in which they will be efficacious.

## **A population-based study of birth defects in Malaysia**

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Data on birth defects from population-based studies originating from developing countries are lacking. The objectives of this study are to determine the epidemiology of birth defects and to identify risk factors for major birth defects in Malaysian births from 22 weeks gestation until one week of life, delivered at the Kinta district, PERAK, Malaysia over a 14-month period using a case-controlled population-based birth defect registry. There were 253 babies with major birth defects in 17,720 births, giving birth prevalence of 1 in 70 (1.43%; 95%CI:0.87-1.99). The exact syndromic diagnosis of the babies with multiple birth defects could be identified in 62 (77.5%) babies. Isolated major birth defects were cardiovascular (13.8%), cleft lip and palate (11.9%), clubfeet (9.1%) and central nervous system abnormalities (7.9%). The babies with major birth defects were lighter, more premature, had higher Caesarean section rates, required prolonged hospitalization and more specialist care and had a perinatal mortality rate of 25.2%. Mothers with affected babies were older, had birth defects themselves or were in their relatives, had a consanguinity rate of 2.4%, and had higher rates of previous abortions. Risk factors identified for birth defects using multivariate logistic regression were maternal insulin-dependent diabetes, previous abortions, maternal recall of exposure to teratogens during pregnancy but not lack of periconceptional folate supplementation. Further investigations are required to investigate the

role of periconceptional folate supplementation and to confirm the above findings. Pre-natal screening for insulin-dependent diabetes, counselling and investigating causes for previous abortions and public education on avoidance of teratogens may reduce birth defects in this population. A Birth Defect Register must be set up to monitor these developments in Malaysia.

### **A database profile of Angelman and Prader-Willi syndromes in Western Australia**

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The study focused on the life histories of individuals diagnosed with Prader-Willi (PWS) or Angelman syndrome (AS) in Western Australia. Data obtained from the client files of the Disability Services Commission (DSC) were supplemented by information from the state Genetic Services database, and the Hospital Morbidity data system. A total of 90 individuals were identified from the DSC database: 19 female and 15 male AS, and 26 female and 30 male PWS. Nine of the 90 subjects were deceased (7 PWS and 2 AS); the age range of living patients was 0.9-46.8y (mean 19.5y). The level of intellectual function varied from normal to profoundly handicapped (IQ<40), with 9% of undetermined capacity. Average age at diagnosis was ~six years for both syndromes (range, 0.1-27.0y). Information collected included clinical presentation, details of laboratory investigations, and hospital admissions for each individual. Analysis of these data has enabled the establishment of a database that offers detailed advice to families and support agencies on the life-courses of both disorders. Further information will be added to the database as it becomes available, to maximise the benefit to these groups.

### **A global perspective of genetic disease**

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The inherited disorders of haemoglobin, notably the thalassaemias and sickle cell anaemia, are the commonest monogenic diseases. As countries pass through the epidemiological transition, whereby childhood mortality rates in the first five years of life fall due to improved nutrition, better sanitation, and the control of infectious disease, babies with inherited diseases who had previously not survived are now presenting for treatment. Although accurate data are still limited, it is clear that this process has resulted in the thalassaemias becoming an increasing health burden to the countries of Asia; sickle cell anaemia will present a similar problem in sub-Saharan Africa for the future and is already producing a major drain on health resources in parts of the Middle East and India. Because of the major global health problems presented by malnutrition and infectious disease, the world health community has been slow in appreciating the increasing importance of these common genetic diseases. Recently, however, some progress has been made. The WHO Report, Genomics and World Health, which made important recommendations for the control of the haemoglobinopathies, was adapted for action at the 53rd World Health Assembly in May 2004. At least this should ensure that the governments of the member states are aware of the problem and about some of the steps that are necessary for the better control of the haemoglobinopathies worldwide. Since the development of methods for the radical cure of the haemoglobin disorders, with the exception of bone marrow transplantation, may take many years

and may be very expensive when they are available, there are a number of priorities which need to be met in the immediate future: better information about the carrier frequency of the haemoglobin disorders as the basis for more accurate predictions of health burdens; more accurate information about the mechanisms for the genetic heterogeneity and the natural history of the intermediate forms of thalassaemia such as Hb E b thalassaemia; the development of adequate screening and counselling facilities and, where acceptable, prenatal diagnosis services; more extensive screening for blood borne pathogens; and the development of regional networks for updating, training, and help for countries with inadequate control programmes.

