

Introduction

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Adoption

Adoption is the legal transfer of parental responsibility from the birth family to a new adoptive family. In the UK the Adoption Act 1976 states that to be eligible for adoption the child must be under the age of 18 years and there must be no possibility of continuing in the care of his/her birth parents. Should the child be married or have been married he cannot be adopted. In the UK, an Adoption Order severs all legal ties with the birth family and confers parental rights and responsibilities on the new adoptive family. The birth parents no longer have any legal rights over the child and they are not entitled to claim him/her back. The child becomes a full member of the adoptive family; he/she takes the surname and assumes the same rights and privileges as if he/she had been born to her adoptive parents, including the right of inheritance.

Adoption continues to provide an important service for children, offering a positive and beneficial outcome. Research shows that, generally, adopted children make very good progress through their childhood and into adulthood and do considerably better than children who have remained in the care system throughout most of their childhood (Department of Health, UK).

Fostering is an agreement to offer a temporary home to children whose parents are unable to care for them. It is usually organized by social workers working for local authorities. The authority pays for the children's accommodation and food.

Adoption agency. This is the organization that has arranged the adoption and has had contact with the birth and adoptive parents. The agency may be a state-run organization, a charity, or a profit-making company. The agencies have a statutory obligation to keep records of the adoption process.

Confidentiality. In the UK when an adopted individual reaches the age of 18 he/she can request the original birth certificate that will contain the mother's name and address at the time of the birth. A birth parent is not able to obtain details of the child's new family and name, though some contact between the birth and adoptive parents is more common now.

Genetic issues relating to adoption

(1) Genetic information given to adoptive parents

Family history

The birth parents are asked to give information about medical problems in the family. Often there is no contact with the father and this limits the information that can be given.

In the USA, the American Society of Human Genetics (1991) endorsed a statement concerning the importance of including a genetic history as part of the adoption process. Their recommendations are as follows and were written to encourage state and private agencies to collect helpful genetic histories.

- Every person should have the right to gain access to his or her medical record, including genetic data that may reside therein.
- A child entering foster care or the adoption process is at risk of losing access to relevant genetic facts about himself or herself.
- The compilation of an appropriate genetic history and the inclusion of genetic data in the adoptee's medical files should be a routine part of the adoption process.

- Genetic information should be obtained, organized, and stored in a manner that permits review, including periodic updating, by appropriate individuals.
- When medically appropriate, genetic data may be shared among the adoptive parents, biological parents, and adoptees. This should be done with the utmost respect for the right to privacy of the parties. The sharing of information should be bidirectional between the adoptive and biological parents until the child reaches an appropriate age to receive such information himself or herself.
- The right to privacy includes the right of any party to refuse to enter into or cease to participate in the process of gathering genetic information.

Known genetic disease prior to adoption

When there is a known genetic condition in the family (e.g. single gene or chromosomal disorder) the question of whether to test a healthy child for the condition may arise prior to adoption. 'It should not be assumed that genetic (predictive or carrier) testing will be required before a suitable placement can be achieved. In each case, we would advise discussion between the medical adviser to the adoption agency and a clinical geneticist. The important factors other than the possible laboratory test results need to be identified for future attention in advance of any test being performed' (Clinical Genetics Society 1994). See below (4) for a further discussion of issues relating to genetic testing and adoption.

(2) Genetic disorder diagnosed in child after adoption

The geneticist may be involved in the diagnosis of a genetic condition in an adopted individual that may be of importance to his/her birth family.

Some adopted adults are in contact with their birth families but in most the route to passing on this information is through the adoption agency. The geneticist may write a brief letter stating the name of the condition that has been diagnosed in the adopted child and that this is a condition that could have genetic implications for the biological family and recommending referral to their local genetic service. The medical advisor to the agency can assess the information and it may be feasible for them then to contact the birth family. Records made many years ago are less complete and for individuals >18 years these may not be adequate to enable contact to be made with the birth family.

