Understanding the role of genetics and genomics in health 1: background

Advances in research has created a knowledge revolution, which is helping our understanding on the effect of genetics and genomics on health and disease.

**INTRODUCTION**

Consider the following scenario: at a recent family gathering, Marie Scott, a nurse, was approached by her cousin Jane (not their real names):

“Please can you give me some advice for my close friend, Sarah. She is undergoing treatment for advanced breast cancer – it was only recently diagnosed and the outlook isn’t good. She’s only 47, and both her mother and aunt died from breast cancer, in their early 50s, and I think her grandmother also. Sarah is fretting that her 22 year old daughter should have a genetic test to see if she is at risk of breast cancer too. What should I suggest? I want to support her as much as I can.”

There are some interesting issues in this real-life scenario. On the face of it, the family history appears to warrant referral for specialist advice (NICE, 2006). A more formal family history would be required to ascertain that the affected people are blood relatives and are all on the same side of the family, and that the diagnoses and other information are accurate. This highlights the importance and relevance of full, accurate family history-taking by the healthcare professional involved in Sarah’s care. It also raises a question about whether Sarah’s risk of breast cancer could have been identified sooner by an alert practitioner. Another interesting issue is the level of awareness indicated by both Jane and Sarah that breast cancer may have a significant genetic component, and may have implications for people other than the patient.

The scenario provides an example of how the focus on inherited conditions in healthcare has broadened from the rarer single-gene and chromosomal disorders, to encompass common long term conditions such as cancer, cardiovascular disease, diabetes, stroke and bipolar disorder. The greatest public health benefits of advances in understanding human genetic make-up lie in this expansion to common diseases (Scheuner et al, 2008). However, the nature of such advances is complex and there is no single timeframe for their application to healthcare. Some developments have already entered practice, while others may be a decade or more away.

What is clear is that nurses and other healthcare professionals need to understand where and how genetics and genomics are relevant to their professional role, and to appreciate what additional challenges they face in delivering “genomic healthcare”.

**FROM GENETICS TO GENOMICS**

With his studies using pea plants, the Austrian monk Gregor Mendel laid the foundation for traditional genetics studies of how characteristics or traits are passed from one generation to another. From genetics to genomics (HGP) was completed in 2003 and revealed there are probably about 22,000 genes. The project provided the sequence of the entire human genome and mapped the locations of genes on major sections of all chromosomes (International Human Genome Sequencing Consortium, 2004).

**BOX 1. MAJOR STUDIES ADVANCING UNDERSTANDING OF DISEASE MECHANISMS**

Three key initiatives have shaped, and continue to drive, knowledge and understanding of the role of genetics in health and disease:

- The Human Genome Project (HGP) was completed in 2003 and revealed there are probably about 22,000 genes. The project provided the sequence of the entire human genome and mapped the locations of genes on major sections of all chromosomes (International Human Genome Sequencing Consortium, 2004).
- The HapMap project was another international collaborative work, which looked at common patterns of human variation. While unrelated people share 99.9% of their DNA sequences, variations in the remaining 0.1% provide important information on how people differ in their response to disease or drugs (International HapMap Consortium, 2005).
- Genome-Wide Association Studies (GWAS) build on the findings of the first two projects. DNA from very large groups of people (those with and those without the disease under study) can be scanned to find genetic variation. Specific variations found to be significantly more frequent in those with the disease can be used to identify the genetic component involved in its expression (for further information see tinyurl.com/talking-glossary).
- Manolio et al (2008) reported on the success of the GWAS studies, with nearly 100 sites for 40 common diseases and traits identified, including macular degeneration, Crohn’s disease, type 2 diabetes, prostate cancer and cardiovascular disease.

**ADVANCES IN GENETICS/GENOMICS ARE BEGINNING TO PERMEATE CLINICAL PRACTICE ACROSS THE NHS.**

The scientific advances in knowledge apply across the spectrum of common complex diseases as well as to the rarer inherited conditions.

- Nurses need to have a basic knowledge of genetics and genomics to understand their relevance to their area of practice.

**PRACTICE POINTS**

- Advances in genetics/genomics are beginning to permeate clinical practice across the NHS.
- The scientific advances in knowledge apply across the spectrum of common complex diseases as well as the rarer inherited conditions.
- Nurses need to have a basic knowledge of genetics and genomics to understand their relevance to their area of practice.

