REGULAR REVIEW

DNA repair disorders

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Over the past 30 years a number of rare DNA repair disorder phenotypes have been delineated, for example Bloom's syndrome, ataxia telangiectasia, and Fanconi's anaemia. In each phenotype it was hypothesised that the underlying defect was an inability to repair a particular type of DNA damage. For some of these disorders this hypothesis was supported by cytogenetics studies using DNA damaging agents, these tests defined the so-called chromosome breakage syndromes. A number of the aetiological genes have recently been cloned, confirming that some DNA repair disorder phenotypes can be caused by more than one gene and vice versa. This review deals only with the more common DNA repair disorders. Rarer entities, such as Rothmund-Thomson syndrome and dyskeratosis congenita, are excluded. Some useful addresses are given at the end of the paper.

DNA damage

DNA is continually subjected to both exogenous and endogenous mutagenesis. Cells have built up sophisticated mechanisms to minimise the effects of this. Mutations in actively transcribed genes are preferentially repaired and all DNA should be repaired before DNA replication when a mutation can become "fixed" and be transmitted to daughter cells.

Endogenous mutagenesis is the inevitable consequence of a large complex molecule present in a metabolically active environment, for example depurination (which occurs because of the reaction of DNA in water), the effect of oxygen and free radicals (causing base damage and DNA strand breaks), and errors caused by DNA replication (causing base mismatches and deletions). The scale of endogenous mutagenesis is considerable. Depurination has been estimated to occur at a rate of 10 000 bases per day per cell.¹ Other DNA hydrolysis reactions occur at a lesser rate, approximately 100-fold slower than depurination and reactive oxygen species cause more than 70 different chemical alterations to DNA. DNA replication has a very high fidelity, probably less than one mutation per cell copied.² However, occasional mistakes are made by the DNA polymerases miscopying bases (despite proof reading abilities) and also because the DNA polymerase complex skips areas of DNA in which there is a pre-existing mutation present. Such mutations are detected and repaired by specific postreplication repair mechanisms.

Exogenous DNA mutants have been classically divided into ultraviolet irradiation, ionising irradiation, and alkylating agents. Ultraviolet irradiation and alkylating agents can cause a number of specific base changes, as well as cross linking bases together. Ionising irradiation is thought to generate the majority of its mutational load by free radical production. A wide variety of other DNA damaging agents, both natural and man made, are known, many are used as chemotherapeutic agents.

DNA repair

The DNA double helix seems to have evolved so that mutations, even as small as individual base damage, are easily recognised. Such recognition is usually by a change to the physical structure of the DNA double helix. A number of different pathways are involved in DNA repair. Furthermore, these pathways are coordinated with other cellular functions, in particular gene transcription and the cell cycle.

DNA repair pathways can be classified into four groups: (1) specific base change repair mechanisms; (2) excision repair; (3) recombinational repair; and (4) postreplication repair. For many individual base mutations, specific glycosylases have evolved to detect and remove the damaged base. DNA polymerase and ligase repair the deletion caused by the removed base. The excision repair pathway has been intensively studied and, although complex, is capable of repairing a wide variety of types of DNA damage (see fig 1). Many of the proteins involved in excision repair have other functions.³ This pathway preferentially repairs actively transcribed genes, because of the transcription complex TFIIH. TFIIH is involved in initiating transcription but should transcription halt, TFIIH can recruit excision repair pathway proteins and when the repair is complete reconstitute the proteins required to continue transcription. The cell has recombination mechanisms and these are used in meiosis, mitosis, gene rearrangements, for example antibody production, and DNA repair. Recombination repair is vital where both DNA strands have been damaged, or there has been a double strand DNA break. This mechanism involves proteins which can detect free DNA strands (one such protein is DNA dependent protein kinase, the cause of autosomal recessive severe combined immune deficiency), and recombine the DNA strands and recruit the DNA polymerase/ligase complex, as in stage 1e of

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Figure 1 Excision repair is involved in repair of the majority of DNA mutations. Mutations in the XPA-G genes cause the various types of xeroderma pigmentosa, ERCC1 is a protein whose mutated gene causes the excision repair cross complementation group 1 cell line, RPA is replication protein A which binds to single stranded DNA and DNA polymerase synthesise a new DNA strand complementary to the template strand and DNA ligase links two deoxyribose sugars together with a phosphate group. (A) A site of a mutation in DNA is detected either by the DNA transcription complex "stalling" or by XPA and XPE detecting a conformational change in the DNA double helix. (B) The protein ERCC1 binds to XPA/XPE and recruits XPF which introduces a upstream (5') nick into the mutation bearing DNA strand (arrow). (C) XPB and XPD unwind the 5' end of the mutation bearing single stranded DNA. XPC and XPG introduces a downstream (3') nick into the mutation bearing DNA strand (arrow). (D) XPB and XPD unwind the 3' end of the mutation bearing single stranded DNA, allowing it to detach from its sister chromosome strand. RPA and other proteins stabilise and protect the resultant single stranded gap in DNA. (E) DNA polymerase E/D and other proteins repair the gap using the non-mutated sister DNA strand as a template. (F) DNA ligase links two ribose units together with a phosphate bond. (G) Methylation, other base modification, and tertiary structural changes then occur to yield repaired and functional double stranded DNA.

