Future Medical Practice and Genetics

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Significant progress has been made in the rapidly evolving sub-specialty of medical genetics. In this article, breast cancer has been used as an example to highlight recent developments in this field of medicine, with a discussion on the implications this has on medical practice and policy. The potential of medical genetics is staggering but not without its limitations, and we must consider all aspects of use before advancing further. Consequently, students and physicians alike need to have a thorough understanding of all components of clinical genetics in order to be ready for this new era of healthcare.

Keywords: *medical student; breast cancer; single nucleotide polymorphisms; genome-wide association studies.*

INTRODUCTION

Our understanding of medical genetics has grown rapidly, with major discoveries in the structure and function of DNA since Mendel's experiments in plant hybridization, published in 1865.[1] These discoveries have formed the basis of screening programs and treatments, which were inconceivable earlier. In 1990 – the year the Human Genome Project commenced – 53 genes were known to cause disease. After less than 25 years of research, we have identified over 2,900 disease-related genes.[2] This knowledge has empowered the medical profession with non-invasive diagnostic techniques and sophisticated therapies that now supersede invasive methods. Antenatal diagnosis of Trisomy 21 (Down syndrome) demonstrates this point; multiplexed maternal plasma DNA sequencing has the potential to be a more effective and safer screening tool compared to traditional, invasive, and costly methods such as chorionic villous sampling (CVS) and amniocentesis and may even eliminate up to 98% of invasive diagnostic methods.[3]

DISCUSSION

Even for medical students planning to pursue careers outside of genetics, it is inevitable that they will encounter variants in their patients' genetic constitutions that have contributed to the disease phenotypes from which they suffer. The importance of genetics is becoming well-recognized in many conditions with an increasing prevalence, including hypertension and type II diabetes mellitus, which are now known to have a polygenic and multifactorial basis, respectively. Substantial evidence of the interaction of multiple genes with each other and the environment through various mechanisms has furthered understanding of these diseases.

It is essential that medical students acquire the clinical skill of taking a complete family history to determine the risk involved and offer treatments appropriately. Furthermore, familiarization with new techniques involved in genomic analysis when samples are sent for genetic testing will ensure appropriate investigation, selection, and interpretation. Above all, a doctor's ability to take a thorough family history could be the difference between an affected patient receiving proper screening, treatment, or prophylaxis for early stage disease, identified via testing, and presenting with advanced and potentially incurable disease.

A prime example is cancer, which has historically afflicted families with grief, stress, and uncertainty of their own future. Thankfully, patients with a known family history of specific cancers or gene mutations can now receive genetic counseling from the National Health Service (NHS) in the United Kingdom. Since the completion of the Human Genome Project in 2003, costing $3 billion (£1.81 billion) and taking 13 years,[1] the accessibility and affordability of genome sequencing has dramatically improved. Major commercial competition has brought down the cost of whole genome sequencing, with the analysis completed in a matter of days for as little as $6,995 in April 2013.[4] Many companies are currently striving to achieve sequencing at a cost of $1,000 by the end of 2014. With the link yet to be made between many genetic abnormalities and viable

treatment options, it could be argued that this test is currently academic in most cases. Consequently, in the foreseeable future, many patients could present with results from privately obtained genome sequencing that potentially require action, possibly in the form of increased surveillance, treatment, or genetic counseling of relatives. Such health-seeking behaviors may increase the workloads of general practitioners and specialists alike, demanding confidence in their own understanding of genetics to effectively communicate a multitude of genetic concepts, particularly regarding genetic susceptibility.

Some clinicians may believe that assessing whether a patient meets the referral criteria for genetic testing is the extent of their application of genetics in practice. This attitude is likely to change significantly. Progress in the diagnosis and treatment of breast cancer can be used to demonstrate how changes in this field of medicine are changing clinical practice. Breast cancer is the most common female malignancy with a lifetime risk of 8–10%,[5] and much research has been done looking into this disease. Moreover, breakthroughs achieved in the genetics of breast cancer can be applied to a wide range of other conditions with a genetic component.

In broad terms, two main groups of genetic susceptibility have been established with regard to breast cancer.[6] Rare, highly penetrant monogenic mutations in fundamental DNA repair genes on the one hand and multiple, relatively common, low penetrance Single Nucleotide Polymorphisms (SNPs), which confer an increased risk to breast cancer, on the other. However, breast cancer has presented epidemiologists and geneticists with a number of difficult questions, especially why no genetic mutations can be attributed to over 70% of cases of breast cancer in which there is a significant familial clustering. Many advances have helped answer this question by providing powerful evidence that has changed how we approach cancer genetics. These findings have implications for the clinical treatment of other diseases and are on course to bring about change with improved outcomes.