(3) Genetic disorder diagnosed in birth family after a child has been adopted out

The geneticist may be involved in the diagnosis of a genetic condition or carrier status in the biological parent of a child who has been adopted out of the family. In most situations the route to passing on this information is through the adoption agency. The geneticist may write a brief letter stating the name of the condition that has been diagnosed in the biological family and that it could have genetic implications for the adopted child and recommending referral to their local genetic service. The medical adviser to the agency can assess the information and, for those who are still <18 years of age, should have the information to contact the parents of the adopted child. Records made many years ago are less complete and it may be more difficult to trace an individual, adopted as a child, who is now an adult.

(4) Genetic testing

When a child is being considered for adoption the guidelines for genetic testing should be followed as for other children. The American Society of Human Genetics (ASHG) and the American College of Medical Genetics (ACMG) recommend the following.

- All genetic testing of newborns and children in the adoption process should be consistent with the tests performed on all children of a similar age for the purposes of diagnosis or of identifying appropriate prevention strategies.
- Because the primary justification for genetic testing of any child is a timely medical benefit to the child, genetic testing of newborns and children in the adoption process should be limited to testing for conditions that manifest themselves during childhood or for which preventive measures or therapies may be undertaken during childhood.
- In the adoption process, it is not appropriate to test newborns and children for the purpose of detecting genetic variations of or predispositions to physical, mental, or behavioural traits within the normal range.

(Some dissent from this consensus view and argue that special ethical considerations arise in the pre-adoption context (Jansen and Ross 2001).)

Support group: Adoption UK <www.adoption.org.uk>.

Expert adviser: Angus Clarke, Professor in Clinical Genetics, University of Wales College of Medicine, Cardiff, Wales.

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Approach to the consultation with a child with dysmorphism, congenital malformation, or developmental delay

Terminology

Dysmorphology is the recognition and study of birth defects and syndromes. The term was first used by David Smith from the USA in the 1960s to describe the study of human congenital malformations and patterns of birth defects.

Malformation is a morphological abnormality that arises because of an abnormal developmental process (a primary error in morphogenesis, e.g. cleft lip).

Syndrome is a particular set of developmental anomalies occurring together in a recognizable and consistent pattern (from the Greek 'running together') and known or assumed to be the result of a single aetiology.

Sequence is a pattern of developmental anomalies consequent upon a primary defect, often with heterogeneous aetiology, e.g. the oligohydramnios sequence in which renal aplasia leads to lack of fetal urine production leading to deformation (micrognathia and talipes) and pulmonary hypoplasia. Robin sequence describes the combination of micrognathia, a wide U-shaped cleft palate and upper airway obstruction, with the cleft palate and airway compromise consequent upon failure of normal mandibular growth in the 8th–11th weeks of embryonic development.

Association is a non-random collection of developmental anomalies not known to represent a sequence or syndrome that are seen together more frequently than would be expected by chance e.g. VACTERL (vertebral defects–anal atresia–cardiac anomalies–tracheo-oesophageal fistula–(o)esophageal atresia–renal anomalies–limb defects) associations.

Dysplasia is abnormal cellular organization within a tissue resulting in structural changes, e.g. within cartilage and bone in skeletal dysplasias.

Congenital anomalies

Approximately 2–3% of singleton neonates have an obvious major congenital anomaly. However, with follow-up this rate doubles. Results of several studies suggest that there is a 2–3-fold increase of congenital anomalies in monozygotic (MZ) twins, i.e. ~10% of MZ twins are born with a congenital anomaly. Congenital anomalies (birth defects) may arise due to a number of mechanisms:

- 1 localized errors** in morphogenesis, e.g. cleft lip/palate;
- 2 deformation**, i.e. distortion by physical force of normally programmed structures, e.g. oligohydramnios sequence;
- 3 disruption**, i.e. destruction of normally programmed structures, e.g. limb defects caused by amniotic bands;
- 4 teratogenic exposure** disturbing normally programmed morphogenesis, e.g. fetal alcohol syndrome, fetal anticonvulsant syndrome, diabetic embryopathy;
- 5 germline genetic alterations affecting morphogenesis**, i.e. abnormal programming of development (Donnai and Read 2003). This may result in:
 - failure of structural integrity—qualitative or quantitative defects of structural molecules, e.g. mutations in *COL2A1* in Stickler syndrome;

- failure to regulate cell numbers appropriately—e.g. mutations in *MCPH5* (*ASPM*) causing primary autosomal recessive (AR) microcephaly;
- failure of cell migration such that cells do not reach their correct location, e.g. mutations in *MID1* in Opitz syndrome;
- failure of a developmental switch—many developmental defects result from deficiencies in transcription factors or cell–cell signalling systems.

