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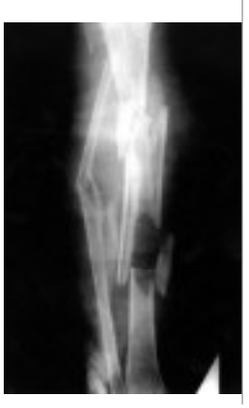

Cover Picture:
Radiograph showing segmental fracture of tibia and fibula open grade IIIB, on admission. This was initially treated by surgical debridement and external fixator.
(Refer to page 020-025)

What Molecular Genetics Holds for the Future?

B T Teh

The completion of the human and many other genome projects has heralded a new era in life sciences, from health science to agriculture. We can expect revolutionary changes in our medical diagnosis and treatments as well as in our code of ethics for delivering these new practices. Increasingly, the public is more curious and much better informed about genetics and biomedical research. It is imperative that we educate the public and help chart the best possible applications of these new developments in the most beneficial ways.

First, let us review the present technologies that are related to molecular genetics. It is hard to envisage a biomedical tool we use today that is going to hold sway for a decade, let alone a century. Today, the hallmark of cutting-edge technologies is speed and most of these machines fall into the following two groups: 1) high-throughput tools that can churn out very large amount of data at high speed; and 2) high-capacity computational tools that can store, integrate and analyse complex data sets to produce meaningful end products. Here three technologies that have these characteristics are discussed.

1) Sequencing: We all know that the blueprint of every life organism lies in its genome and to date a number of genomes have been conquered including the holy grail of human science - the human genome. Besides the ingenuity of the scientists involved, these achievements were made possible by high-throughput sequencing machines and high-capacity computers, both of which are now more prevalent but also less expensive and more powerful. It is fair to say that with time all genomes will be fully sequenced. What we may see in the near future will be the sequence of all proteins (proteome), which are the functional products of the genome – if genome is the blueprint proteins are its building blocks. The combination of the genomic and proteomic data will be formidable allowing us to understand their functions, as well as their intricate relationships between the two.

2) DNA/Protein Microarrary or "Chip": This is a truly high-throughput tool that will allow studies of thousands of genes or proteins in one experiment[1]. This is in contrast with single gene/protein studies we commonly do. Today, the power of microarray is evident and felt in many fields as more and more promising data are produced[1,2]. It looks like finally we have a fast and reliable means to study the complex processes of biology. The power of microarray is only going to increase with more genes and proteins added to the "chip" and the enormous amount of data accumulated will require very large storage and analysis capacity.

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3) Bio-informatics: If the two technologies described above represent the eyes, then bio-informatics serves as the brain that decodes and interprets what the eyes see. Bio-informatics is a tool that encompasses software and other information technology that allows us to process and "mine" biological data. For example, bio-informatics can be used to predict, from a sequence, the molecule encoded, its structure and its function. As the power of these bio-informatic tools is expected to increase exponentially in the next few decades, we can also anticipate an explosion of novel biological knowledge. One important aspect of bio-informatics is that it is mainly Internet-based and therefore its data and applications can be distributed all over the world via Internet, crossing all boundaries, nations and cultures – a true globalisation in life sciences that if managed and used properly, will benefit all mankind and its environment.

Now let us consider what impact these technologies will have on clinical medicine. Undoubtedly, the underlying causes of most human illnesses such as cancer, cardiovascular pathology, infectious disease and neuro-degeneration have one or more molecular basis, which, with time, can be elucidated by the above technologies. Even in diseases caused by pathogens, we can work out the molecular pathways of their infection and further elucidate the intricate relationship between the pathogen and their hosts by studying their genomes and proteomes. Below are a few scenarios in clinical medicine that are already taking place and will continue to develop in the future.

1) Genetic Predictive Testing: Already we have seen the use of genetic testing in identifying risk carriers for monogenic disorders such as familial cancer syndrome (e.g., familial breast cancer), metabolic disease (e.g., familial hypercholesterolaemia), neuro-degenerative disorders (e.g., Huntington's chorea), and many more. What we will see in the future is the identification of disease-modifying genes and polygenic disease-susceptibility genes that will help us in managing these patients as well as those with complex diseases (e.g., cardiovascular, diabetes, etc). With better understanding of their pathophysiology and natural history, we can fine-tune and tailor our management based on the patients' genetic profiles.

