

The genomic basis of therapeutics

A series of factsheets illustrating basic concepts and clinical
applications of pharmacogenetics and genomic science



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This pack of factsheets is one of a series of resources developed by the NHS National Genetics Education and Development Centre. The factsheets may be photocopied for non-commercial education purposes for healthcare staff and you are welcome to use the pack or individual sheets to share with colleagues or to use within your teaching. The series can be downloaded from our website www.geneticseducation.nhs.uk along with a range of other support material.

Perspectives

Illustration - Pharmacogenetics in Practice - Clinical Examples

The factsheets:

- Part 1:** When usual doses lead to adverse effects: Dose level relationships
- Part 2:** When usual doses lead to adverse effects: Polymorphisms of metabolic enzymes
- Part 3:** The cancer treatment revolution: Controlling the renegade cell
- Part 4:** Genotyping the invader and developing new vaccines
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Information about the NHS National Genetics Education and Development Centre, our website and resources



“Pharmacogenetics” is the study of the influence of heredity on drug response; that is, how genetic differences between individuals may cause them to respond differently to a particular drug. The term, first proposed in 1956, predates the reading of the complete human DNA sequence in the Human Genome Project in 2000. Therefore the initial emphasis was on single genes, particularly those encoding enzymes involved in drug metabolism.

“Genomics” refers to the science and technology used to examine the complete sequence of genetic material in humans and other organisms. Pharmacogenomics is the genome-wide study of the influence of heredity on drug response, to identify new drug targets and features of the genome that are useful for optimising therapy.

Like many groups we use the terms pharmacogenetics and pharmacogenomics interchangeably. In an increasing number of areas of clinical practice, pharmacogenetics information is being used to guide decision-making. Pharmacogenetics should be relevant to all health professionals who are interested in the prescription or usage of drugs, including nurses, clinicians and pharmacists.

As well as highlighting the relevance of pharmacogenetics to clinical practice, we believe it is vital to recognise its limitations. In most cases where genetic differences may affect the drug regimen, it is still more reliable to base clinical decisions on traditional testing methods, such as monitoring of blood levels, as opposed to genetic tests. It is important to adopt an evidence-based perspective, as an increasing number of genetic tests are being promoting for diagnostic, prognostic, or drug-response prediction purposes with little clinical validation.

Like any other tests, pharmacogenetic tests need to be properly evaluated to demonstrate clinical validity and utility. Health professionals should benefit from an understanding of the test evaluation process, the scientific and clinical evidence in pharmacogenetic studies, and the associated genomic sciences.

The following factsheets illustrate some of the core concepts and potential clinical applications.

1: When usual doses lead to adverse effects: Dose level relationships

For most drugs there is a clear dose-effect relationship and dosing involves a trade-off between beneficial and adverse effects.

2: When usual doses lead to adverse effects: Polymorphisms of metabolic enzymes

Our bodies produce metabolic enzymes that detoxify and process most drugs. These enzymes may be impaired by genetic mutations or interactions with other drugs or foods, and lead to serious clinical effects.

3: The cancer treatment revolution: Controlling the renegade cell

This factsheet describes how genomic insights have led to improved treatments for many types of cancer.

4: Genotyping the invader and developing new vaccines

Genomic science is helping to improve prevention and treatment of infectious diseases. This factsheet describes developments which may contribute to rapid identification of microbial resistance and formulation of effective vaccines.

5: Gene therapy: repairing or replacing defective genes

This factsheet describes the principles, progress, and challenges of gene therapy.

6: Genomics, stem cells and regenerative medicine

Stem cells and genomic information hold much promise for regenerating lost or destroyed cells or tissues, such as in neurological disease or heart disease. This factsheet introduces approaches used to induce pluripotent stem cells from somatic cells.

7: Gene expression signatures

New genetic technologies can assist diagnosis, for example by identifying the subtype of a cancer; and prognosis, for example in monitoring the progression of Alzheimer's disease. This factsheet introduces the technology and application of gene signatures to guide practice.

8: Pharmacogenetic Testing

Pharmacogenetic testing can be used to guide decision-making about drug therapy. In many clinical situations, "traditional" testing, such as monitoring of blood levels, may be more appropriate. Like any test, it is important to demonstrate evidence of the utility and cost-effectiveness of a pharmacogenetic test before. This factsheet illustrates some of the issues involved in assessing clinical utility.