Very many genes may be involved, e.g. chromosomal aneuploidy, or a number of genes, e.g. chromosomal microdeletion disorders such as Williams syndrome, or a single gene. Some single gene mutations have devastating consequences for development, e.g. Lys650Glu mutations in *FGFR3* cause the perinatal lethal condition thanatophoric dysplasia type 2.

The term 'dysmorphic' is used to describe children whose physical features are not usually found in a child of the same age or ethnic background. Some features are abnormal in all circumstances, e.g. premature fusion of the cranial sutures, whereas other features may be a non-significant familial trait, e.g. 2/3 toe syndactyly. The recognition of which features are good diagnostic aids comes with experience, but most trainees will be able to come to a differential diagnosis, if not the exact diagnosis, by pursuing a plan such as we outline here.

Although 'dysmorphic' is generally used to refer to visible malformations or distinctive features, the term more correctly means the presence of an abnormality of structure. Internal organs may therefore be affected by the same mechanism as the visible malformations. Knowledge of normal fetal development is necessary to an understanding of dysmorphology.

Background

The clinical geneticist is asked to see children for the following reasons:

- 1** to give a diagnostic opinion;
- 2** to help understand the aetiology;
- 3** to discuss the genetic aspects of the condition;
- 4** to advise if there are other investigations pertinent to the diagnosis;
- 5** to advise about the prognosis and suggest various therapeutic options;
- 6** to discuss the risk of recurrence in another pregnancy;
- 7** to discuss if prenatal testing is available.

This chapter will deal primarily with the diagnostic aspects of the consultation and the gathering of clinical information necessary to answer the other questions.

The consultation

A consultation starts with a *referral* or a request for a *ward visit*. Use the information you have been given. Determine what questions are being asked by the referee. Ask for the hospital notes and X-rays. A call to the paediatrician, or indeed the family, may help your pre-clinic work-up.

A child will usually attend with his parents, but ask, do not assume this, during introductions to save embarrassment later. Parents can give you the child's history and family history and also you are able to observe, and later ask,

if they have features in common with their child. Family photographs may be helpful.

Structure of the consultation

This is dependent on the circumstances, place, and age of the child. Even if you recognize the diagnosis at first sight, hold back. Build up a rapport with the family and check that the history and examination support your diagnosis. Below is a suggested approach.

- 1 Introductions.** Explain why you have been asked to see the child. Ask the parents about their main concerns and what they would like you to help with.
- 2 Observation.** Watch the child during the consultation. Try to involve him/her in the history and take note of spontaneous language and interaction between the child and adults, as well as looking at the face.
- 3 History**
 - **Family history.** Draw the family tree, usually extending over three generations, but extend further if there are known affected individuals in one branch of the family. Photographs of family members may be helpful.
 - **Pregnancy history.** Bleeding, fever, medication, investigations, alcohol/non-prescription drugs (ask with tact), fetal movements, liquor volume, gestation, mode of delivery.
 - **Neonatal history.** Birthweight, length, head circumference. Resuscitation, feeding difficulties, ventilation, malformations, surgery, seizures, other medical problems?
 - **Developmental milestones and current schooling provision** (e.g. mainstream school with 1:1 learning support assistant (LSA), special needs nursery). If developmentally delayed ask about agencies involved, e.g. physical therapist.
 - **Photographs** of the child at various ages may be helpful, especially if assessing an older child/adult.
 - **Behavioural phenotype.**
 - **Vision, hearing, seizures.**
 - **Other questions.** Any other questions that may be of relevance.
- 4 Physical examination** including clinical photographs (face, profile of face, hands, and any unusual features). A photograph of the child with his/her parents is helpful in assessing any familial contribution to facial dysmorphism). See 'Dysmorphism examination checklist' in the Appendix, page 670.
- 5 Further investigations.**
- 6 Conclusions.** Assessment of genetic risk and counselling.
- 7 Correspondence.**
- 8 Follow-up.**

Normal variation

Without a thorough knowledge of normal pregnancy, delivery, developmental milestones, and usual infant/child behaviour you may miss many important diagnostic clues in the history. It is of equal importance to the physical examination in establishing the diagnosis.