   As an extension of these findings, we are witnessing an exciting and fast-developing field called pharmacogenomics – population study of genetic polymorphisms that are related to drug response. Again with the technologies described above, such genetic studies have become more ambitious and larger-scale involving hundreds of thousands and even millions of subjects whose medical records (phenotypes) will be correlated with their genetic profiles (genotypes). The immense costs of these projects are usually supported by governments and/or pharmaceutical companies or governments. Today, these projects have already begun in countries of homogenous populations like Iceland[4] and Estonia[5], and soon we will see them running in heterogeneous populations like Singapore[6]. If these projects succeed as anticipated, we will see the day when every medication or therapy is prescribed based on patients' genetic profiles (see below also).

   In conjunction with the above, genetic information can also be used for better prevention against diseases. It is possible that based

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on these data, one can be advised to avoid certain disease-specific risk factors which otherwise impose no harm on those who do not carry such genetic susceptibility. This maybe a very expensive measure of public health, but with the technologies described above, it may one day be affordable and cost-effective.

2) Diagnosis and Prognosis – Already we have heard about "molecular profiling", "molecular staging" and "molecular imaging" of diseases, all of which appear to hold great promise for future medicine. What we are seeing is a systematic compilation of molecular data that can be used to provide accurate diagnosis and prognosis of diseases. With the use of microarray technology, for example, we will be able to characterize the molecular profiles of individual cells and correlate them with histology and clinical outcomes. In imaging, based on the molecules data of the disease such as cancer, we will be able to design special bio-imaging that will make use of disease-specific molecules or bio-markers that will provide early and accurate detection of diseases. All these technologies will revolutionize clinical medicine as machines will screen the many possibilities, reach a conclusion and provide a diagnosis and/or prognosis with a p-value.

In imaging, based on the molecular data of the disease such as cancer, we will be able to design special bio-imaging that will make use of disease-specific molecules or bio-markers that will provide early and accurate detection of diseases.

3) Therapy – With the vast genomic and proteomic data, we are most certainly going to witness an explosion of new drug discoveries. These new-age drugs will be carefully designed to specifically target the underlying molecular defects of diseases. We will see designer drugs that are inherently non-toxic to normal cells but only target the diseased ones. This will impact our medicine costs, and FDA type governmental regulations. Coupled with pharmacogenomics described above, these drugs may be tailor-made or individualised to suit different patients based on their genetic profiles. Despite early setbacks and expected hiccups along its route to gain acceptance as mainstream medicine, gene therapy (the conspicuous product of advances in molecular genetics), will mature into a formidable weapon in our fights against diseases. Desired genes can now be introduced or removed in the cells to deliver their therapeutic values. In addition, our knowledge in molecular genetics will also revolutionize the field of transplantation. Through manipulation of their genes, tissues can be better grown and engineered to suit the host environment. Coupled with improved animal cloning techniques, this will make transplantation a common and easy practice.

We are fortunate enough to live in this revolutionary age of biomedical science and it appears inevitable for these new developments to take place. Unfortunately, they have also cast ethical challenges on many of us (just think of the debates and arguments ensuing the cloning of Dolly). It is imperative that trained scientists, physicians, educators and technologists get involved in the dissemination of this information to the public and the governments. The latter should certainly consider incorporating them in their education curriculum. In the meantime, new policies and guidelines regarding the applications of these new technologies should be drawn up to ensure the interests of all parties, in particular the general public. All these should be done sooner rather than later as whether we will reap the rewards of these powerful technologies or face disastrous outcomes will depend on our choices and selection of what is present on our doorsteps now!

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REFERENCES

1. The Chipping Forecast. Nature Genetics (suppl) 21:1-60.
2. Bittner M, Meltzer P, Chen Y, et al. Molecular classification of cutaneous malignant melanoma by gene expression profiling. Nature 2000; 406:536-40.
3. Clark EA, Golub TR, Lander ES, Hynes RO. Genomic analysis of metastasis reveals an essential role for RhoC. Nature 2000; 406:532-5.
4. Marshall E. Tapping Iceland's DNA. Science 1997; 278:566.
5. Frank L. Storm brews over gene bank of Estonian population. Science 1999; 286:1262.
6. Cyranoski D. Singapore to create nationwide disease database. Nature 2000; 407:935.

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ERRATUM

We wish to apologise for these names and keywords which were inadvertently missed out from the Dec issue of the SMJ:

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