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Report on the First International Workshop on the Genetic Epidemiology of Complex Traits using Twins and Sib-Pairs

The First International Workshop on the Genetic Epidemiology of Complex Traits using Twins and Sib-Pairs took place in Cambridge, UK, 26–27 March 1998. The organisers, the Twin Research Unit of St Thomas' Hospital, London, UK, called on experts in twin and genetic research from such well-known centres as the Queensland Institute of Medical Research (Brisbane, Australia), the Medical College of Virginia (Richmond, VA, USA), the MRC Environmental Epidemiology Unit of the University of Southampton, UK, the Department of Public Health of the University of Helsinki, Finland, and the Department of Psychophysiology of the Free University of Amsterdam, The Netherlands. One hundred and ten participants, faculty included, attended the workshop.

It is a hopeless task to report on all presentations. I shall limit myself to the topics that are of major medical interest.

Day 1 was devoted to the use of twins and sib-pairs in epidemiological research. David Strachan (Department of Public Health Sciences, St George's Hospital Medical School, London, UK) analysed the influence of design on the outcome of twin studies. Twins affected by a disease of interest may be ascertained either from medical records like case series, disease registers, or among sets of twins responding to media appeal. Alternatively, affected twin pairs can be ascertained systematically from birth records or other population registers. Concordance and co-twin studies published in recent decades were reviewed and used to illustrate the potential biases arising from the main study designs.

Jaakko Kaprio (Department of Public Health, University of Helsinki, Finland) has wide experience of using the population-based Scandinavian twin registers, which can be considered models for unbiased studies. He illustrated the principles and the practical issues in subject selection and case ascertainment in large-scale twin studies on cancer and selected other chronic diseases in adults.

Why select twins for sib-pair studies was one of the questions he raised.

(1) Twins are easier to identify from birth records than ordinary sibs.

(2) The existence of a register with twin and/or family data is of great assistance in defining study samples.

(3) Dizygotic pairs are sib-pairs that are matched for age, cohort effects (eg number of older sibs, family environment, school and cultural factors), and full sibs (low probability of false paternity).

Possible disadvantages are intra-pair interaction (in utero, childhood); dizygotic twinning is a heritable trait.

He discussed many other aspects of twin studies, eg the representativeness of twin data sets, the screening for disease-concordant pairs, the effect of age on the selection of the target population, the case definition, prevalence versus incidence data, prospective versus retrospective data, etc.

David Phillips (MRC Environmental Epidemiology Unit, University of Southampton, Southampton, UK) attempted to answer the question 'Foetal programming or genes?' Recent findings in singletons suggest that non-insulin-dependent diabetes (NIDDM), hypertension and circulatory disease are linked with impaired growth during foetal life and early infancy. Because genes do not appear to play a major role in controlling foetal growth, it has been suggested that these associations arise as a result of 'programming' rather than the operation of genetic factors. Programming occurs when a stimulus or insult at a critical period of development results in long-term changes in physiology and metabolism. There is increasing evidence that long-term alterations in the set point of major hormonal systems (for example, adrenocortical hormones and GH-IGK1 system) may be important mediators of programming.

In contrast, twin studies of people with NIDDM or hypertension show greater concordance in monozygous (MZ) than dizygous (DZ) twins, suggesting a significant genetic component to their etiology. Because MZ twins often share a placenta and tend to have vascular anastomoses between the two members of a pair, it is possible that the greater similarity of MZ compared with DZ twins may be due to their more similar early environment. However, it is also possible that the relationships between birth size and NIDDM or hypertension represent the lifelong operation of disease susceptibility genes. The author and his co-workers studied twins identified through a longitudinal study of births within the city of Birmingham, where from 1950 onwards details of all births were recorded, including weight and size at

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birth. Out of 477 pairs born in 1950–54, 136 complete pairs (45 MZ and 91 DZ, aged 40–46) attended a local clinic for a 75 g oral glucose tolerance test. A classical twin analysis revealed greater similarities in adult glucose tolerance in the MZ pairs compared with DZ twins (intraclass correlation for 2 h plasma glucose 0.4 vs 0.1). Multilevel modelling analysis, however, suggested that the twin similarities were not explained by their size at birth.