Examination

In the examination, the key to good practice is meticulous and accurate observation, measurement, and documentation of your findings (*photography* is extremely helpful

in providing an accurate record of unusual features). Syndrome features alter with age and the geneticist tries to overcome this problem by noting serial measurements, e.g. of head circumference, and by asking the parents to bring photographs of the child at different ages. A natural history of the condition can then be seen. Trainees may find it helpful to use an examination checklist, such as the one on page 670. The descriptive terms used may seem like a completely new language. The Glossary on page xvii describes these, but if in doubt use everyday words or draw a simple sketch in the notes.

Diagnostic 'handles'

Some features are more likely to be of diagnostic help. These are sometimes called good 'handles' and these are not found as normal or familial traits or variations but are only present in a small number of conditions. A poor handle may occur as a normal variant or be found in a large number of syndromes. Diagnostic databases assist you most when a child has one or more of these distinctive features.

Making a diagnosis

It takes several years to develop the confidence to come to a diagnosis and several more to know when you won't! Many senior colleagues talk about 'gestalt' diagnoses. Such a diagnosis is made on the basis of recognition of previously having seen the condition. Many syndromes have characteristic facial movements, e.g. Down syndrome. The trainee should be assisted by a senior colleague for the diagnostic conclusions and counselling, having first presented the history and demonstrated the physical signs. Further investigations are often necessary to establish a diagnosis. You will find these listed in the chapters of the book that refer to specific features, e.g. 'Short limbs' in Chapter 6, 'Pregnancy and fertility'.

Making an accurate diagnosis is central to the practice of clinical genetics. With a diagnosis, the genetic advice is usually accurate, the prognosis and natural history can be discussed, surveillance can be targeted appropriately, prenatal diagnosis may be possible, and the family can be given details of support groups and are empowered to access further information. Although it is satisfying to make a diagnosis, time spent ensuring that the diagnosis is correct and establishing a rapport with the parents and making an assessment of their state of readiness to receive a diagnosis will be valuable when you come to give this news to the family.

Expert adviser: Judith G. Hall, Professor of Pediatrics and Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada.

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Autosomal dominant (AD) inheritance

AD disorders are encoded on the autosomes and the disorder manifests in heterozygotes, i.e. when a single copy of the mutant allele is present. AD disorders are characterized by inter- and intrafamilial variability. Factors influencing this variability may include modifier genes, environmental exposure, and stochastic effects.

Some AD disorders such as retinoblastoma and von Hippel–Lindau (VHL) disease are recessive at the cellular level. The mutation confers increased susceptibility to tumours because of a heritable germline mutation in one allele, but cell behaviour appears normal in the heterozygous state. Tumorigenesis requires inactivation of the second allele ('second-hit').

Aspects of AD inheritance

Penetrance is the percentage of individuals expressing the disorder to any degree, from the most trivial to the most severe. Many dominant disorders show *age-dependent penetrance*, e.g. hereditary motor and sensory neuropathies (HMSN), hereditary spastic paresis (HSP), Huntington disease (HD). Features of the condition are not present at birth, but become evident over time. Some conditions show *incomplete penetrance*, i.e. not all mutation carriers will manifest the disorder during a natural lifespan, e.g. hereditary nonpolyposis colorectal cancer (HNPCC).

Expressivity is the variation in the severity of a disorder in individuals who have inherited the same disease alleles. Many AD conditions show quite striking variation in severity between families (interfamilial variation) and also within families carrying the same mutation (intrafamilial variation). A mildly affected parent can have a severely affected child and vice versa. For example, in tuberous sclerosis a parent with minimal cutaneous signs may have a child who develops infantile spasms and severe developmental delay.

