The clinical impact of the Human Genome Project: inherited variants in cancer care

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Introduction

The publication of more than 93% of the complete human genomic sequence simultaneously by two independent groups, in February 2001 [1, 2], was greeted with great delight by the scientific community. It was hailed as one of the great achievements of the twentieth century. Dr Mike Dexter of the Wellcome Trust said “for the first time we can look upon the genetic inheritance shared by every person on the planet. Researchers now have the complete human genetic tool kit with which to work; we are promised research that will provide knowledge and understanding of the human condition and highlight ways in which health can be safeguarded and ill health tackled” [3].

The potential impact of the availability of ‘complete’ human genome sequence data on disease diagnosis and therapy is immense, but the challenge of how to rapidly translate this into improvements in the prevention, diagnosis and treatment of cancer remains. Numerous articles, about the potential impact of the human genome sequence on the practice of clinical medicine have been published in the scientific, clinical and lay press during the last 2 years [4, 5]. In this short paper, we will use a small number of examples to illustrate how new genetic information may influence the clinical management of inherited cancers in the short and medium term. This subject falls naturally into two parallel streams.

The impact on individuals at risk of developing cancer

The impact on individuals who are well, but have been identified as members of a specific ‘at-risk’ cohort because of their genetic make-up. These individuals may be considered in the following sub-groups:

• Individuals who are at a higher or lower risk of developing a certain type or certain types of cancer than the general population.

• Individuals who are more or less susceptible to certain carcinogenic elements in the environment, such as compounds in tobacco smoke.

• Individuals who are likely to be more or less successfully protected by different chemo-preventative measures.

The impact on individuals diagnosed with cancer

Patient advocacy groups, particularly in the USA, prefer the use of the term cancer survivor rather than cancer patient or cancer victim to denote individuals who have been diagnosed with cancer. Nancy Holmes of Breast Cancer Care says “you are a cancer survivor from the day of diagnosis of the cancer until the day of your death” [6].

Most of the cancer susceptibility genes that have been identified are long genes with mutations distributed throughout the gene, e.g. the complete BRCA1 genomic sequence is 84 kb in length [7] and more than 1216 distinct mutations, polymorphisms and variants have been described in this gene [8]. The size of these genes and the distribution of the mutations require a two-step approach to clinical genetic testing:

• Step 1: The identification of a genetic mutation in a blood sample taken from a cancer survivor in the family.

• Step 2: Genetic testing can only be offered to unaffected individuals in a family once a mutation has been identified in a cancer survivor in the family, to determine whether they carry that same mutation.

In many countries in Europe, including the UK, the detection rate for mutations in high-penetrance genes such as BRCA1, BRCA2, MSH2 or MLH1 is poor and requires the use of a series of different techniques, even when mutation searching (step 1) is restricted to high-risk families. There are a variety of reasons for this poor detection rate, including the size of the genes involved and the number of potentially cancer-causing mutations in these genes; although, these technical problems are likely to be overcome during the next 2 years. The ascertainment criteria on which genetic testing is offered are crude—they are usually based only on the strength of the family history. Methods of ascertainment based on tumour histology, prognostic factors and age are being developed for BRCA1 and BRCA2 mutation searching [9], and immunohistochemistry staining of tumour tissue is being evaluated for
several of the genes involved in hereditary non-polyposis colon cancer [10]. More sophisticated ascertainment models combining family history, histopathological factors and age will evolve over the next few years, resulting in an increase in the number of unaffected individuals who will be offered testing, increasing the workload of cancer genetics services.

There is at present a focus on the identification and characterisation of lower penetrance susceptibility genes for a number of common cancers supported by governmental, charitable and industrial funding sources. The identification of these lower penetrance cancer-associated genes will undoubtedly increase the workload of the cancer genetics service. It is at present unclear whether the identification and characterisation of such genes would justify the expenditure involved, in terms of improvements in the diagnosis and therapy of common cancers.

Another area of intense laboratory research activity has been the elucidation of the functions of the proteins encoded by the high-penetrance cancer-associated genes. Detailed mechanistic studies on cells that lack functional BRCA2 activity show that they are sensitive to agents that induce inter-DNA strand cross-links, indicating that mitomycin C and platinum analogues may be of particular value in treating cancers in BRCA2 mutation carriers [11, 12]. It is not clear whether this in cellulo observation can be effectively translated into the treatment of cancers in BRCA2 mutation carriers who are heterozygous for the cancer causing mutations (i.e. in the patient’s cells one copy of the gene has the cancer causing mutation, whilst the other does not). If it is demonstrated that tumours in patients with BRCA2 mutations are more sensitive to platinum-based chemotherapy, the therapeutic ratio of different chemotherapeutic agents may be different in BRCA2 carriers, compared with BRCA1 carriers, carriers of other cancer susceptibility genes and patients with sporadic cancers. This will be tested in a randomised trial of a platinum-containing regimen versus a non-platinum-containing regimen, in patients with mutations in BRCA2, at first relapse following treatment of the primary tumour. The logistics of instituting and completing such a clinical trial of sufficient power are challenging, because the cohort of known BRCA2 carriers in remission after definitive treatment is relatively small. The recent creation, in the UK, of the National Cancer Research Institute (NRCI) and the National Cancer Research Network to facilitate collaborative clinical research is an important step forward.

**Impact on individuals who are members of specific high-risk groups**

**Individuals at higher or lower risk of developing a certain type or certain types of cancer than the general population**

An example of a cohort of individuals who are at a higher than average risk of developing breast cancer is the Ashkenazi Jewish population. Two mutations in BRCA1, 185delAG and 5382insC, and one in BRCA2, 6174delT, occur relatively frequently in Ashkenazi Jews (~1–1.5% each) [13]. The occurrence of these three common mutations in the Ashkenazim at consistent sites in the BRCA1 and BRCA2 genes facilitates their detection. There has been discussion concerning whether screening programmes for these mutations should be initiated in this at-risk group; although, the value of this has been questioned in view of the limited therapeutic options that are available in the event of a mutation being identified.

**Individuals more or less susceptible to certain carcinogenic elements in the environment, such as chemicals in tobacco smoke**

Variant alleles of both phase I and phase II carcinogen-metabolising enzymes have been shown to confer variable susceptibility to the development of lung cancer in smokers [14], with some of these variants being associated with the inevitable development of lung cancer in smokers. It is possible that the ability to provide specific individualised risk assessments, derived on the basis of genotype testing, for individual patients may be a powerful tool in modifying patients’ smoking behaviour.

**Individuals likely to be more or less successfully protected by different chemo-preventative measures**

The preliminary results of the International Breast Cancer Intervention study (IBIS) of tamoxifen chemoprevention in breast cancer have been very encouraging [15]. However, no studies have yet examined the effects of allelic sub-variants of drug and hormone metabolising enzymes. It remains unclear whether tamoxifen is an effective preventative agent in BRCA1 mutation carriers who tend to develop estrogen receptor-negative tumours [16].

**Summary**

The potential impact of the availability of the complete human genome sequence on the practice of medicine is immense. We have highlighted several areas in the provision of clinical care to cancer survivors and their families in which this impact will be felt. Rapid translation of laboratory advance into effective management is dependent on well organised collaborative clinical research.

**References**

3. Dexter M. The human genome; the present, the past, the future. Welcome News Supplement 2001; 2–3.
8. BRCA1 data summary, Breast Cancer Information Core (BIH) [on-line] 2002; http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/Member/ (28 August 2002, date last accessed).