The Centre is working with a range of groups to develop pharmacogenetics education resources for health professionals, trainers and educators. The Centre would like to hear from any group or individual with suggestions about how to improve this document and our website, or to comment on pharmacogenetics in clinical practice, or on genetics education in general. Please contact enquiries@geneticseducation.nhs.uk

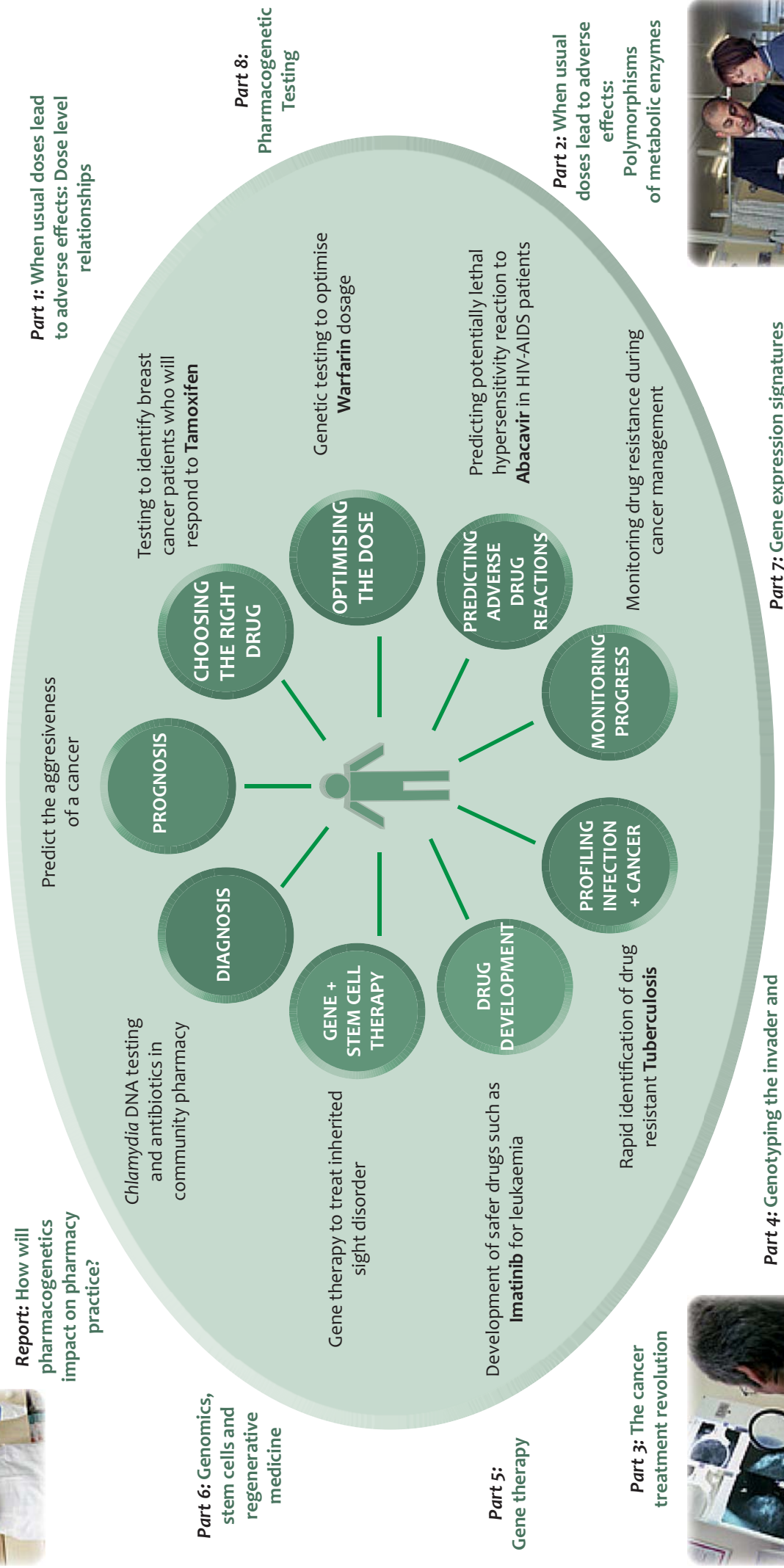


In many areas of clinical practice, pharmacogenetics information is used to guide decision making. Our pharmacogenetics education programme should be relevant to all health professionals interested in prescription or usage of drugs. A series of factsheets, resources, and further information is available at www.geneticseducation.nhs.uk/pgx



National Genetics Education and Development Centre

Report: How will pharmacogenetics impact on pharmacy practice?