Although among the MZ pairs (19 male and 26 female), the shorter twin at birth had evidence of insulin resistance, with highest levels of 2 h insulin ($P = 0.03$) and fasting 32–33 split proinsulin ($P = 0.003$), in general within-pair differences in birthweight did not correlate with adult glucose tolerance. However, where there were substantial within-pair birthweight differences (1.0 lb or more) both twins of the pair were more obese as indicated by a higher BMI, and had higher 2 h-plasma glucose ($P < 0.05$) and 2 h-plasma insulin levels ($P < 0.01$) than the MZ twins with lesser within-pair differences in birthweight. These trends were not observed in DZ pairs. This study suggests that the association between size at birth, insulin resistance and glucose tolerance is, at least in part, independent of genetic factors but is complicated by twin–twin interaction.

Commercial, legal and ethical issues were discussed by Paul Kelly, chief executive officer of Gemini Research Ltd, Cambridge, UK. Dr Kelly is an endocrinologist and himself a twin. Genomics is poised to revolutionise the way we think about human health and disease and the delivery of compounds for treatment of disease. While many are still waiting for substance behind the 'genomic hype', the generation of genomic information, genomic databases and platforms to facilitate rapid high throughput genomic analysis indicate that this revolution in health care is already upon us. There is, however, a relative glut of genomic information with an emphasis on target validation more than discovery. Moreover, aging is redefining our concepts of disease; human physiology has little regard for 'disease' boundaries. The challenge is for those working in human genetics, whether they be from industry or academia, to maximise the utility of human genetic information particularly as it relates to complex trait disorder. This requires forethought to deal with ethical consent and issues that may arise from future data analysis. Human genetics offers solutions to many of the current problems in genomics and major discoveries will be made with co-operation and trust between academia and industry, with both groups working to each other's strengths to fulfil each other's goals. The company is looking for academic partners among those conducting twin studies in Europe, North America, Australia and Asia.

From heritability to QTL (quantitative trait loci) detection was the main topic of Day 2. Joe Christian (Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN, USA), a pioneer in the statistical analysis of twin data, compared ANOVA and maximum likelihood power using 1000 simulation of 50 MZ and 50 DZ twin pairs and normally distributed variables. He emphasised that, in using the classical twin method, population random mating, no gene-environmental interactions and equal zygosity environmental covariances are usually assumed. In the comparison of MZ and DZ twins, ANOVA and likelihood methods have similar results and power when used to estimate genetic variance, and environmental variances unique to individuals or common to co-twins. Violation of the assumptions of equal total zygosity and common environmental variances has the potential of causing significant biases in estimates. Recent evidence suggests that prenatal environmental influence, as measured by placental type or dermatoglyphic variation, influences phenotypes later in life. The strongest evidence for the prolonged effects of prenatal environment has come from studies of personality and cognitive function.

According to Nik Schork (Case Western University School of Medicine, Department of Epidemiology & Biostatistics, Cleveland, OH, USA), the detection of loci influencing variation in human quantitative traits (QTLs) is, and will probably continue to be, a major challenge facing human geneticists and epidemiologists. Aspects of the two traditional marker-based methods for mapping human QTLs – parametric modelling and allele sharing methods – can be combined into a more flexible and powerful analysis tool based on standard linear models and variance components models. He showed how these newer models could be applied to twin data and take advantage of MZ/DZ differences, covariates, and multiple locus effects. He examined the power of this new approach in both linkage and association analysis settings via analytical derivation and simulation studies. One of the main themes of the research he presented was the contrast of association and linkage analysis.

Cathryn Lewis (Division of Medical & Molecular Genetics, Guy's Hospital, London, UK) developed the use of sib pairs and parent–child trios in association studies. Linkage disequilibrium can be detected through case-control studies where a particular allele or genotype is detected at higher frequency among cases than controls. A population-based design would use affected and unaffected twins, where twins may be discordant pairs, or

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chosen from the set of genotyped and phenotyped twins.