### **Major haemoglobinopathies in a children's hospital: a 20 year review**

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We reviewed records of the 102 children with a major haemoglobin disorder diagnosed in our laboratory in the years 1984 to 2003 inclusive. Forty-four children had a severe b-globin thalassaemia state (homozygous b-thalassaemia - 37, HbE/b-thalassaemia - 5, with single cases of HbLepore/b-thalassaemia and db-/b-thalassaemia double heterozygotes). Six children were not born in Australia. The remainder presented with anaemia; 22 by 12 months and all but 4 by 4 years of age. The parental background was varied - (Arabic - 15, Mediterranean - 12, South Chinese - 8, SE Asian - 7 and Indian -2). a-thalassaemia disorders were less frequent with 16 children, mostly of SE Asian background, diagnosed with HbH disease, usually by the age of 5. Forty-two children have a major Sickle cell disorder-(HbSS - 25, HbS/b-thalassaemia - 11, HbS/D - 2, HbS/OArab - 2, HbS/C - 1 and HbCC - 1). Nine of these children were born outside Australia; the remainder presented with various symptoms, usually by 8 years. The parental background was mostly Arabic - 29, with African - 11 and 2 with parents born in Turkey. Children with major haemoglobinopathies continue to present to our Hospital. In this cohort, 34 children with b-thalassaemia major and 6 with Sickle cell disease currently require regular blood transfusion and iron chelation therapy.

### **Redirecting pre-mRNA splicing with antisense oligonucleotides**

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Antisense oligonucleotides (AOs) are typically used to down-regulate expression of a target gene, normally through the specific degradation of that gene transcript through RNaseH induction or blockade of protein translation. Another application of AOs is to displace factors involved in pre-mRNA processing, where intronic sequences are removed and the exonic regions are precisely spliced together. In this manner, specific exon(s) may be targeted for removal to skip particular regions from the mature mRNA. We have used this targeted exon skipping approach to by-pass disease-causing mutations from the huge dystrophin gene transcript, by removing exons carrying nonsense mutations or restoring the reading frame around frame-shifting genomic deletions). With an estimated 15% of all human gene mutations altering splicing patterns, such an AO-based re-modulation of splicing could be applied to a variety of conditions, from the rare Hutchinson-Gilford Progeria Syndrome to some of the more common b-thalassaemia mutations. Furthermore, it has been estimated that some 200,000 different gene transcripts are

present in the human transcriptome from only approximately 25,000 genes. Some transcripts arise from the use of alternative promoters while the majority result from alternative splicing. Redirecting splicing patterns could therefore be relevant to over two thirds of all human genes.

### **Y-chromosome and mtDNA studies into the population structure of the Christmas Island community**

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Christmas Island is a remote Australian territory located close to the main Indonesian island of Java, and 1,540 km from the coast of Western Australia. The Island was annexed by Great Britain in 1888 and indentured Chinese labourers were recruited to mine the phosphate deposits. After WWII additional labourers were hired from Malaysia. The present population comprises approximately 60% Chinese, 25% Malay and 15% European or other. To determine the genetic structure of the Christmas Island population, markers on the Y-chromosome and mitochondrial DNA (mtDNA) were investigated in 92 individuals. Y-chromosome biallelic polymorphisms revealed moderate to high frequencies of markers M95 (15%), M119 (23.3%) and M122 (36.7%), consistent with ancient male origins in Southern China and SE Asia. mtDNA hypervariable segment I (HVS-I) sequences revealed high levels of genetic similarity to the Southern Chinese, Hong Kong Cantonese, Indonesian Moluccas and Thai. The mtDNA COII/tRNA<sup>Lys</sup> 9-bp deletion was present at a relatively high frequency (31.5%), and in conjunction with the HVS-I polymorphisms suggested two distinct origins from China and SE Asia. The present study provides a useful model for the investigation of contemporary populations derived from different origins and could play an important role in the study of inherited disease.