Part 6: Genomics, stem cells and regenerative medicine

Part 5: Gene therapy

Part 3: The cancer treatment revolution



Part 4: Genotyping the invader and developing new vaccines

Part 7: Gene expression signatures

Part 1: When usual doses lead to adverse effects: Dose level relationships

Part 8: Pharmacogenetic Testing

Part 2: When usual doses lead to adverse effects: Polymorphisms of metabolic enzymes



When usual doses lead to adverse effects: Dose level relationships

Genetic mutations may lead to formation of inactive metabolic enzymes. These defects may lead to drug accumulation even with normal doses.

Clinical perspective: Many diseases, and most chronic ones, are treated with several drugs. It is not unusual to see elderly patients on several drugs, thereby increasing the risk of drug-drug interactions. In the presence of genetic polymorphisms of metabolic enzymes or drug receptors, even usually minor interactions may lead to serious clinical effects.

The pharmacogenetic basis

- Most drugs are characterised by a range of doses within which they are safe (the therapeutic window). An increase in dose beyond that range leads to adverse effects due to excessively high blood levels (see Figure 1).
 - The drug level observed after a given dose of a drug is the result of interplay between absorption and excretion.
 - To facilitate excretion most drugs are metabolised by a family of proteins known as the Cytochrome P450 enzymes.
- Prominent members are CYP3A4, CYP2D6, CYP2C9 and CYP2C19.
- Different drugs are metabolised by different CYP450 enzymes.
 - The activity of these enzymes may be impaired by genetic mutations or by interactions with various drugs or even dietary components (e.g. grapefruit).
 - Adverse effects then follow.

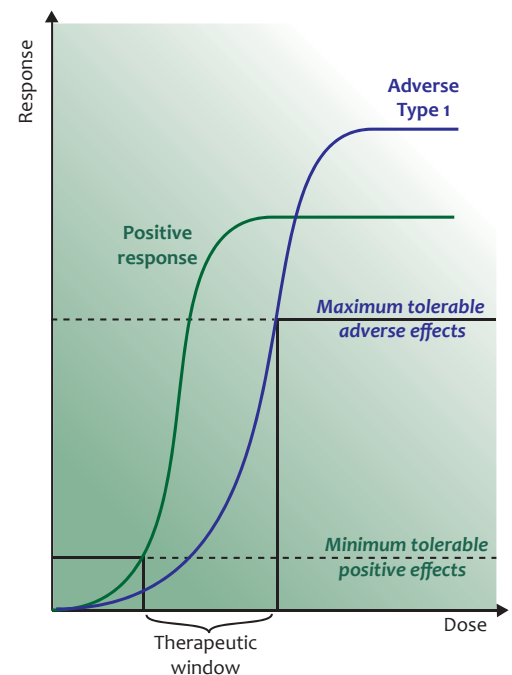


Fig. 1 Adverse effects due to high blood levels

Example of genetic polymorphism leading to adverse drug effect

Statins, a class of drugs widely used for controlling blood cholesterol have an excellent safety record. A 74 year-old woman developed the rare complication of rhabdomyolysis (severe muscle pain and breakdown) on normal doses. Investigation showed that she most likely had low levels of a cerivastatin metabolite, suggesting deficiency in CYP2C8, an enzyme involved in the metabolism of cerivastatin.

Further reading

(1) Ozaki H, Ishikawa CT, Ishii T, et al. (2005) Clearance rates of cerivastatin metabolites in a patient with cerivastatin-induced rhabdomyolysis. *Journal of Clinical Pharmacy and Therapeutics* 30(2):189-192.



When usual doses lead to adverse effects: Polymorphisms of metabolic enzymes

Genetic mutations may lead to formation of inactive metabolic enzymes and drug accumulation to toxic levels, particularly in the presence of physiological abnormalities.

Clinical case study

A 62-year-old man (Mr X) with a history of chronic lymphocytic leukaemia, was admitted to hospital for suspected pneumonia. Except for chemotherapy three months prior to admission, his only therapy on admission was valproic acid. He was given ceftriaxone, clarithromycin and voriconazole as antimicrobial therapy, and a normal dose of codeine (25mg tid) for his cough. On day 4 his level of consciousness deteriorated and he became unresponsive. Subsequent investigations indicated codeine intoxication due to drug-drug interaction, presence of genetically impaired metabolic enzyme and poor renal function (1).

The pharmacogenetic basis

- After ingestion, most drugs are metabolised to facilitate excretion, usually in the urine. Cytochrome P450 enzymes, most notably CYP3A4, CYP2C9, and CYP2C19, and CYP2D6, are most commonly involved in drug metabolism.
- Genetic mutations can lead to formation of less active, or inactive, enzymes. This leads to higher drug levels, or reduced levels of active metabolites, with the same dose of drug. Conversely, gene duplication may lead to accelerated (ultra-rapid) metabolism.
- A drug may be metabolised via several pathways. Genetic mutations may affect each of these and therefore amplify the dose-response.
- Concomitant drugs may interfere with the metabolic pathways and further accentuate any effect due to polymorphism.
- Liver and renal malfunction may complicate matters further.

