Translating knowledge of the human genome into clinical practice in nephrology dialysis and transplantation: the renal genome network (ReGeNet)

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The success of unravelling the human genome in 2001 [1] has provided clinical researchers with an estimate of the number of genes, their relative position on chromosomes and access to the entire nucleotide sequence. Despite the promises of the daily press/news that this achievement heralds the introduction of genetically tailored treatment and the answer to every known disease, the reality of the situation is very different. Six years later, nephrologists may justifiably ask how this knowledge of the human genome has had impact on their clinical practices and may correctly conclude that it has made, as yet, a little impact. While encouraging advances have been made in relation to single-gene disorders for a large majority of the renal patient population, renal damage and its complications should be considered as complex traits with contributions of multiple genetic and environmental factors. So, facing this complexity, what is required to translate novel genetic knowledge into improved clinical practice? The answer, we suggest, lies in three areas

(a) developing new knowledge,
(b) developing new ways of working together as a renal research community and
(c) designing specific renal research programmes

Developing new knowledge

Progressing from the sequence itself to identifying the extent of the natural variation (in terms of nucleotide position and frequency) within ethnic populations was the natural outcome of the Human Genome Project. This study was initiated by the single nucleotide polymorphism (SNP) consortium and by a publicly funded global programme, the HapMap project. Hapmap, initiated in Autumn 2002, was a collaboration between scientists from Japan, UK, Canada, China, Nigeria and USA to analyse 270 DNA samples from four ethnic populations; Han Chinese (Beijing), Japanese (Tokyo), Yoruba (Ibadan) and Utah (European ancestry). The goal was to compare the genetic sequences of different individuals to identify chromosomal regions where genetic variants are shared, i.e. to identify and map the common genome haplotypes in major ethnic populations. HapMap delivered the first haplotype map in 2005 [2] based on over 1 million SNPs. The results demonstrate the generality of recombination hot spots, a block-like structure of linkage disequilibrium and low haplotype diversity, which leads to substantial correlations of SNPs with many neighbouring SNPs. The next goal of HapMap II is to add another 4.6 million SNPs from public databases, which will increase the density of the SNP haplotype map from 1 in 3000 bases to 1 in 600.

Fortunately, genotyping technology has kept pace with the desire to type more and more SNPs rapidly and accurately on high throughput platforms that are cost-effective. Over just a few years, single SNP assays based on gel separation or real time polymerase chain reaction have given way to whole genome SNP chips or multiplexed bead-based methodology. These developments are paralleled by rapid developments in animal
developing new ways of working together as a renal research community

Gene association studies are potentially valuable tools to elucidate the linkage of a genetic marker/gene with a disease, with disease comorbidity or response to treatment or other outcome [5]. This epidemiological approach has been used widely throughout all areas of clinical research including renal disease. In general, however, the results of gene association studies have been inconsistent with early studies failing to be replicated in other populations [6]. This has led to criticism of the approach and a focus on the quality issues on which such study designs are based. Problems in study design have been highlighted including confounding due to population structure, misclassification of phenotype or outcome and allelic heterogeneity [7]. Moreover, heterogeneity in environmental factors may be involved. A common weakness of many studies has been a small sample size, which leads to inadequately powered studies or inability to interrogate subpopulations [7,8]. A brief survey of the size of study populations in genetic association papers published in NDT between 2000 and 2002 produces an average of 329 cases (n = 12). In these 3 years, 2003–05, this figure remained essentially the same in 356 cases (n = 19); study designs have not yet adapted to these justifiable criticisms.

In most of these studies, only with a high allele frequency and increased numbers of controls compared with cases will such a number lead to a highly powered study, even then, subgroup analysis may fail to be powered adequately. Meta-analysis is proposed by some as a solution to this problem [9,10] and would certainly allow advancements. However, a common realization amongst the research community participating in genetic epidemiology has been the benefits accrued from operating as a research network to increase the study size. By pooling patient phenotypes from many centres, and provided a consensus has been reached on measurement, definition and classification of phenotypes, the networks have thousands of patients available for study. This will allow rapid independent confirmation of results from different patient cohorts; moreover, it will provide a variety of environmental backgrounds to address relevant gene-environment interaction.

Single centres across Europe experienced in ‘nephro-genetics’ using candidate gene association studies to study important clinical morbidities have accepted the difficulties of collecting sufficiently large numbers of patient phenotypes. Similarly, not every centre necessarily has access to high throughput genotyping platforms, validated processes for DNA storage and expertise in bioinformatics, statistics and data storage.

