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Genetics in modern medicine

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ABSTRACT Over the past 20 years there has been a massive worldwide investment in genetic research. Many claims have been made about the power of genetic knowledge to transform the practice of medicine. This aim of this symposium was to explore the role of genetic knowledge in the medical management at the present time and to anticipate future advances in treatment.

KEYWORDS Arryhthmia, cancer, diabetes, ethics, muscular dystrophy.

LIST OF ABBREVIATIONS Developmental delay, Epilepsy Neonatal diabetes, Dysmorphic facies (DEND), electrocardiogram (ECG), hereditary non-polyposis colorectal cancer (HNPCC), hypertrophic cardiomyopathy (HOCM), maturity-onset diabetes of the young (MODY)

DECLARATION OF INTERESTS MEM Porteous was the symposium co-ordinator.

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SESSION 1: THE GENETICS OF SUDDEN DEATH

The first session, the genetics of sudden death, focused on the heart. Professor K Bushby presented a compelling case for pursuing accurate diagnoses in muscular dystrophies. Emery-Dreifuss is a rare muscular dystrophy associated with muscle contractures and a high frequency of cardiac involvement. It may be caused by mutations in either the Emerin gene, in which case it follows an X-linked inheritance pattern, or the LMNA gene, in which case it can be inherited in either an autosomal dominant or recessive form. The clinical phenotype of LMNA mutations is broader than just Emery-Dreifuss, and Professor Bushby cautioned that clinicians should have a high index of suspicion in an undiagnosed dystrophy. Whilst X-linked Emery-Dreifuss can be diagnosed on muscle biopsy using antibodies raised against Emerin protein, LMNA muscular dystrophies can only be diagnosed on mutation analysis of the LMNA gene. It is important that the diagnosis is made, because more than 95% of patients will have cardiac conduction abnormalities by the age of 30, and one series put the risk of cardiac death at 46% even with cardiac pacing.[1] Consideration of an implantable defibrillator should be given because of a significant risk of ventricular arrhythmias. Muscular dystrophies have varying risks of cardiac arrhythmias depending on the underlying genotype and it is important that an accurate diagnosis is made to inform screening. Facio-Scapulo-Humeral and Limb-Girdle types 2A and 2B muscular dystrophies have a low risk of cardiac involvement and patients can be reassured.

Professor B McKenna considered the challenges of cardiomyopathy and showed that genetic testing is of variable importance depending on the diagnostic subgroup. Hypertrophic cardiomyopathy is a disease of the sarcomere. Over the past decade, ten different sarcomeric genes have been cloned. In hypertrophic cardiomyopathy, caused by mutations in the β myosin heavy chain, the clinical pattern or phenotype varies more between families rather than within families. Each family generally has a different mutation, so it is important to look at family history rather than molecular testing to determine prognosis. In families with Troponin I mutations, penetrance, or the chance of a mutation carrier exhibiting symptoms, is around 50%. Sudden death is associated with severe morphology. Troponin T mutations are associated with mild ventricular hypertrophy but more severe myocyte disarray. Troponin T associated HOCM is diagnosed on family history and subtle ECG changes. Mutation analysis is valuable because of a lack of robust clinical data and high risk of sudden cardiac death. Professor McKenna gave some tragic examples and emphasised the need to consider implantable defibrillators.

Arrhythmogenic right ventricular hypertrophic cardiomyopathy, characterised by a 'pork chop' appearance with replacement of myocytes by fat and fibrous tissue, predominantly in the right ventricle, is now recognised by many pathologists as the number one cause of sudden cardiac death in the young. Standard cardiac imaging will not make the diagnosis according to Professor McKenna; it is important to look at the right ventricle with tissue Doppler. The condition is 30–80% penetrant, causing asymptomatic arrhythmias in childhood and a risk of sudden death in adolescence and young adulthood. Mutation carriers that survive through this period often present later with a dilated cardiomyopathy. To date, seven causative genes have been identified.[2] Expert review of histology, then DNA

extraction and mutation analysis from tissue block, leads to a 50% mutation pick-up in histologically characteristic cases and the possibility of accurate testing of other family members.

Dr A Grace introduced us to the concept that the fundamental determinants for the clinical risk of arrhythmias and sudden cardiac death reside within the heart itself, and much of this risk has a genetic basis. The concept holds not just for rare inherited conduction abnormalities, but also for the way an individual will react to a myocardial infarction – the risk of subsequent arrhythmia is an intrinsic property of the cardiac myocytes. In future might we be able to predict an individual's likely clinical course post myocardial infarction and take appropriate preventative measures?

SESSION 2: FROM GENOTYPE TO TREATMENT

Professor A Hattersley posed the question 'How do you pick out patients with monogenic diabetes from the mass of diabetics in the clinic?' Maturity-Onset Diabetes of the Young is an autosomal dominant defect affecting the beta cell in the pancreas. As the population has got fatter there are more young people with type 2 diabetes and a family history – how can we tell if they have MODY or not? Genetic analysis of families with MODY show 14% to have mutations in the Glucokinase gene, 75% mutations in transcription factor genes of which 69% have mutations in HNF1α. Professor Hattersley showed convincingly that diagnosing monogenic diabetes matters as the optimum treatment depends on the underlying molecular basis of the disease. Individuals with a Glucokinase mutation have stable, mild, fasting hyperglycaemia and no treatment is required. In patients with HNF1α mutations, low dose sulfonylureas are more effective than metformin.[3]

Kir6.2 mutations give rise to a spectrum of severity from a polymorphism found in 40% of the population that increases susceptibility to diabetes by 20% to DEND syndrome; the position of the mutation in the gene determines the phenotype.[4] The majority of patients can transfer from insulin to sulfonylurea treatment leading to better control.

