SCIENCE, MEDICINE, AND THE FUTURE

Translating genomics into improved healthcare

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Since the work of Mendel,1 genetic research has been punctuated by key, shifting advances (box 1), which culminated in the first draft sequence of the human genome in 2001.2,4 Although most of the human genome sequence is shared by everyone, a small proportion varies between individuals. This variation, acting together with environmental factors, is thought to underlie differences in physiology, susceptibility to disease, and responses to drugs. We summarise the recent discoveries and review the implications of newly acquired knowledge for medical practice and public health.

Box 1 | Key early milestones in genetic research

Discovery of nucleic acid (Meisscher 1869)
Identification of its key constituents—the organic bases adenine (A), thymine (T), guanine (G), and cytosine (C) (Kossel 1879) held on a backbone of deoxyribose or ribose sugars in DNA and RNA, respectively
The Boveri-Sutton chromosome theory of inheritance (1902)
The proposal that DNA (not protein) is the heritable genetic material that distinguishes organisms of different species (Chargaff 1950)
The discovery of the double helical structure of DNA (Crick and Watson 1953) provided the necessary insight into how base sequence information can be replicated and transmitted from parent to offspring. It also pointed the way to understanding how the DNA sequence is translated into the primary amino sequence of proteins, which, in turn, determines the structure and function of an organism. The unidirectional flow of information from DNA to RNA to protein was subsequently summarised in the central dogma (Crick 1958)

SUMMARY POINTS

Until recently the genetic basis of most common diseases remained elusive
Genome wide association analysis has now uncovered thousands of regions of human DNA where sequence variation influences susceptibility to common diseases
Common single nucleotide polymorphisms associated with disease are distributed across multiple chromosomal regions, have modest affects on disease risk, act additively, and explain only part of disease heritability
Association analysis is starting to provide data on the causes of common human diseases that should accelerate the design and development of new treatments
Emerging technologies, including rapid, less costly sequencing of whole genomes, bring the prospect of better diagnostics and treatment
Clinicians will need to keep updated on genetic advances that have healthcare applications
The presence of a particular genetic variation is neither necessary nor sufficient to cause disease but confers a modest increase in risk.

After publication of the draft human sequence in 2001, attention turned to cataloguing and studying the effects of common variations in the DNA sequence on the risk of common diseases. Single nucleotide polymorphisms (SNPs) are variations at a single base pair (fig 1) and are the most common type of human sequence variation, occurring about every 500-1000 DNA base pairs. Less common types of variation include single nucleotide insertions and deletions (indels) and deletion or duplication of longer tracts of DNA (copy number variation) (fig 1).

The SNP Consortium developed the SNP database (www.ncbi.nlm.nih.gov/SNP) to identify the most common single nucleotide variations in the genome. Each SNP in this database is allocated a unique reference number. The Human HapMap consortium (http://hapmap.ncbi.nlm.nih.gov/index.html.en) was then established to quantify the association between SNPs in the genomes of human populations with differing ancestry (linkage disequilibrium). Coupled with new technological developments, this provided the framework to develop arrays capable of typing around 500,000 SNPs across the genome. Information on another million or more SNPs could then be inferred on the basis of the known associations between SNPs. These arrays or “SNP chips” provide a cost effective way to genotype many thousands of people.

To investigate the genetic basis of common diseases, genome-wide case-control studies have compared the frequency of typed (and inferred) SNPs in large numbers of unrelated people affected by a disease and unaffected unrelated controls. Instead of the single exposure evaluated in a non-genetic case-control study (such as smoking), these studies examine hundreds of thousands of genetic exposures simultaneously. Points in the genome at which the frequency of typed (and inferred) SNPs in large numbers of unrelated people affected by a disease and unaffected unrelated controls.

What is known about the genetic basis of complex diseases?

Diseases that commonly affect adults (such as cardiovascular disease, diabetes, Parkinson’s disease, Alzheimer’s disease, and common cancers) result from a more complex interplay between genetic and environmental factors. Such diseases exhibit familial clustering, but there is no clear inheritance pattern because of the polygenic aetiology and the substantial contribution from the environment. Family based linkage analysis can rarely identify genetic mutations associated with these disorders because people are typically over 50 years before clinical presentation; by this time their parents may be dead and susceptible children too young to manifest the disorder. The “common-disease common-variant” hypothesis proposes that these diseases arise from many common DNA variants, each with a modest influence on disease risk. The presence of a particular genetic variation is neither necessary nor sufficient to cause disease but confers a modest increase in risk.