**Practitioner in depth**

**KEYWORDS** Genetics | Genomics | Genomic healthcare

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International research efforts are resulting in a knowledge revolution which is constantly improving our understanding of the role of genetics and genomics in health and ill health. This first article in a two part series outlines the progress of this research and discusses its implications for healthcare.

**Human Genome Project**

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**Box 1. Major studies advancing understanding of disease mechanisms**

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one generation to the next. He noted that specific numerical ratios were associated with the inheritance of different traits and concluded that some traits were dominant over others.

Nearly 150 years since Mendel’s first published work, we now know that human characteristics, from height and hair colour to response to infections, are at least partly determined by genes. The modes of inheritance of these (dominant, recessive and sex-linked) are referred to as Mendelian inheritance and the typical numerical ratios he identified are still used to calculate the likelihood of a condition occurring in a family member. However, our knowledge and understanding of inheritance and the role of genes has increased substantially, taking us beyond genetics and into the “genomic era” (Box 1).

We now know that humans have about 22,000 genes, providing instructions for cells to produce proteins, protein sub-units, or ribonucleic acid (RNA) molecules, for different cell functions including controlling other genes. The genes themselves form part of a very long molecule of deoxyribonucleic acid (DNA). DNA is made up of a four-letter alphabet of chemicals A, C, T and G (nucleotides), each attached to a sugar and phosphate backbone. Molecules of DNA exist as complementary pairs, twisted into a helix shape and then tightly packaged around histone proteins into chromosomes (Fig 1).

Most of the DNA exists in the 46 chromosomes (23 pairs) in the cell nucleus, with each chromosome containing hundreds to thousands of genes. Of each pair of chromosomes, one is inherited from the mother and one from the father. The small amount of DNA in the cell mitochondria is inherited only from the mother.

A gene is composed of a string of the four nucleotides, each sequence of three letters providing a code for selecting one amino acid. For example, the amino acid glycine is coded by GGA. This code is deciphered by the cell’s protein-making machinery and some of the three-letter codes provide additional instructions about where to start and stop “reading” the code. This is a useful feature as only about 2% of the genome is made up of genes. The genes are spaced along the DNA molecule in each chromosome and we have two sets of genes, as chromosomes occur in pairs, other than the two sex chromosomes X and Y.

There are large sections of non-coding DNA between genes. Even within a gene, there are sections of DNA that do not code for amino acid sequences. Once referred to as “junk DNA”, these sections are now thought to play an important role in regulating gene activity.

The human genome is the entire DNA sequence of an individual, containing 3,000,000,000 (three billion) nucleotides. The study of the structure and function of the genome, including the interaction between genes and between genes and the environment, is known as genomics.

**THE GENOME AND DISEASE**

The single-gene conditions such as sickle cell disease, cystic fibrosis, Huntington’s disease and Duchenne muscular dystrophy have provided valuable models for understanding how alterations within a gene (mutations) can lead to disease. Mutations can be caused by exposure to external agents such as radiation or chemicals, or by internal malfunction during DNA replication. Mutations in somatic cells will be passed on to future offspring.

The effects of mutations vary and are unrelated to their size. Not all are harmful. Generally, harmful mutations result from a loss of function, where the gene product is not produced, is produced in a smaller amount, or does not function properly. Gaining function can also be harmful when the new product is abnormal.

Small-scale mutations include point mutations, when a single nucleotide is exchanged for another. There are three possible outcomes:

- No effect, where the replacement also codes for the original amino acid, for example, GGA and GGT both code for glycine, so an exchange of a T for the A would not alter the gene product;
- The resulting change to the code signals to the cells to stop synthesis of that protein. This is known as a nonsense mutation;
- The alteration now codes for a different amino acid. This is a missense mutation. One such example is sickle cell disease, which results when the letter A in the code for glutamic acid within the ß-haemoglobin gene on chromosome 11 is exchanged for T.
This changes the amino acid used to valine, and this simple change in the amino acid sequence leads to a significant change in the structure of the haemoglobin molecule synthesised, with devastating effects on health.