Professor B Sykes entertained and informed us on wider issues surrounding population genetics in the Marjorie Robertson Lecture entitled 'Sex, genetics and the extinction of men'. This lecture is available online at www.rcpe.ac.uk/streamingdemo/sykes/

SESSION 3: CANCER GENETICS

This session focused on cancer genetics; in particular colorectal cancer, breast cancer and melanoma.

Professor J Burn reminded us of the importance of environment in the development of bowel cancer which will affect 1 in 30 Scots during their lifetime. Individuals in social class 5 are twice as likely to develop the condition as individuals in social class 1. The autosomal dominant syndrome HNPCC is associated with mutations in the mismatch repair genes. Professor Burn suggested that there might be a significant benefit in testing colorectal tumours for mismatch repair instability, a hallmark of HNPCC associated tumours, citing the work of Ribic *et al.* who showed patients with mismatch repair deficient cancers (MSI-H) do not benefit from 5FU adjuvant therapy.[5] Not all mismatch repair deficient tumours are associated with germline mutations in mismatch repair genes. Young *et al.* showed a BRAF V599E mutation in 40% of sporadic MSI-H tumours and 0% of HNPCC associated tumours.[6] Lack of a V599E mutation in a tumour could therefore be used as a marker to define which patients should be put forward for mismatch repair gene mutation analysis.

Professor G Evans addressed the problem of genetic testing in familial breast cancer, likening the chances of finding a mutation in BRCA1 or 2 to finding a spelling mistake in 'War and Peace' and 'Lord of the Rings'. Even in families where a mutation has been identified penetrance is variable and risk of cancer depends, in part, on a family history of cancer. He also pointed out the dangers of data misinterpretation through the story of the association between CHK2 mutations and breast cancer. *CHK2* is a low risk breast cancer susceptibility gene. The 1100 Del C mutation in *CHK2* is associated with doubling of breast cancer risk. Initial reports of CHK2 mutations causing the autosomal dominant Li-Fraumeni syndrome in which breast cancer is observed were erroneous and arose because 1100 Del C is present in around 1% of the general population and therefore observed in Li-Fraumeni families by chance only.[7]

The final presentation of the cancer genetics session was given by Professor J Rees who dramatically illustrated the problem of finding melanomas. A dermatology department serving around 1 million people would have to examine the equivalent of around 250 Cardiff Millennium Stadium rugby pitches worth of skin to find 120 melanomas. Five to ten per cent of patients with melanomas have a family history of the condition. This reflects both shared genes and shared environment. Mutations in the *CDKN2A* gene cause a syndrome characterised by atypical moles. The original families described in the literature had a high rate of melanoma, naevi and atypical naevi. However, 10% of the patients with melanoma did not carry the family CDKN2 mutation suggesting an ascertainment effect (families with multiple cancers more likely to be studied) similar to that seen in the early breast cancer genetic papers. Two per cent of melanomas are due to high penetrance genes; with 0·2% of all melanoma due to CDKN2A mutations. So should we look for CDKN2A mutations in families with atypical moles? Professor Rees thinks not. Some mutation

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carriers have 'funny' moles but most do not. In families with more than three melanomas, the mutation pick-up rate is around 10% and the penetrance, depending on country of residence, is only around 0·13 at the age of 50.

SESSION 4: GENETICS AND SOCIETY

The final session was chaired by Professor A Emery who established the first Genetic Register in Europe at the Clinical Genetics Department in Edinburgh. Professor Emery introduced the session by reminding us of the assertion by Lord Rutherford in 1908 that 'All science was either physics or stamp collecting' and suggested that 'All medicine is now genetics or stamp collecting'.

Dr I Ellis tackled the question 'Are we creating a genetic underclass through genetic testing?' giving an insight into the constraints faced by insurance companies. Mutuality is a voluntary system that relies on fairly assessed contributions. If people have access to genetic information and use it to modify their behaviour, then the premium is no longer appropriate – so called adverse selection. The Association of British Insurers gave an undertaking to work with geneticists to find a solution that is both commercially viable and is fair to genetic patients.

Dr R Ashcroft discussed issues raised by the availability of genetic testing from a Philosopher's perspective asking 'Is genetic information special?' One of the 'special' features of genetic information is its familial nature. Dr Ashcroft gave us an example of a woman, Mrs P, requesting information about her genetic risk of breast cancer. The woman's aunt was known to the department and had been shown to carry a mutation in BRCA1 that had lead to breast cancer. The aunt was estranged from the family and did not want her information used to help them in any way. It could be argued that the mutation information is confidential and could not be used without the aunt's consent. Breaking of confidentiality has to be justified 'in the public interest'. Perhaps a better question is 'Does Mrs P have a right to know?' This information is of direct relevance to her.

Professor G Laurie gave us a legal perspective, highlighting the limitations of using current law to argue issues around consent and confidentiality. In common law, if someone has done work on a sample, it becomes the intellectual property of the person that did the work. Extrapolating from this, the Genetics team should be able to make the decision on using Mrs P's aunt's data to manage Mrs Ps care. Professor Laurie cautioned against making a fetish of consent in the writing of law: consent is only one way of legitimising processing of personal data.

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