What caused the intoxication?

- Codeine exerts its analgesic and opioid side-effects largely through morphine, its metabolite:
- Mr X had a CYP2D6 genotype which led to ultrarapid metabolism to morphine.
- He was taking drugs which inhibited CYP3A4 metabolism leading to more codeine being available for metabolism to morphine.
- Renal impairment led to less morphine being removed from the circulation.
- The morphine accumulation from this combination of factors led to toxicity.

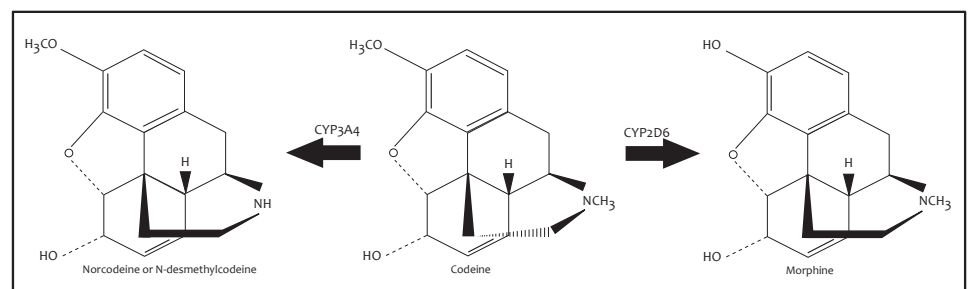


Fig. 1 Metabolism of codeine

Further reading

(1) Gasche Y DY, Fathi M, Chiappe A, Cottini S, Dayer P, Desmeules J. (2004)

Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *New England Journal of Medicine* 57:2827-2831.



The cancer treatment revolution: Controlling the renegade cell

Cancer is now widely described as a genetic disease. Gene mutations lead to cancer. Genomic insights have led to dramatic improvement in the treatment of many forms of the disease.

Clinical case study

'Ken nearly died one night in 1999. He awoke suddenly with terrible abdominal pain and went into shock... immediate abdominal surgery revealed a tumour attached to his small intestine. He had a form of cancer that would result in an utterly unmanageable situation'. His doctor 'started treating him with the drug and the tumours vanished' (1). That drug, Imatinib, has come to symbolise the fruits of genomics research in cancer treatment. Its first dramatic success was in the treatment of chronic myelogenous leukaemia (CML).

The pharmacogenomic basis

- Cancer is the result of genetic mutations which cause uncontrolled cell growth.
- Mutagenic agents may be microbial (e.g. papilloma virus in cervical cancer), chemical (e.g. tobacco smoke in lung cancer) or electromagnetic (e.g. ultraviolet radiation leading to skin carcinoma).
- With recent major advances in our understanding of the biology of cancer, a new generation of much more selective anti-cancer drugs have become available.
- Because these drugs target specific abnormal signalling pathways in tumour cells, they cause fewer and less severe adverse effects than older drugs.
- CML is a rare blood cancer caused by a reciprocal gene translocation involving chromosomes 9 and 22 in haematopoietic stem cells. This leads to constitutive expression of bcr-abl, a fusion gene which encodes a receptor tyrosine kinase (TK) protein called Bcr-Abl.
- Bcr-Abl is a cell proliferation signal and leads to tumour formation (see Figure 1).
- Imatinib blocks the ATP-binding site of the Bcr-Abl protein, blocking the TK signalling pathway and normalising the cell cycle.
- Subsequent work showed that Imatinib was also active against KIT, a different type of tyrosine kinase overexpressed in the type of cancer that Ken suffered.

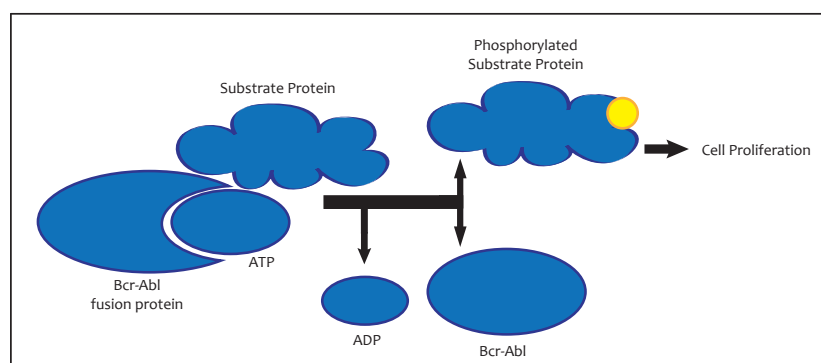


Fig. 1 Phosphorylation of Substrate Protein leading to Cell Proliferation

Further reading

(1) Nathan DG. (2007) The cancer treatment revolution. Hoboken: John Wiley and Sons, Inc.