The consequences of other mutations such as small-scale deletions or insertions of one or more nucleotides depend on how the reading frame is altered. If any number of nucleotides other than exact multiples of three are inserted or deleted, the reading frame downstream of that segment is disrupted (frameshift mutation). Where exact multiples of three nucleotides are involved, there is less disruption and the outcome can result in milder disease (in-frame mutation). Duchenne muscular dystrophy results from a frameshift mutation (deletion) within the dystrophin gene. The milder Becker muscular dystrophy results from an in-frame deletion in the same gene.

Mis-sense, nonsense, frameshift and in-frame mutations can all occur in the same gene. The cystic fibrosis transmembrane regulator (CFTR) gene on chromosome 7 is an example of this (Collins, 2009). Where both chromosomes of a pair carry a mutation in the CFTR gene, the individual will have cystic fibrosis, although the severity and clinical outcome will vary according to the type of mutation.

Another mutation that can be associated with disease is where a short sequence of nucleotides (typically three) is repeated within the gene, and the number of repeats increases above a specific threshold. Huntington’s disease is caused by repeating units of CAG within the HD gene on chromosome 4. The normal range of such repeats is 5-35, but anything above 37 is pathogenic, leading to the disease. The size of the expanding repeat can vary substantially in other genes too, up to many thousands, and repeat length is often correlated with the severity and/or age of onset of the condition. Conditions caused by expanding repeats include Fragile X syndrome and myotonic dystrophy.

Deletions, insertions and inversions of genetic material are all alterations to the chromosomal structure. These changes can involve much larger segments of DNA, sometimes spanning one or more genes, where there have been breaks in the DNA molecule that have not been repaired correctly. Alterations to chromosome number as a result of faults during meiosis also lead to duplication or deletion of genetic material, such as with Down’s syndrome.

The diseases that can result from mutations within a single gene show characteristic patterns of inheritance, as first described by Mendel. The type of pattern depends on the outcome of the mutation, that is, whether there is a loss or gain of function. If the outcome is sufficiently marked for it to be shown when only one gene of a pair is mutated, the inheritance pattern is said to be dominant. There is a

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**FIG 2. GENETIC AND ENVIRONMENTAL CONTRIBUTIONS TO SINGLE-GENE AND COMPLEX DISORDERS**

A – single-gene disorders. A variant in a single gene is the primary determinant of a disease and is responsible for most of the disease risk or trait variation (dark grey sector), with possible minor contributions from modifier genes (light grey sectors) or environment (blue sector)

B – complex disease. Many variants of small effect (light grey sectors) contribute to disease risk, along with many environmental factors (blue sector)


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**FIG 3. THE INTERPLAY BETWEEN GENOME AND ENVIRONMENT**

- **GENETIC**
  - Duchenne muscular dystrophy
  - Haemophilia
  - Cystic fibrosis
  - Crohn’s disease
  - Pyloric stenosis
  - Asthma
  - Diabetes
  - Skin cancer
  - Infectious diseases

- **ENVIRONMENTAL**
  - Road traffic accidents

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**BOX 2. PACE OF DISCOVERY**

At its outset, many felt the Human Genome Project was hugely ambitious, but it was completed in 2003 under budget and ahead of time. The pace of studies continues to increase because:

- Breakthrough technological developments lead to quicker and cheaper genome sequencing. The costs of genome sequencing are halved approximately every 22 months (Guttmacher and Collins, 2005);
- Large cohorts of people are being used, often in multinational studies. Large sample sizes are important in detecting relatively modest effect sizes associated with genetic variants. For example, the UK Biobank provides a sample of around 500,000 volunteers;
- Bioinformatics has also advanced to deal more efficiently with massive datasets.

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**B – complex disease. Many variants of small effect (light grey sectors) contribute to disease risk, along with many environmental factors (blue sector)**

50% chance that people with such a mutation will pass it on to their children. Where the effect is seen only if both genes have a mutation, the pattern is referred to as recessive. In this case, both parents would have to have the mutation to pass on two copies (one from each parent) to the child, and there is a 25% chance that this would happen for each conception.

**Single-gene and common complex diseases**

Although single-gene conditions are relatively rare, it is worth remembering that collectively, they are numerous. Together with chromosomal disorders, they affect around one in 25 of the population (Genetic Interest Group, 2009). The Human Genome Project and other initiatives have also helped to identify sub-sets of common diseases caused by single-gene alterations and displaying the typical Mendelian inheritance patterns. Breast and bowel cancer, and cardiovascular disease (such as familial hypercholesterolaemia), are examples of these.