Physicians have already recognized their new role in medical practice and now acknowledge the need to appreciate the genetics of disease in order to optimize clinical outcomes.[7] Surveys have found that results from the 21 gene assay, a genetic test that provides a likelihood of recurrence of breast cancer, influence the decisions made regarding adjuvant therapies in breast cancer, with a 19% reduction in the rate of chemotherapy recommendations and a 15% increase in hormonal therapy recommendations.[8]

Through comparison of allele frequencies in candidate genes between breast cancer cases and unaffected controls, genome-wide association studies (GWAS) have been the driving force for vast progress with regard to our knowledge of genetic susceptibility. Conclusions drawn from such studies continue to support the widely accepted notion that breast cancer exhibits a polygenic model of inheritance.[9] Emerging evidence supports the assertion that, in the vast majority of cases, multiple genes are responsible for producing the breast cancer phenotype, involving a large number of low-risk variants with a cumulative effect in determining the overall risk. Many of these mutations are thought to coexist in highly penetrant combinations.[6]

It is interesting to note that monogenic mutations in breast cancer 1 and 2 (BRCA 1 and BRCA 2) have received the majority of the media's attention despite being responsible for less than 5% of the total cases of breast cancer.[6] BRCA-positive patients are informed that they have up to an 80% risk of developing breast cancer. However, variation is commonly witnessed in these patients in terms of penetrance, receptor status, and natural history.[5] Modifier genes have been offered as an explanation for differences observed in these patients; research to determine the genes with silencing or enhancing effects of other gene mutations that may contribute is ongoing. It has been speculated that modifier genes may also have an effect on the risk factors associated with breast cancer. Risk factors such as mammographic density and age at menarche are being scrutinized through GWAS to establish the SNPs involved in the expression of these phenotypes. Although this research is still in its infancy, it has the potential to take us even closer to accurately determining individualized risk.

Over the past decade, molecular genetics has facilitated the construction of a pathophysiological 'map', illustrating the roles and interactions of all the genes known to be involved in fundamental pathways, including the DNA damage response network. Susceptibility genes may operate at any level within this network, from sensing the DNA lesion through to transduction of the damage signal (e.g., ATM) or even effector roles in cell death or repair pathways (e.g., BRCA1/2). Consequently, it is possible to relate each identified mutation to a loss of gene function and thus the associated risk. For example, using existing knowledge of the molecular mechanisms involved in the DNA damage response

network, Bartkova et al.[10] identified *MRE11* as a new possible candidate gene in *BRCA*-negative patients that operates through sensing the double stranded break in DNA.

As of June 2012, 25 SNPs had been implicated in the pathogenesis of breast cancer,[11] with many involved in different stages of a common pathway. However, the clinical consequence of many of these genes is not yet clear, and, as a result, genetic testing for these SNPs as a means of risk stratification is not yet justified. Importantly, these developments may be applicable to sporadic cases, which constitute over 70% of breast cancer cases.[6]

We are already at a stage of using individual genomic information to inform treatment decisions. For example, the genetically determined *HER-2* receptor status of the tumor is used to determine whether trastuzumab (Herceptin) should be used in the treatment of breast cancer. Similar drugs (e.g., gefitinib) exist for EGFR receptor–positive lung cancer, demonstrating that this area of medicine is already making an impact in the survival of cancer patients. The fact that somatic mutations are being used to inform treatment decisions demonstrates that this new approach can be applied to the management of all breast cancer cases and transferred to other cancers with known genetic markers.

Genetic risk prediction models have been developed to optimize patient care.[12] Such models have raised a number of ethical and legal issues that must be considered when implementing genetic testing in clinical practice.[13] Using risk prediction models arguably enables clinicians to offer testing only to those who are likely to benefit. Equally, it may spare unnecessary investigations and treatment in those unlikely to benefit, thereby abiding by the principles of non-maleficence and beneficence, respectively.[14] Providing treatment in this way is also likely to be more cost-effective. However, current risk prediction models for breast cancer favor only patients with more extensive knowledge of their family history.[15] Furthermore, the use of genetic information may create inequalities in the context of employment or health insurance, suggesting that such models may act as vehicles for 'genetic discrimination'.[16]

The National Human Genome Research Institute (NHGRI), which is part of the National Institutes of Health in the United States, created the Clinical Sequencing Exploratory Research program in 2010, which focuses on the technical, ethical, psychosocial, and clinical implications of genetic testing.[17] Research into this sensitive area is ongoing and is required if the true potential of genetic testing is to be realized.

CONCLUSION

Through exploring the vast progress made in breast cancer diagnosis and treatment over a short period of time, the potential for individualized diagnosis and treatment of this disease is obvious. In recent years, the discovery of a large number of relevant SNPs identified through GWAS has enabled risk stratification at a far greater level of detail than achieved with previous methodology. Our knowledge is being translated into techniques that are being integrated into daily practice. Given that parallel progress has been made across a wide array of conditions, it is evident that we as medical students will be entering into a new world of medicine and we owe it to our patients to be prepared for it.

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