Genotyping the invader and developing new vaccines

Clinical and policy perspectives

MRSA and H5N1 are codes that have developed street recognition as identifiers for particularly virulent bacteria and viruses. Such virulent strains emerge as a result of genetic mutations in the microorganisms concerned. Indeed each year new vaccines are developed to combat strains of the influenza virus prevalent at the time. The task of developing better defence strategies, including new vaccines, against the dangerous invaders is made easier through genotyping.

With functional studies informed by genotyping, likely features of potential microbial variants can be inferred, and preparatory preventive strategies developed. Such work is already underway with a view to protect us against new H5N1 flu variants with the ability to cause highly lethal pandemics due to their greater human infectivity. Genotyping can be considerably more rapid than conventional microbial culture methods (see Figure 1). Results of prospective microbial genotyping can also help to inform preventive strategies at the policy level.

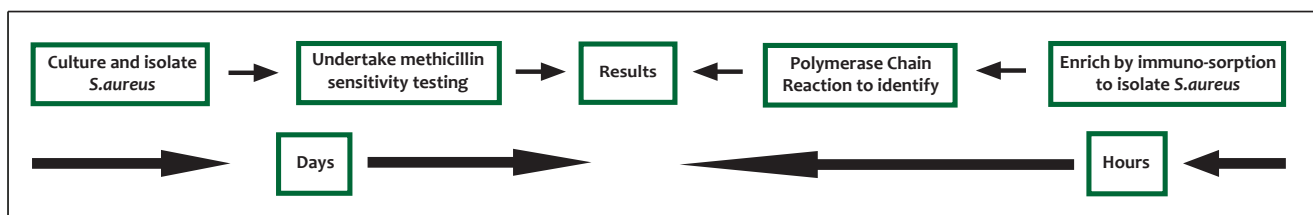


Fig. 1 Comparison of genotyping versus classical microbial culture for identifying antibiotic-resistant microorganisms

The genomic basis for new vaccines

- Genomic profiling (including proteomic profiling), is used to identify features (epitopes) which impart specific functional characteristics to the flu virus.
- The relevant gene sequences (coding for the traits) are genetically-engineered into the virus. The resulting viruses are evaluated for characteristics such as immunogenicity, lethality and infectivity.
- Genes associated with pathogenicity are “knocked out” (deleted or inactivated).
- The appropriate knock-out variants are formulated into vaccines and evaluated in animals, including non-human primates, and then after more extensive toxicology, in humans.
- One major problem is that since any new vaccine cannot be tested against a virus yet to be seen in the wild, its effectiveness cannot be validated.

Further reading

- (1) Itoh Y, Ozaki H, Tsuchiya H, et al. (2008) A vaccine prepared from a non-pathogenic H5N1 avian influenza virus strain confers protective immunity against highly pathogenic avian influenza virus infection in cynomolgus macaques. *Vaccine* 26(4):562-572.
- (2) Shi H, Liu XF, Zhang X, Chen S, Sun L, Lu J. (2007) Generation of an attenuated H5N1 avian influenza virus vaccine with all eight genes from avian viruses. *Vaccine* 25(42):7379-7384.
- (3) Harbarth S, Fankhauser C, Schrenzel J, et al. (2008) Universal screening for methicillin-resistant *Staphylococcus aureus* at hospital admission and nosocomial infection in surgical patients. *JAMA* 299(10):1149-1157.



Gene therapy: repairing or replacing defective genes

Many diseases are known to involve genetic mutations. Although most are due to complex interactions between the environment and multiple genes at several different loci, a significant number are caused by mutations in, or deficiency of, a single gene. Examples are phenylketonuria (PKU), cystic fibrosis (CF), and X-linked severe combined immunodeficiency (X-SCID). Replacement or repair of the defective gene, by gene therapy, should cure these monogenic diseases.

Clinical perspectives

Cystic fibrosis results from genetic mutations causing a transmembrane conductance regulator protein (CFTR) to be dysfunctional, and hence chloride ion transport across cells is impaired. Clinically, disturbance of lung function is seen due to altered rheology of lung fluids. This in turn leads to chronic *Pseudomonas aeruginosa* infection. Unless the defective gene can be repaired or replaced, treatment is essentially symptomatic, and prophylactic against the complications caused by pathogenic bacteria.