There is no doubt that the scientific basis of the single-gene conditions (and the conditions associated with alterations to the structure or numbers of chromosomes) is complex. However, this knowledge is crucial to understanding the genetic mechanisms that underpin common, genetically complex diseases. These develop under the influence of multiple genes, and as a result of the interactions between these genes and between genes and the environment, both the internal environment of the cell and the external environment (Fig 2).

With the genetically complex common diseases, each gene alteration known to be associated with a particular disease confers some degree of susceptibility to developing that disease and so contributes to the relative risk of developing it. By itself, one gene alteration may contribute little to the overall risk. In contrast, with a single-gene condition such as Huntington’s disease, a person with the mutated gene has a 100% chance of developing the condition over the course of their lifetime. Table 1 outlines some of the differences between single-gene conditions and common complex diseases.

**Copy number variation**

A common form of human genome diversity is copy number variation, involving gain or loss of large segments of DNA (thousands or even millions of nucleotides). This is thought to play a role in both single-gene and complex diseases, particularly where there are gene dosage effects. Interest in this phenomenon is growing as technological advances have facilitated study (Box 2), and because of its potential significance in relation to predisposition or resistance to disease (Freeman et al, 2006).

**EPIGENOMICS**

Although the genome and the DNA code contained within it are sometimes referred to as the “blueprint for life”, the genome itself is subject to biochemical processes that influence gene activity. Epigenomics is the study of the chemical “tags” that mark the genome at specific places to regulate which genes are active in a cell at any given point in time. This allows differentiation between cell types – thus skin cells behave like skin cells, and liver cells act like liver cells.

There are two main ways in which the epigenome “marks” the genome:

- Chemical tags on the histone proteins (Fig 1) affect how tightly or loosely the DNA molecule is wrapped up in the chromosome. Tight wrapping can conceal a gene from the cell’s activation mechanisms;
- The attachment of a methyl (CH₃) group to the backbone of the DNA molecule at a specific place is called methylation, and this has a direct effect on gene activity.

The epigenome in turn is influenced by environmental agents such as specific nutrients or chemical pollutants such as tobacco smoke. It is most susceptible to change during embryogenesis. Interest in epigenomics has grown as researchers have become aware that changes to the epigenome can cause or contribute to diseases such as cancer, and could provide explanations for diseases with known “parent-of-origin” effects such as autism and schizophrenia. Furthermore, epigenomic changes themselves can be passed on to the next generation, but they can also be reversed (Jirtle and Skinner, 2007).

**A CHANGING PARADIGM FOR DISEASE**

That genes play a fundamental role in the development of disease (single-gene and complex) is understood. However, variations in the non-coding regions of the genome may be a significant causative factor in disease, by altering regulation of the gene product. The epigenome also plays its part. What is emerging is that single-gene  

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**TABLE 1. COMPARISON OF SINGLE-GENE AND GENETICALLY COMPLEX CONDITIONS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Single-gene</th>
<th>Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>Relatively rare (generally &lt;1 in 1,000) but collectively numerous</td>
<td>Common (up to one person in three)</td>
</tr>
<tr>
<td>Underlying cause</td>
<td>Caused by DNA mutation in a single gene. Disease severity and age at onset</td>
<td>Disease susceptibility influenced by DNA sequence variation in multiple genes interacting with environmental factors. Individual DNA sequence variations each contribute a small proportion of the overall risk of disease.</td>
</tr>
<tr>
<td>Role of environment</td>
<td>Often overridden by effect(s) of gene mutation</td>
<td>More important</td>
</tr>
<tr>
<td>Familial inheritance</td>
<td>Simple dominant, recessive or sex-linked</td>
<td>No simple mode of inheritance</td>
</tr>
<tr>
<td>Risk for relatives</td>
<td>More predictable and often high (typically around 25-50%)</td>
<td>Less predictable, often smaller risk</td>
</tr>
<tr>
<td>Gene identification before 2005</td>
<td>Over 2,000 disease genes identified</td>
<td>Fewer than 20 disease genes identified</td>
</tr>
<tr>
<td>Gene identification after 2005</td>
<td>Similar rate of discovery. Most disease genes not identified are exceptionally rare.</td>
<td>500 new disease genes located and many identified</td>
</tr>
<tr>
<td>Treatment</td>
<td>Limited</td>
<td>More likely to be effective</td>
</tr>
<tr>
<td>Examples</td>
<td>Cystic fibrosis, haemophilia, sickle cell disease, familial hypercholesterolaemia, Huntington’s disease</td>
<td>Autism, asthma, cancer, coronary heart disease, diabetes, bipolar disorder, rheumatoid arthritis</td>
</tr>
</tbody>
</table>

Source: adapted from House of Lords Science and Technology Committee (2009)
conditions are not simple and the genetic basis of all disease is multifaceted. When environmental interaction is taken into account, the conceptual boundaries between rarer single-gene conditions and common complex conditions become even more blurred (Fig 3).