Most methods for detecting linkage disequilibrium were developed for discrete traits, but extension to quantitative traits is possible, either with non-parametric methods (Rabinovitz et al 1997) or using a parametric approach (Allison 1997) for parents where precisely one parent is heterozygous with genotype AB (alleles A and B).

Nick Martin gave a masterly review of gene–environment interaction and twin studies. It is important first to define the scale of interest. For a continuous trait (eg bone density) a non-normal distribution will generate scale-dependent G × E which can be removed by appropriate transformation. For a dichotomous trait (eg disease status) non-additivity on the risk scale can occur even when there is additivity on the liability scale that underlies it, and the reverse applies too. MZ twins provide a unique opportunity to detect various types of G × E. For measured genotypes, MZ intra-pair variances should be compared to detect genes affecting environmental sensitivity. Such genes are potentially even more important than 'level' ones and provide a sound rationale for collecting DNA from MZ as well as DZ twins.

To demonstrate the importance of such variability genes, Martin and co-workers predicted from their findings on intra-pair variances of MZ twins that serum lipid levels of individuals who were blood group N would respond more to a low fat diet than those who were M+. They had their chance to test their hypothesis in the course of a case-control study to investigate the effect of diet on the recurrence of colorectal polyps. One of the dietary factors was an intervention to reduce fat in the diet, and over an 18-month period they indeed observed that individuals who were blood group N had the greatest lowering of LDL cholesterol. However, the most significant effect was the contrast between the two homozygotes (blood group M and N) and the heterozygote MN group who appeared most impervious to the changed diet. This is in line with a large body of population genetic theory which suggests that heterozygotes are more buffered against environmental extremes. In the modern world, with ready access to fatty diets, MN heterozygotes may not be at such risk of succumbing to hypercholesterolaemia. On the other hand, people of blood group N may be the best targets of cholesterol-lowering therapies. In general, the identification of such variability genes is likely to have great potential in targeting public health measures not just to the most susceptible individuals (the usual diagnostic sales pitch) but also to the individuals most responsive to treatment.

Dorret Boomsma (Department of Biological Psychology, Free University of Amsterdam, The Netherlands) presented multiple approaches in QTL analysis. In linkage analysis of quantitative traits the detection of loci that explain a small to medium proportion of the gene variance is problematic. In her contribution she addressed the question of how multivariate genetic analysis can be employed to increase the power to detect a quantitative trait locus (QTL).

The organisation of the workshop is a timely initiative, mostly from the medical point of view. The future of classical studies is promising. The participants of the workshop must have been convinced that, far from becoming irrelevant alongside advances in molecular biology, the twin studies can improve the efficiency of quantitative trait loci detection as well as play an important role in unravelling developmental genetic mechanisms.

Unfortunately, many twin studies lack the proper methodology. The organisers have to be congratulated for filling a gap. The workshop achieved its aim to a great extent, ie to overview the 'methodological and epidemiological issues concerning the use of twins and sib pairs in the analysis of complex traits'. An important aspect of twin research that has only been alluded to by Christian and Phillips should be extensively discussed in the next workshop, that is the influence of the intrauterine environment, especially the structure of the placenta and its membranes. I do hope that a second and possibly a third edition will follow this First International Workshop. In my view, future courses would meet with the same tremendous success as the International Workshops on Methodology of Twin and Family Studies, started in 1987 by the International Society for Twin Studies. The XIth session of those courses was held in Leuven, Belgium, three months ago and the coming XIIth session, an advanced course, will be held in Boulder, CO, USA, on 8–12 March of 1999.

The setting of the workshop deserves praise. The aura of the University of Cambridge and the city in which it is located is famous worldwide. St Catharine's College is one of the jewels of the city and an ideal place to study the future of twin research.

Most, if not all, presentations will be published in a book entitled Advances in Twin and Sib-pair Analysis (T Spector, H Snieder, A MacGregor, eds) by Greenwich Medical Media Ltd, London (£14.95; paperback: est. 140 pages; ISBN 84110 004 8).

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