Somatic mosaicism. A new mutation arising at an early stage in embryogenesis can give rise to a partial phenotype, often present in a dermatomal distribution, e.g. segmental neurofibromatosis type 1 (NF1). If the mutation is also present in the germline (*germline mosaicism*) it can be transmitted to future generations.

Germline mosaicism (gonadal mosaicism). A new mutation arising during oogenesis or spermatogenesis may cause no phenotype in the parent unless the somatic cells are involved as well (gonosomal mosaicism), but can be transmitted to the offspring. If a population of germ cells harbours the mutation there may be a significant recurrence risk, e.g. osteogenesis imperfecta types IIA and IIB.

Reproductive fitness. Some AD disorders, e.g. lissencephaly due to a *LIS1* mutation, have a reproductive fitness of zero, i.e. mutation carriers do not reproduce. Such a condition is maintained in the population entirely by new mutation. Many other AD disorders have only modest effects on reproductive fitness.

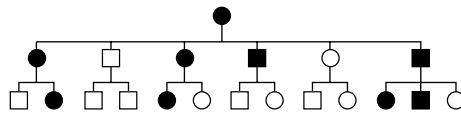
New mutation rate. The *de novo* mutation rate varies considerably between different AD conditions. It is high in NF1 with as many as 50% of cases representing new mutations; for other conditions, e.g. HD, new mutation is unusual.

Paternal age effect. For some AD disorders the chance of a new mutation increases with advancing paternal age. In Apert syndrome this observation is explained by germ cell selection for the pathogenic *FGFR2* mutation (Goriely *et al.* 2003).

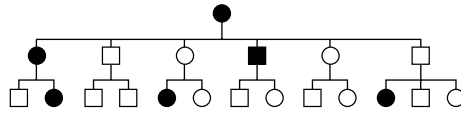
Anticipation is worsening of disease severity in successive generations. This is a feature of a few AD conditions and characteristically occurs in triplet repeat disorders where there is expansion of the triplet repeat in the maternal or paternal germline, e.g. myotonic dystrophy (maternal), HD (paternal). In addition to variable expressivity the mutation itself is unstably transmitted and varies in size between different generations (dynamic mutation).

Typical family tree

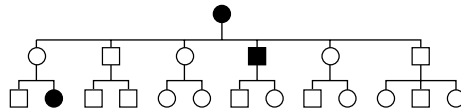
Autosomal dominant inheritance



A typical family tree showing autosomal dominant inheritance. An affected parent has a 50% risk of transmitting the condition to each child whether they are male or female.



The same family tree showing AD inheritance with incomplete penetrance. In this example the penetrance is reduced from 100% to 67%.

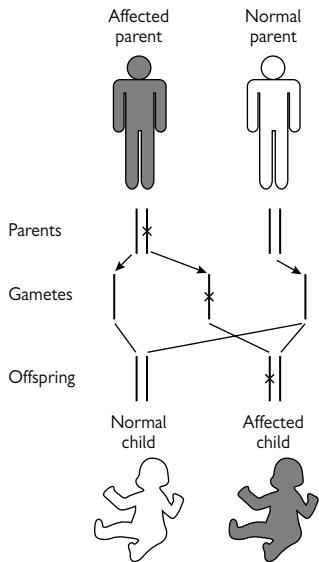


In this example the family tree still shows AD inheritance, but with the penetrance reduced to 33%. The family tree then begins to look suggestive of a disorder following multifactorial inheritance (see 'Multifactorial inheritance', this chapter for further discussion).

Some conditions show incomplete and age-dependent penetrance and these factors can make it difficult to give accurate genetic advice where the familial mutation is unknown.

Genetic advice

- Males and females are affected equally.
- Males and females can both transmit the disorder.
- There is a 50% risk to offspring in any pregnancy that they will inherit the mutation. (NB. Depending on penetrance and expressivity the risk of becoming symptomatic may be less than this.)
- The severity of the disorder in the offspring may vary, being similar, more severe, or less severe than in the parent.
- Examine parents very carefully before concluding that they are unaffected. For disorders with incomplete penetrance, apparently unaffected individuals will still be at some risk of transmitting the disorder (see above).

Autosomal dominant inheritance

Expert adviser: Ian D. Young, Consultant Clinical Geneticist, Leicester, England.