excision repair. Postreplication repair occurs immediately after DNA polymerase has produced a daughter strand. Before the newly synthesised daughter strand is methylated, any DNA mutations are detected and repaired. Germ line mutations in genes in this pathway cause the adult onset autosomal dominant predisposition to bowel cancer, known as hereditary non-polyposis colon cancer.⁴

Bloom's syndrome

This condition was first described by Bloom in 1954.⁵ In the past two decades, James German in New York, has been the major publisher of clinical and laboratory data.

The principal clinical features of this condition are prenatal and postnatal growth retardation, a thin triangular face and a telangiectatic rash in sun exposed areas, particularly on the cheeks (see fig 2A). Birth weight is typically <2500 g at term. Postnatal growth retardation results in an average adult height in males of approximately 151 cm and, in females, 144 cm. Because of the growth retardation, children may be investigated, often extensively, for causes of failure to thrive.⁶ Fertility is normal in females but probably all males are infertile. Intelligence is normal. The major complication of Bloom's syndrome is a substantially increased incidence of malignancies. The cancer

spectrum mirrors that seen in the normal population with leukaemia developing at an average age of 22 years and other solid tumours, particularly of the breast and gastrointestinal tract, by 35 years.⁷

While the diagnosis of Bloom's syndrome can be suspected clinically, the condition is probably not characteristic enough for cytogenetic/molecular genetic confirmation to be omitted. The clinical differential diagnosis includes Dubowitz's syndrome, Russell-Silver syndrome (including maternal chromosome 7 uniparental disomy), chromosome anomalies, fetal alcohol syndrome, and Rothmund-Thomson syndrome. In only Bloom's syndrome does cytogenetic analysis show a six to 10-fold increased rate of sister-chromatid exchanges (see fig 3A). The cytogenetic laboratory test for sister-chromatid exchange is simple to perform and reliable. Prenatal diagnosis has rarely been performed. Therefore, it should be carried out by a centre with previous experience and with a combination of techniques, that is sister-chromatid exchange rate and mutation detection or linked polymorphic markers.

Bloom's syndrome is an autosomal recessive disorder. The condition is extremely rare, anecdotally less than one case per million in the UK population. The exception is the

Ashkenazi Jewish population where the incidence is one in 10 000. The gene causing Bloom's syndrome has recently been cloned and is located on chromosome 15q21.3.⁸ The discovery was made by the exploitation of the increased rate of sister-chromatid exchange seen in Bloom's syndrome. Occasional cell lines were present in affected individuals, which appeared to be "cured". It was reasoned that this was because the patient had a different mutation in each of their two Bloom genes and that a sister-chromatid exchange had separated these, hence producing a "healed" gene and a gene with two mutations. Such a cell line would be expected to have no increase in sister-chromatid exchange, as this is the finding in parents of affected children who are obligate carriers. By analysis of such cell lines a 2 centimorgan region (approximately 2 million base

pairs of DNA) was delineated. A gene within this region proved to be the cause of Bloom's syndrome, and is a member of the RecQ helicase protein family, which are capable of unwinding DNA and RNA. Another gene in the same family of proteins is known to cause Werner's syndrome (a rare recessive disorder causing growth retardation with accelerated aging). Quite why growth retardation, increased sister-chromatid exchanges, and the increased predisposition to cancer occur in Bloom's syndrome, is not yet understood.

Ataxia telangiectasia (Louis-Bar syndrome)

This condition was initially reported by Madame Louis-Bar in 1941, but it was Boder and Sedgwick in the United States, who were responsible for bringing it to medical

Figure 2 Clinical features of DNA repair disorders. (A) Facial appearance of Bloom's syndrome. (B) Ocular telangiectasia in ataxia telangiectasia. (C) Radial ray anomaly and unilateral microphthalmia in Fanconi's anaemia. (D) Facial freckles in a 3 year old Asian child living in the UK with xeroderma pigmentosa. (E) Facial appearance of Cockayne's syndrome.