The genomic basis and the challenges

- Identification of the genetic defect and successful cloning of the normal gene opened up the possibility of gene therapy for this disease.
- The challenge was how to get a normal, functional gene inserted into the genome, or to get the defective gene repaired without disrupting other genes or creating new detrimental genes.
- The observation that viruses could integrate their genes within a host genome without apparent adverse effects led to their use as vectors for functional genes.
- Despite 20 years of effort to solve what was seen as an easy problem when the gene was identified in 1989, effective gene therapy of cystic fibrosis remains elusive (1).
- The major problems have been unacceptable immune response against viral vectors, and poor delivery of the gene into cells.
- The apparently “successful” gene therapy of X-SCID has been associated with serious adverse effects (2).

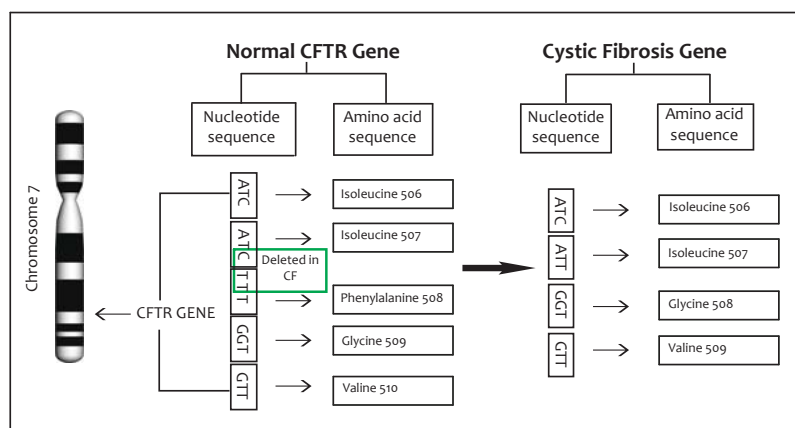


Fig. 1 Most common genetic mutation in cystic fibrosis

Further reading

- (1) Griesenbach U, Geddes DM, Alton EW. (2006) Gene therapy progress and prospects: cystic fibrosis. *Gene Therapy* 13(14):1061-1067.
- (2) Kaiser J. (2005) Gene Therapy: Panel Urges Limits on X-SCID Trials. *Science* 307(5715):1544-1545.



Genomics, stem cells and regenerative medicine

Clinical perspectives

For many diseases such as Alzheimer's disease, Parkinson's disease and myocardial infarction, the pathological process leads to cell death. Treatment therefore requires cell regeneration, and stem cell transplantation offers considerable promise for this. Genomic manipulation is at the core of the necessary technology.

The genomic basis

- One of the remaining puzzles of how a fertilised egg develops into an embryo, eventually producing many specialised tissues and organs, is slowly being unravelled.
- Initially pluripotent (i.e. able to differentiate into many types of cells), the fertilised cell becomes increasingly specialised as it divides to produce cells with specific functions. In doing so it loses its pluripotency.
- If we could find the triggers to make pluripotent cells develop into mature cardiac cells, nerve cells, or insulin-secreting cells; and better still, make mature cells regain their pluripotency and re-develop them back into specialised cells, then we would be able to regenerate lost tissues and organs, and replace defective genes. This is indeed what has been achieved in animals (1).

Regenerative medicine: demonstrating how it works in practice

In an exciting study, sickle cell anaemia, caused by a genetic mutation, was induced in a mouse and then corrected with stem cell therapy (1) as follows:

- Fibroblast cells with the defective gene were harvested from the mouse.
- A set of genes, which act in concert to induce pluripotency, were inserted into the fibroblasts by infecting them with genetically engineered viruses (reprogramming stage).
- The induced pluripotent cells were cultured to produce clones.
- The functional gene was injected into the clone cells, and replaced the defective gene via a process called homologous recombination (repair stage).
- The repaired clone cells were induced to differentiate into haematopoietic progenitor cells (differentiation stage).
- The mouse was irradiated to destroy the defective cells, and the repaired progenitor cells transplanted back into the mouse to correct the disease (transplantation stage).
- Unlike previous approaches which used harvested embryonic cells, this one used somatic cells, overcoming the ethical dilemma associated with using embryos.