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Genome-wide association studies involve hundreds of thousands of tests of association, so the number of false positive SNP-disease associations would be high if conventional thresholds were used to determine significant associations. Thus, stringent criteria are used before “genome-wide significance” can be declared. Typically, P value thresholds of $1\times10^{-7}$ or $5\times10^{-8}$ are used. A P value of $5\times10^{-8}$ can be thought of as a P value of 0.05 with a Bonferroni correction for one million statistical tests—a typical number of variants genotyped or inferred in a genome-wide association study. Even with such stringent thresholds, positive findings are routinely replicated in independent datasets to confirm or refute association. Because SNPs of smaller effect size can be identified by increasing the available sample size, research consortiums focus on a single disease so that data from several case-control collections can be pooled and summarised using meta-analysis. This approach has increased the number of genetic loci identified for many disorders.
**How might findings from genome-wide association studies affect healthcare?**

Accumulated evidence from such studies is now helping to determine the direction of future research and to clarify where the future healthcare applications will be. Typically, many genetic regions contribute to increased risk of complex disease (20 loci have been identified for type 2 diabetes and 40 for Crohn’s disease), but the effect at each region is weak (5-10% increase in risk) and seems to be additive and independent. As a result, genome-wide association studies to date have explained only a small part of the heritability of common disorders (table). The findings currently have limited value for predicting disease risk but may have other important implications for healthcare provision (box 2).

**Can genetics help predict risk of common disease?**

Predictive genetic tests based on findings from genome-wide association studies are being offered commercially, despite concerns about their clinical value. With a few notable exceptions (such as age related macular degeneration; table), carrying any one common risk allele increases the chance of experiencing a common disease event by only a fraction (typically 5-25%). This makes tests based on only one SNP poorly predictive. Several risk alleles, often on different genes, may contribute to increased risk of disease, so would information from a panel of common modest effect alleles be better at predicting disease than a single common risk allele? A person with 10 risk alleles, each in a different gene and each conferring a 20% increase in risk, might be expected to be at double the risk of disease compared with someone carrying none, and such a high risk person might benefit from a targeted preventive intervention. However, people with 10 risk alleles are rare in the population. For example, if the average frequency of a risk allele in a population is 30% (0.3), the probability of inheriting 10 such independent alleles is 0.3^10 (0.0000059). Because the frequency distribution of common independently inherited risk alleles is normal (bell shaped) and the association with risk is additive, more cases of disease would be expected in the many people with an intermediate number of risk alleles than the minority with a large number of alleles. Thus, the frequency distributions of risk alleles should overlap substantially among eventual cases and controls, making it difficult to separate the two groups by the number of risk alleles carried (fig 3).

In disease prevention the aim is often to stratify risk rather than to discriminate events. This is because many preventive interventions produce the same relative risk reduction whatever the risk so that the absolute benefit is larger (and the number needed to treat smaller) in people at high risk. If the number needed to treat to prevent one event in a person with 10 risk alleles was 100, the number needed to screen to prevent one event would be 100/0.000006 (16 666 666). Although genotype based tests are cheap, screening such a large number of people just to alter risk of disease in one would be very costly.

Genetic tests that capture a wider range of variability in a given gene or region, rather than simply a few SNPs, may be better for prediction. The discovery of rare or intermediate frequency alleles that have a much larger effect size than common HapMap alleles may also open up greater opportunities. Tests of rarer alleles may be useful in family based screening, such as that used for monogenic familial hypercholesterolaemia, which currently uses cholesterol measurement rather than genotyping.

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**Box 2 | Insight into disease aetiology from genome-wide association studies**

In Crohn’s disease, many of the single nucleotide polymorphisms (SNPs) associated with disease susceptibility lie in and around genes concerned with autophagy, which was previously not considered an important disease mechanism in Crohn’s disease.

In type 2 diabetes many of the loci encode proteins concerned with insulin secretion rather than insulin signalling, which had previously been the focus of research.

Several of the genetic loci associated with the risk of coronary heart disease influence low density lipoprotein-cholesterol, but some are located distant from known genes and seem not to influence any of the known risk factors for myocardial infarction. Thus, previously unknown disease mechanisms might be at work.