Figure 3 Cytogenetic features of DNA repair disorders. (A) Lymphocyte cytogenetic preparations labelled with BRdU showing a harlequin pattern, characteristic of an increased rate of sister-chromatid exchanges pathognomonic of Bloom's syndrome. (B) Cruciate exchange figures seen in a cytogenetic spread of an individual with Fanconi's anaemia.

attention.⁹ Since then significant work in the field has been performed by Richard Gatti in the United States and the team of Malcolm Taylor in Britain.

The principal clinical features of ataxia telangiectasia are a progressive complex neurodegeneration, bulbar telangiectasia (see fig 2B), variable immune deficiency, and an increased predisposition for lymphoreticular malignancies.¹⁰ The majority of children present within the first five years of life with motor delay. Eye movements are usually abnormal by the age of 3 years and involve a dyspraxia of rapid saccadic eye movements, both in the vertical and horizontal fields of vision. (A very similar eye movement disorder is seen in Cogan's ocular motor apraxia, but with only horizontal saccades involved.) Approximately a quarter of patients have clinically significant immunodeficiency.

Clinical diagnosis of ataxia telangiectasia can be difficult to make in the first five years of life. The diagnostic laboratory test is a six to 10-fold increased level of chromosome breakage, after ionising irradiation. There is also an increased incidence of spontaneous chromosome breakage and specific translocations involving the T cell receptor genes on chromosomes 7 and 14. These findings are not pathognomonic and are almost identical to those seen in the much rarer Nijmegen breakage syndrome (autosomal recessive borderline microcephaly, moderate to severe immune deficiency, increased incidence of lymphoreticular malignancies). Therefore,

the diagnosis of ataxia telangiectasia should be made by a combination of clinical and laboratory investigations. While α -fetoprotein is often raised in the condition and immunoglobulins IgA, IgG and, particularly, IgG₂ and IgG₄ subgroups can be deficient, these findings are not as sensitive as cytogenetic studies and certainly not as specific.

Prenatal diagnosis is available, but should only be carried out in centres with a specialist interest and previous experience. Chromosome breakage analysis at amniocentesis is reliable. Doubt remains for chorionic villus sampling; I know of one case where a false negative result was obtained. A further proviso is that prenatal diagnosis should not be performed without the radiosensitivity of the index case in the family being tested by the laboratory that will carry out the prenatal diagnosis. With the discovery of the ATM (ataxia telangiectasia mutated) gene, mutation and linkage analysis on chorionic villus sampling tissue will probably become the prenatal diagnosis method of choice in the foreseeable future.

Ataxia telangiectasia is a single gene autosomal recessive disorder. Initial cell line fusing experiments had suggested that there would be at least four genes that could cause ataxia telangiectasia. However, this proved erroneous. Linkage in ataxia telangiectasia was initially found in a Pennsylvanian Amish family by Gatti *et al* on chromosome 11q23.¹¹ Subsequent work by groups in the UK, United States, and Israel refined the position of the gene and, eventually, found an extremely large hitherto unknown gene, which was called ATM.¹² The gene seems homologous to a group of phosphatidylinositol-3 kinases involved in signal transduction, meiotic recombination and cell cycle controls. Mutations in the ATM gene have been found in all of the four apparent groups of ataxia telangiectasia. The inferred function of the gene is in the coordination of DNA damage repair.

Approximately 10% of individuals with ataxia telangiectasia have a later onset and slower disease progression of the condition; this is known as variant ataxia telangiectasia.¹³ Such individuals exhibit less sensitivity to ionising irradiation and they may be less cancer prone. In some cases the sensitivity to ionising irradiation can only be shown in fibroblasts; lymphocyte testing is normal. The majority of variant ataxia telangiectasia is caused by ATM gene mutations. However, one Asian family has been described with variant ataxia telangiectasia not linked to the ATM gene.

A comment needs to be made about the reported increased risk of cancer of ATM gene mutation carriers (ataxia telangiectasia heterozygotes, that is parents and two thirds of the siblings of affected children). Epidemiological studies had suggested that female heterozygotes had an increased risk of developing breast cancer. Furthermore, it was suggested that mammography may be deleterious in this population because of increased radiosensitivity. This is a vexed field but recent reanalysis of the British data has not shown the significant increased risk of breast cancer in known ataxia

telangiectasia heterozygotes, with a relative risk of approximately two contrasting with the earlier American figure of six. Furthermore, ataxia telangiectasia heterozygotes have not been shown to have an adversely clinical respond to irradiation and only subtle experiments can show an increased ionising irradiation sensitivity in them as a group. The Department of Health has advised that female ataxia telangiectasia heterozygotes under the age of 50 should only have mammography symptomatically. They should enter the National Breast Screening Programme at 50 and should avoid inessential radiography.