At a meeting in Manchester in February 2003, attended by renal groups from 10 European countries and representatives from industry, it was decided to develop a European Renal Genome Network (ReGeNet) to facilitate the application of clinical genetic epidemiology studies to important renal comorbidities affecting patients progressing to end-stage kidney disease, patients on CAPD and haemodialysis modalities and post-renal transplantation patients. ReGeNet (www.regenet.org), an investigator-led inclusive network of clinicians and scientists from academia and industry, has met regularly (Berlin, June 2003; Naarden, January 2004; Amsterdam, August 2004; Naarden, June, August and October 2005) and seeks to promote and facilitate clinical studies of genetic epidemiology in renal disease by

- establishing large numbers of patients at different stages of renal failure, and with different modes of renal replacement therapy with clearly defined phenotype for collaborative study by the network,
- establishing new cohorts and coordinating the availability of existing renal cohorts for prospective study by the network,
- validating genotyping methodology and seeking integration of data capture and storage,
- providing expertise in genetic statistics, epidemiology and bioinformatics,
- enabling the study of rare renal conditions and morbidities,
- providing education and training opportunities for young investigators and
- promoting quality, best practice and high standards of research governance.

ReGeNet is part of the Network of Investigator Networks sponsored by Human Genome Epidemiology Network (www.cdc.gov/genomics/hugenet) set up to share best practices, tools and methods for analysis of associations between genetic variation and common diseases [11].

Designing specific renal research programmes

ReGeNet has prioritized the importance of developing a pan-European research programme in an area of nephro-genetics. Such programmes require significant resources and the first option has been to target the EU Framework 6 Research Programme. In July 2005, there was a suitable call for a genetic epidemiology programme in kidney disease. ReGeNet has sponsored and will host GENECURE; a STREP led by Prof. G. Navis, University of Groningen, to investigate the genomic basis of accelerated cardiovascular comorbidity in uraemia. This has recently been selected
for funding to run 2007–09 and will act as a catalyst to enable the network approach to function and develop and, hopefully, enable future collaborations. There are many more interesting and relevant programmes to develop in other specific areas of nephrology. For example, a small but significant example of the power of the network approach is that of the unravelling of the genetic background to encapsulating peritoneal sclerosis (EPS). This rare (but seemingly increasing) condition requires a global study, as no country or continent has enough cases for a genetic association study. ReGeNet is sponsoring, together with ISPD who are funding the DNA collection, the study of EPS genetics (contact angela.summers@cmmc.nhs.uk if you wish to enter EPS patients). Other potential areas for collaborations within ReGeNet include genetic factors determining progression of chronic kidney diseases, development of diabetic nephropathy, rejection of kidney transplants etc.

The other priority has been to work closely with EDTA/ERA Registry to develop a collaborative pathway of enabling and promoting renal genetic epidemiology across Europe. ReGeNet is supportive of Quest, an EDTA/ERA initiative to improve the collection of registry data suitable for epidemiology research. Likewise, EDTA/ERA Registry is a collaborative partner in GENECURE. There is much to be done in the renal community in terms of integrating genetics and epidemiology and some suggestions for developing future renal research programmes are:

- National renal associations, EDTA/ERA, could lobby relevant European government departments/officers to get more renal genetic/genomics/epidemiology research topics (and resources) integrated into future EU Frameworks e.g. FP7.
- ReGeNet with EDTA/ERA Registry and appropriate national registries should be encouraged to collaborate in nephrogenetic epidemiology. This synthesis of detailed robust registry data and genetic data through carefully designed and appropriately powered studies will deliver important insights into clinical comorbidities and outcomes, and this will modify clinical renal practices in the future.
- ReGeNet could provide expertise and advice for parallel academic studies using genetic approaches within large scale industry-sponsored clinical trials
- Renal centres across Europe with an interest in a pursuing a nephrogenetic approach to the study of disease, catering for well-defined populations of renal patients, are welcome to use the forum of ReGeNet to persuade others to collaborate in studies.

The next decade will judge the quality of European nephrogenetics, which in our view is dependent on harnessing the power of the network. It is our hope that ReGeNet will attract appropriate funding. We seek active participation from all the European researchers interested in the field of genetic aspects of kidney diseases and its complications. ReGeNet is an open scientific network and we encourage everyone who is working in this area to register their interest to participate via the ReGeNet website.

Conflict of interest statement. None declared.

(See related article by Mondry et al. Nephrol Dial Transplant 2006; 21: 2775–2779.)

References


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