Data from different disorders show that some genetic regions or SNPs affect the risk of more than one disease. For example, different SNPs in the same region on chromosome 12 influence the risk of coeliac disease, type 1 diabetes, and myocardial infarction. The same SNP near the TCP2 gene on chromosome 8 is associated with the risk of developing type 2 diabetes and prostate cancer. These, and other examples indicate that some common disorders have a partially overlapping aetiological basis, and this may lead to new disease taxonomy.

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**Recently identified genetic variants associated with disease**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Examples of research consortiums</th>
<th>Examples of associated genes</th>
<th>Insight on mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease</td>
<td>WTCCC</td>
<td>NOD2, IRGM, ATG16L1, IL23R, PTPN2, PTGER4</td>
<td>Autophagy, immunity</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>DIAGRAM WTCCC DGI</td>
<td>TCF7L2, CAPN10, VNTR, SLC2A1, IRS1, CDKAL1, FO, CDKN2B</td>
<td>Insulin secretion unknown</td>
</tr>
<tr>
<td>Myocardial infarction and coronary heart disease</td>
<td>CARDIOGRAM WTCCC</td>
<td>APOE, PCSK9, CELSR2/PSRC1, CDKN2A/CDKN2B</td>
<td>Low density lipoprotein-cholesterol pathway unknown</td>
</tr>
<tr>
<td>Age related macular disease</td>
<td></td>
<td>CFH, C2/C4B, C1, CFI, ARMS2, TIMP3, LIPC, CETP, LPL, ABCA1</td>
<td>Complement pathway, high density lipoprotein-cholesterol pathway?</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Asia Breast Cancer Consortium</td>
<td>BRCA1, BRCA2, PTEN, TP53, FGF19, TRAF9</td>
<td>DNA and cell repair, tumour suppression pathway</td>
</tr>
<tr>
<td>Meningococcal disease</td>
<td>International Meningococcal Genetics Consortium</td>
<td>CFH/CFHR3</td>
<td>Complement pathway</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>African Tuberculosis Genetics Consortium and WTCCC</td>
<td>GATA6, CTAGE1, RBBP8, CABLE5</td>
<td>As yet unknown</td>
</tr>
</tbody>
</table>

*The variants vary in their strength of effect. Some variants (such as BRCA1 in breast cancer and CFH in age related macular disease) are strongly associated with disease risk and thus highly predictive of disease risk, whereas others (such as those listed for myocardial infarction and coronary heart disease) are only weakly associated with disease risk and provide little predictive power.*
Can genetics improve understanding of the non-genetic causes of disease?

The genotype is unique among naturally occurring differences between people because it is allocated at random, fixed throughout life, and not modified by disease. Interpretation of genetic associations is therefore not limited by confounding (where exposure and disease seem to be associated because of common association with a third factor) or reverse causation (where the association between an exposure and disease is caused by the disease itself leading to an alteration in the exposure). Thus when the function of a gene is known, its association with a disease (however weak) can provide clear insight into the causal mechanisms leading to disease (fig 4). For example, ADH1 (alcohol dehydrogenase) gene variants are associated with differences in long term alcohol consumption, which is otherwise difficult to measure accurately. ADH1 variants can provide a useful index of long term usual alcohol consumption. Association between these variants and oesophageal cancer provides evidence for a causal role of alcohol consumption in the disease. Another example is C reactive protein (CRP) and its role in coronary heart disease. Raised concentrations of CRP are associated with an increased risk of heart disease. However, bias and confounding by reverse causality may partially or wholly explain these associations, so we do not know whether lowering CRP would reduce the risk of cardiovascular events. Genetic variants that influence CRP values are less prone to confounding, and reverse causality is not a problem. The presence or absence of an association between CRP genetic variants and disease can thus provide clear evidence on whether CRP actually plays a causal role in disease.

Can genetics lead to improved therapeutics?

Using pharmacogenomic approaches to develop genotype based predictive tests of drug response may help to personalise or stratify therapeutic interventions at an individual or group level. The number of pharmacogenetic tests currently approved for clinical use is limited. A recent systematic review of pharmacogenomic studies highlighted several methodological and other problems in this area, notably small underpowered studies and the widespread use of surrogate outcome measures. However, genetic loci associated with the risk of statin myopathy have recently been identified, as well as loci associated with hypersensitivity to the pro-tease inhibitor abacavir, response to interferon treatment in hepatitis C infection, and dose requirements in people taking warfarin. Pharmacogenetic testing may eventually become common in some therapeutic areas, but the clinical value and cost effectiveness of emergent pharmacogenetic tests have not yet been subject to the same level of scrutiny and careful appraisal as other diagnostic tests.