Fanconi's anaemia

The condition was first described by Fanconi in 1927 in three siblings, who developed pancytopenia.¹⁴ Further work by Schroeder-Kurth and, more latterly, Auerbach, has helped to define the other features of the disease. The Estren-Dameshek syndrome of autosomal recessive congenital pancytopenia is part of the Fanconi's anaemia spectrum.

The three cardinal features of Fanconi's anaemia are chromosome breakage, pancytopenia, and congenital anomalies. While the chromosome breakage and probably the pancytopenia are universal features of Fanconi's anaemia, congenital abnormalities and dysmorphic features and growth retardation are not. This has led to difficulties, both in recognising cases where there are no or few congenital malformations before the onset of pancytopenia and, conversely, failure to recognise that some children with multiple severe congenital malformations actually have Fanconi's anaemia.¹⁵ Furthermore, with regard to the congenital anomalies, not only is there an interfamilial variability, there is also an intrafamilial variability. Three useful features which help distinguish Fanconi's anaemia from other conditions with a similar phenotype are growth retardation, radial ray anomalies, and (usually unilateral) microphthalmia (see fig 2C). There is an increased incidence of acute non-lymphoblastic leukaemia with a mean age of diagnosis at 15 years in individuals who have not received a bone marrow transplantation.¹⁶

The laboratory diagnosis is made by finding an increased incidence of chromosome breakage induced by alkylating agents, such as nitrogen mustards, mitomycin C, and diepoxybutane. An increased incidence of spontaneous chromosome breakage is seen, as are unusual cruciate exchange figures between non-homologous chromosomes (see fig 3B). False negative results have been described in Fanconi's anaemia as have false positive results in some other rare syndromes.¹⁷ If there are any doubts about the cytogenetic diagnosis a repeat sample or testing of another tissue, such as skin, or use of a different alkylating agent, is mandatory.

Prenatal diagnosis is possible, but should only be performed after confirming that the index case is sensitive to the alkylating agent to be used and probably with or by a centre with previous experience (C Mathew, listed in

addresses). Auerbach *et al* have reported a large series using diepoxybutane.¹⁸

There is good evidence for five separate Fanconi's anaemia genes, named groups A to E. Two genes have been cloned, the first was the Fanconi group C gene on chromosome 9q22.3.¹⁹ Preliminary mutation analysis suggests that this gene accounts for 10% of cases. An apparently homologous gene has been found in mice. The second gene causes Fanconi group A and accounts for about two thirds of cases.²⁰ Studies are currently under way to determine how the Fanconi's anaemia A and C gene mutations cause the disease phenotype. At present there seems no clinical differences between the Fanconi's anaemia genotypes.

Xeroderma pigmentosa, Cockayne's syndrome, and trichothiodystrophy

These three conditions are discussed together because of clinical similarities and that they are caused by mutations of excision repair pathway genes. In 1968 Cleaver showed that xeroderma pigmentosa could be caused by a defect in repair of ultraviolet damaged DNA.²¹ His team has since carried out much of the fundamental work into this group of disorders, other important research teams have been that of Lehmann and Arlett in Brighton and Jaspers in the Netherlands.

The predominant feature of xeroderma pigmentosa is a much increased sensitivity to ultraviolet light, present in sunlight.²² The skin is normal at birth but develops progressive atrophy, irregular pigmentation (for example freckles at abnormally young ages; see fig 2D), telangiectasia and, later, keratoses, basal cell and squamous cell carcinomas. Tumours occur by 3 or 4 years of age and most patients die of malignancy in the second and third decade; such is the sun sensitivity that tumours of the tongue can occur. Other malignancies do not occur more often than expected.

A subgroup of individuals with xeroderma pigmentosa develop the de Sanctis-Cacchione variant,²³ with progressive microcephaly, mental retardation, cerebellar ataxia, areflexia, growth retardation leading to dwarfism, and hypogonadism (a considerable phenotypic overlap with Cockayne's syndrome).

The major clinical features of Cockayne's syndrome are progressive leukodystrophy, progressive microcephaly, and progressive growth retardation. The majority of patients present between the ages of 3 and 5, often with sensorineural deafness, initially masquerading as mild developmental delay, but later including developmental delay. Usually at this time growth deficiency, particularly with loss of adipose tissue, is becoming apparent, as is a characteristic facial appearance with sunken eyes (see fig 2E). Other clinical features have been recently reviewed.²⁴ Rare cases presenting in the neonatal period (sometimes called COFS syndrome) and also with later onset and slow progression have been described.