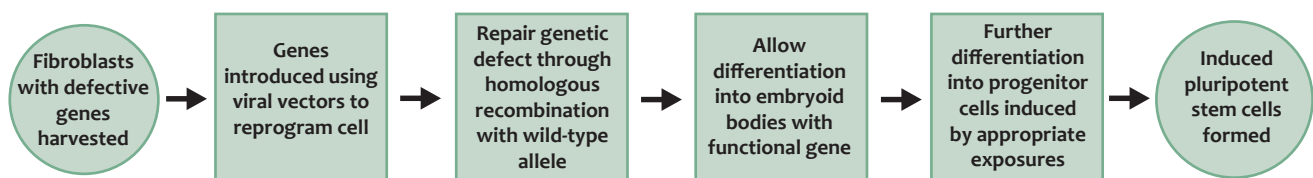


Fig. 1 Steps to regenerate diseased cells and organs

Further reading

(1) Hanna J, Wernig M, Markoulaki S, et al. (2007) Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin. *Science* 318(5858):1920-1923.



Gene expression signatures

Clinical perspectives

Many diseases are characterised by multiple genetic mutations. Cancer is the classical example with genomic instability (high susceptibility to genetic mutations) being a defining characteristic of cancer cells. Identifying the spectrum of mutations in a patient's cancer cell may provide a means for diagnosing the specific subtype of cancer involved, establishing its likely aggressiveness and its likely response to specific therapeutic interventions.

The enabling technology

- DNA microarrays provide the means to define the required gene signatures, through RNA expression profiling.
- Using a single microarray, the expression of many thousands of genes can be assessed simultaneously.
- The expression patterns are subjected to statistical analysis to identify genes that are overexpressed or underexpressed (e.g. in tumour cells compared to cells in normal tissues) and for identifying disease subtypes.
- Correlation analysis to identify association between disease subtype and drug response, or disease subtype and prognoses (e.g. metastasis in cancer and progression of Alzheimer's disease).

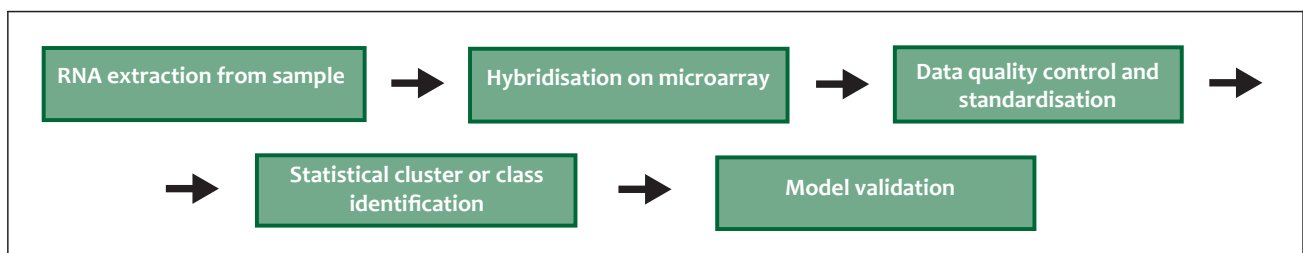


Fig. 1 Development of a gene signature

Practical applications

- **Translational medicine:** Clinically similar diseases (e.g. acute lymphoblastic leukaemia and acute myeloid leukaemia) may have very different underlying molecular mechanisms. Therefore being able to subtype such diseases objectively provides a means to identify the most appropriate molecular targets for therapy and indeed choose the most appropriate treatment regimen. Application of such insights is making drug development more rational and potentially less of a hit and miss endeavour than hitherto.
- **Prognostication:** Tumour cell gene expression signatures are being developed to predict which patients are more likely to develop relapses or metastasis, thereby providing important information for decision making about difficult, or potentially toxic, preventative strategies.
- **Pharmacogenetics:** Tumour cell gene expression signatures are being developed for predicting the most appropriate drug treatment.
- It is important to note however that considerable validation of a gene expression signature is needed before its clinical utility can be established, an aspect we will consider in a separate issue.

Further reading

(1) Golub et al. (1999) Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. *Science* 286(5439):531-7.



Pharmacogenetic Testing

Pharmacogenetic testing aims to identify patients who are more likely to respond, or to develop an adverse effect to a prescribed or self-administered drug.

Clinical case study

An epileptic patient, stable on the anti-epileptic drug carbamazepine, also receives the antacid omeprazole for severe gastro-oesophageal reflux. He has oesophageal candidiasis and an oral azole antifungal agent is thought appropriate. Which one would you recommend? (1)

The pharmacological and pharmacogenomic basis

- Ketoconazole is no longer recommended for acute candidiasis because of its potential hepatotoxicity. Both ketoconazole and itraconazole absorption are also interfered with by changes in gastric pH which would be expected with omeprazole.
- The azoles also show differential effects on the drug-metabolising enzymes CYP3A4, CYP2C9 and CYP2C19.
- Carbamazepine induces CYP3A4 and inhibits CYP2C19. Carbamazepine is also metabolised by CYP3A4, which is inhibited by various azole antifungals to varying extents (see Table).
- Omeprazole is metabolised by CYP2C19.
- Therefore genotyping should be useful for guiding therapy in this case.
- Carriers of HLA-B*1502 (an immune system gene variant) are at increased risk of Stevens-Johnson Syndrome, a potentially lethal adverse effect, when given carbamazepine.