As well as offering the potential for new pharmacogenetic tests, emerging genome-wide association studies of drug response could provide new insights into the pathways by which even well established drugs are handled by the body. The concept of pharmacogenomics is expanding to incorporate not only the use of genetic data to guide treatment but also to inform drug development. This is because studies in populations of variants in genes encoding a drug target protein can be considered to be a type of natural randomised trial and could be used to help predict the on-target effect of modifying the same target pharmacologically. For example, common variants in the CETP gene, which encodes cholesteryl ester transfer protein, the target of the CETP inhibitor torcetrapib, were associated with the same lipid and lipoprotein changes seen with torcetrapib treatment but were not associated with high blood pressure, an off-target effect of torcetrapib. The hope is that by providing randomised evidence of the effects of drugs in humans without requiring participants’ exposure to a new molecule of uncertain safety and efficacy new drug targets might be validated and the risks of late stage failure in drug development reduced through the application of genetic studies during early drug development.

Future directions

Much of the heritability of common diseases cannot be explained by common SNPs, so the focus is now moving towards other types of genetic variation, such as copy number and rare single nucleotide variation. Interest in heritable changes in gene expression caused by other processes, such as DNA methylation or histone modifications, is also increasing. Some alleles with large effects on disease risk are likely to be rare (because natural selection reduces their frequency over time) and thus are not well represented on whole genome arrays. Efforts in this area are being stimulated by another technological advance, the ability to sequence a single human genome (exome sequencing) using “next generation” sequencing technology. In contrast to the first draft human genome sequence, which took several years and millions of pounds to complete, this now takes a few days and costs about £8000 (€9000; $12 600). Systematic rare variant discovery is now being undertaken as part of the international 1000 genomes project (www.1000genomes.org/page.php) and the UK 10k Consortium. Whole exome sequencing is expected to identify rare variants that influence risk in common disorders and identify mutations underlying sporadic single gene disorders that have not been amenable to linkage analysis because of the absence of multigenerational pedigrees. The variants that are discovered may eventually prove valuable as family based genetic tests.
Finally, analysis of the effects of newly discovered genetic loci in representative population based cohort studies (not case-control studies) are beginning to provide better information on the absolute (not relative) risk of common diseases, as well as insight into the modification of genetic effects by environmental factors. The UK Biobank project (www.ukbiobank.ac.uk/) — a prospective study that has recruited more than 500,000 volunteers, stored millions of biological samples (including DNA), and recorded information on lifestyle measures — will provide a new resource for scientists studying the environmental and genetic determinants of a wide range of common diseases in future decades.

Conclusions

As the use of whole genome sequencing becomes more widespread, an improved understanding of the causes of disease, better targeted drug treatments, and perhaps prediction of risk are realistic expectations. As in any area of medical advance, rigorous evaluation of new genetic based technologies will be needed. A major challenge for clinicians will be to keep updated on genetic advances with potential healthcare applications and to develop the ability to critically appraise research findings in this fast moving field.

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1 Mendel G. Experiments in plant hybridization. 1865.
Preventing cell-free fetal DNA and diseases

mitochondrial DNA maternally inherited

implications for safer

BMJ 2009;339:b2451

Preventing transmission of maternally inherited mitochondrial DNA diseases

BMJ 2009; 338:b94

ANSWERS TO ENDGAMES, p 1057. For long answers go to the Education channel on bmj.com

ON EXAMINATION QUIZ

Ketoconazole treatment

Answer C is correct.

STATISTICAL QUESTION

Skewed distributions

Answers a and b are true, whereas c and d are false.

CASE REPORT

Pain after amputation of the lower leg

1 Phantom limb pain

2 Increasing evidence suggests that central and peripheral mechanisms contribute to phantom limb pain

3 Pain before amputation and genetic predisposition may contribute to the development of neuropathic pain

4 Preoperative epidural insertion and nerve sheath catheters have been investigated with varying success

5 Conservative options include transcutaneous electrical nerve stimulation, hypnosis, massage, ultrasound, and mirror box therapy. Medical options include anticonvulsants, tricyclic antidepressants, opiates, NMDA antagonists, and benzodiazepines. Surgical options include neuroectomy, stump revision, and dorsal column stimulation.