Trichothiodystrophy is an extremely rare disorder and is characterised by brittle hair,

ichthyosis, short stature and sometimes a distinctive facial appearance, microcephaly, mental retardation, and sun sensitivity. The natural history of the disorder has not been well documented but there does not appear to be an excess of skin or other malignancies.

The diagnosis of the three conditions, xeroderma pigmentosa, Cockayne's syndrome, and trichothiodystrophy, is made by the characteristic clinical features. The definitive laboratory investigations for all genotypes of xeroderma pigmentosa is the fibroblast survival after ultraviolet irradiation. This investigation is not routinely available in cytogenetic laboratories but may be performed, after discussion with Lehmann, Cleaver, or Jaspers. Lymphocyte cytogenetic studies are normal.

Cockayne's syndrome can usually be diagnosed by clinical findings backed up by abnormal investigation results, particularly basal ganglia intracranial calcification, best detected by magnetic resonance imaging. Gene mutation and cellular defect tests for Cockayne's syndrome, as outlined below, are only available via research laboratories. The diagnosis of trichothiodystrophy is, again, suggested by the clinical phenotype, although other disorders which involve mental retardation and brittle hair, such as argininosuccinicaciduria, Menkes' syndrome, and citrullinaemia need to be considered. The specific test for trichothiodystrophy may be available via Lehmann. Some cases of Pollitt's syndrome (also known as TAY, IBIDS, BIDS) who have brittle hair with low sulphur content and trichorrhexis nodosa, short stature, and mental retardation plus or minus ichthyosis and sun sensitivity have trichothiodystrophy.

All three conditions are rare, have autosomal recessive inheritance, and are found in all racial groups, xeroderma pigmentosa being more common than Cockayne's syndrome and the very rare trichothiodystrophy. The primary defects in this group of disorders involve components of the excision repair pathway, as outlined in the section on DNA repair mechanisms. The diagnosis of an excision repair defect can usually be made by measure of "unscheduled DNA synthesis". This step of nucleotide excision repair (shown in fig 1E) can be assayed by the use of tritiated thymidine in place of normal thymidine in growth media of the test cells. The amount of radioactive thymidine incorporated into the DNA is a measure of the amount of nucleotide excision repair that has been performed.

The majority of the eight genes causing different xeroderma pigmentosa groups "A" to "G" and "variant", have been located and most cloned.²⁵ They are all highly homologous, either in terms of DNA sequence or function to the equivalent genes in mice, bacteria, and yeast. Cockayne's syndrome cells are hypersensitive to ultraviolet C light, though not as marked as in excision repair deficiency of xeroderma pigmentosa cells. The specific defect is in the preferential repair of mutations in transcribed genes, rather than in general excision repair. The diagnostic findings are failure of recovery of RNA synthesis, after

Key messages

- DNA repair disorders are caused by genes involved in DNA mutation detection, repair, or repair coordination. Many of the genes have other cellular functions, possibly explaining the diverse phenotypes seen in this group of disorders
- The disorders are individually rare and suspected diagnoses should always confirmed by laboratory tests (which are reliable even before the full phenotype has evolved)
- The disorders are autosomal recessive: prenatal diagnosis is available for most but may need to be arranged with specialist centres, before pregnancy
- Many of the disorders are cancer prone but, as the individuals can be hypersensitive to chemotherapy and radiotherapy, treatment of any cancer that develops can be problematic

ultraviolet irradiation but normal excision strand repair. Two genes can cause Cockayne's syndrome, have been cloned, and are involved in the coupling of transcription and repair. Mutations in some individuals with trichothiodystrophy have been found in the XPD/ERCC2 gene. This gene is a helicase and part of the transcription factor complex TFIIH. This complex is both involved in transcription and the recruitment of the excision repair pathway. It seems that mutations in the XPD gene either affect the excision repair pathway recruitment giving rise to xeroderma pigmentosa type D, or DNA transcription giving rise to trichothiodystrophy.

Conclusion

The DNA repair disorders are clinically diverse. Most cause growth retardation and a predisposition to malignancy, some cause neurodegeneration and congenital anomalies. Some disorder phenotypes may be caused by mutations in more than one gene. Also different mutations in some genes can cause more than one disease phenotype. The majority of the genes causing DNA repair disorders have recently been cloned. As these genes commonly have DNA repair as well as other cellular functions and are components of complex multistep pathways this goes some way to explain the confusing number of genotypes and phenotypes. Work is now in progress to determine how each gene causes a particular phenotype and what role they may have in human development and disease.

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Useful addresses

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