APPLYING GENOMICS TO HEALTHCARE

What does this mean for healthcare? The Department of Health (2003) published its genetics white paper in recognition that the impact of genetics would be felt across the NHS and there was a need to prepare for this. Department of Health (2003) published its white paper in recognition that the impact of genetics would be felt across the NHS and there was a need to prepare for this. The pace of discovery of genetic variation associated with common conditions is phenomenal, providing insights into causal mechanisms and potential therapeutic responses (Box 3).

“Over time we will see new ways of predicting and preventing ill health, more targeted and effective use of existing drugs and the development of new gene-based drugs and therapies that treat illness in novel ways. Above all, genetics holds out the promise of more personalised healthcare with prevention and treatment tailored according to a person’s individual genetic profile” (DH, 2003).

There is a “knowledge revolution” in genomics that is informing healthcare and challenging how we think about health and ill health. The pace of discovery of genetic variation associated with common conditions is phenomenal, providing insights into causal mechanisms and potential therapeutic responses (Box 3).

With greater understanding comes the potential for applying this knowledge to healthcare, as indicated in the white paper:

- A new classification of disease based on an understanding of the gene expression, chromosomal and molecular abnormalities, for example, in type 2 diabetes and childhood leukaemia;
- The possibility of detecting disease earlier, with an increasing range of genetic tests;
- Greater opportunities for prevention by identifying individuals and sub-populations who might be at increased risk, and identifying ways of modifying or preventing this risk;
- Better targeted and more effective treatments. The new field of pharmacogenomics studies how genetic variation across the genome affects drug metabolism and responsiveness, identifying subtypes of populations who are more likely to show an enhanced response or adverse drug reactions, for example, in response to sulphonylureas, warfarin, trastuzumab (Herceptin) or codeine;
- New types of treatment with drug development based on an understanding of the underlying molecular mechanism, such as imatinib in cancer treatment, with a longer term focus on gene therapy.

The white paper progress review five years later (DH, 2008) was positive, and quoted the Royal Society, one of the respondents to its consultation exercise:

“Increased knowledge of genetics and genomics in the long term will impact substantially on the way in which we understand and treat disease; the impact on healthcare is just beginning and will not be dramatic over a short timescale. Instead, new diagnostic treatments and new disease classifications will emerge with increasing frequency but will not change the basics of clinical care overnight” (DH, 2008).

CONCLUSION

The extent of genetics knowledge nurses have needed until now has at best been rudimentary. However, genomics is changing this as we move to a new paradigm of the contribution of the genome and epigenome to health and ill health. This paradigm is complex, but if we are to provide truly holistic care, we need to understand the role of genomics/epigenomics in mechanisms of disease causation and in the response to drugs, the implications for healthcare, and the nursing role in this. 

- Part 2 of this series, to be published in next week’s issue, examines the implications for nursing practice
- An online resource on the role of genetics and genomics in health and disease to accompany this series is available on nursingtimes.net. The resource reflects the patient pathway and includes the sorts of questions nurses might ask. The resource is available at tinyurl.com/genes-resource

REFERENCES


BOX 3. KEY DISCOVERIES

Some key discoveries of genetic variation associated with common diseases reported by the Wellcome Trust (genome. wellcome.ac.uk) during 2009 include:

- Alzheimer’s disease: two new genes found to be associated with this disease;
- Giomma: five common gene variants associated with a higher risk of the most common form of brain cancer;
- Hypertension: eight genetic variants affecting blood pressure;
- Learning disability: nine genes with strong links to learning disability found on the X chromosome;
- Liver damage: specific gene variation strongly associated with a high risk of liver damage caused by fluocoxacinil;
- Testicular cancer: three common genetic variants associated with increased risk.