Why is CYP450 genotyping not used in daily clinical practice?

- The magnitude of effects of any induction or inhibition of CYP450 enzymes is difficult to quantify in the presence of multiple interactions.
- In practice it is easier to avoid prescribing drugs, known to be metabolised by specific enzymes, when a potential interaction exists. For example, it might be more appropriate to avoid co-prescription of interacting drugs, or to monitor blood levels, rather than to rely on genotyping. Given that epilepsy is more difficult to control, a change of antacid agent is preferable.
- The same applies to the choice of azole antifungal. While dose-reduction may minimise the risk of adverse effects of drug-drug interactions, this needs to be counter-balanced against possible therapeutic failure.
- Even when a theoretically better choice of drug is made, close clinical monitoring is necessary. Therefore genotyping may not contribute much more for the additional costs and effort involved. In other words, the clinical utility and cost-effectiveness of genotyping are not compelling in this case.
- HLA-B*1502 is not an issue here as the patient is stabilised on carbamazepine.

| Azole antifungal | CYP3A4 | CYP2C9 | CYP2C19 |
|------------------|---------------------------------|-------------------------|-------------------------|
| Fluconazole | Weak inhibitor | Potent inhibitor | Potent inhibitor |
| Itraconazole | Substrate and inhibitor | | |
| Ketoconazole | Substrate and inhibitor | | |
| Voriconazole | Substrate (minor) and inhibitor | Substrate and inhibitor | Substrate and inhibitor |

Fig. 1 Table

Further reading

- (1) Baxter K, Marshall A. (2008) Drug interactions that can occur with azole antifungals. *Pharmaceutical Journal* 280:280.
- (2) Chung W-H, Hung S-I, Hong H-S et al. (2004) A marker of Stevens-Johnson syndrome. *Nature* 428:486.



Supporting pharmacogenetics education

The Centre supports pharmacogenetics education for health professionals by identifying and developing resources for pre-registration training and continuing professional development.

www.geneticseducation.nhs.uk/pgx

Our web pages provide free access to resources and information :



- **Clinical examples of current pharmacogenetics applications**
- **Resources: 'The Genomic Basis of Therapeutics Series'**
- **Reports:**
 - Implications for Pharmacy practice
 - Pharmacogenetics education report with the Royal Pharmaceutical Society of Great Britain
- **Reference section:**
 - Glossary
 - Key pharmacogenetics publications relevant to clinical practice and education
 - Links to pharmacogenetics e-learning and website
- **Regular updates**

The website is regularly updated by adding new resources and highlighting new publications and information.

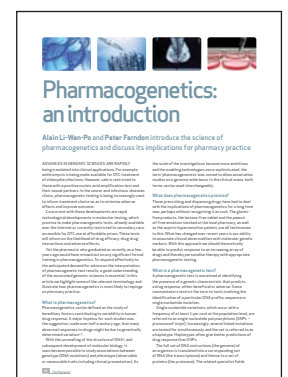
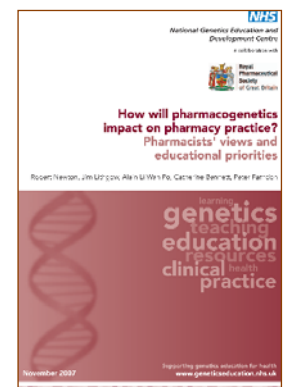
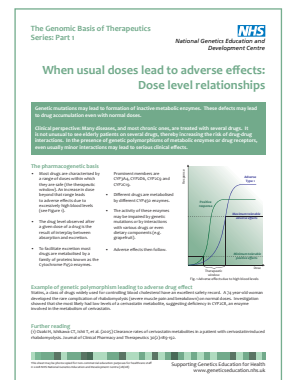
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The Centre works with UK and international groups to facilitate integration of appropriate genetics and family history information into education and training for all health professions, including medicine, nursing, pharmacy and dietetics. Our website contains searchable databases of resources and courses specific to the roles of those teaching genetics, or learning about genetics knowledge in practice.

The Centre would like to hear from any group or individual with suggestions on how to improve our website, or to comment on our report on pharmacogenetics in clinical practice, or on genetics education in general. Please contact:

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