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Autosomal recessive (AR) inheritance

See 'Carrier frequency and carrier testing for autosomal recessive disorders' in the Appendix, page 650.

AR disorders are encoded on the autosomes and the disorder manifests in homozygotes and compound heterozygotes, i.e. when both alleles at a given locus are mutated. Heterozygotes do not manifest a phenotype (e.g. cystic fibrosis (CF)), or if they do this is very mild in comparison with the disease state (e.g. sickle cell trait versus sickle cell disease). Affected siblings often follow a broadly similar clinical course which is more similar than for many autosomal dominant (AD) disorders.

Aspects of AR inheritance

Consanguinity. AR disorders are far more common in the offspring of consanguineous partnerships. See 'Consanguinity', page 284.

Heterozygote advantage. For common recessive conditions, heterozygote advantage is usually much more important than recurrent mutation for maintaining the disease gene at high frequency, e.g. sickle cell disease where heterozygotes are less susceptible than normal individuals to malaria.

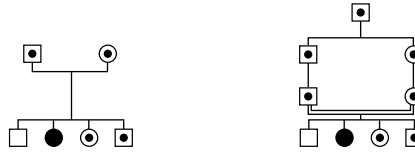
Founder effect is a high prevalence of a genetic disorder in an isolated or inbred population due to the fact that many members of the population are derived from a common ancestor who harboured a disease-causing mutation. The affected individuals in a given population are all homozygous for the same mutation (founder mutation). Examples include the recessive disorders Meckel syndrome, hydrolethrus syndrome, Cohen syndrome, and congenital Finnish nephropathy, which all occur with disproportionately high incidence in Finland compared with other European populations.

Carrier determination for a relative of the proband is reasonably straightforward if the mutations in the proband are defined. Determining whether an unrelated partner is a carrier is usually more problematic. Unless the partner has a family history of the disorder, he/she will be at population risk for carrier status. If the disorder is rare, the risk of affected offspring will be low and equivalent to half the carrier risk in the general population. Carrier testing for those at population risk is possible for a few diseases, e.g. CF, spinal muscular atrophy (SMA), sickle cell disease, thalassaemia, but not for many others. Whereas inborn errors of metabolism often show a marked distinction in enzyme activity (or other biochemical markers) between normal and affected, there is often considerable overlap in levels between heterozygotes and normals making assignment of carrier status problematic. Tay-Sachs disease is a notable exception.

Deriving population risk for carrier status from disease frequency. See 'Carrier frequency and carrier testing for autosomal recessive disorders', page 650.

Family trees

Autosomal recessive inheritance

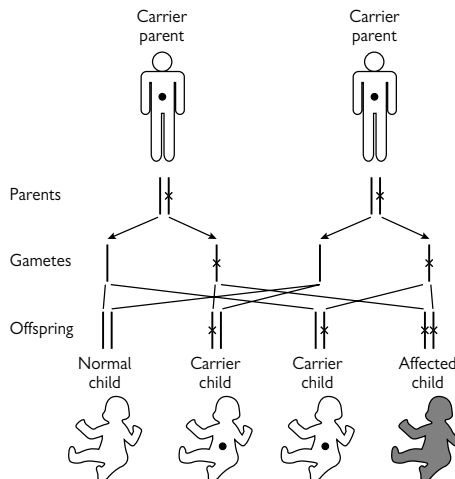


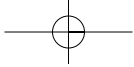
Family trees showing AR inheritance. If both parents are carriers, there is a 25% risk of an affected child in any pregnancy, independent of gender. The diagram on the right illustrates a consanguineous relationship between first cousins. A common ancestor is a carrier for a recessive mutation that may occur in homozygous form in a descendent as a consequence of consanguinity.

Genetic advice

- Disease expressed only in homozygotes and compound heterozygotes.
- Parents are obligate carriers (SMA is an exception to this rule as there is a significant new mutation rate of 1.7%).
- Risk to carrier parents for an affected child is 25% (1 in 4).
- Healthy siblings of affected individuals have a two-thirds risk of carrier status.
- Risk of carrier status diminishes by one-half with every degree of relationship distanced from parents of affected individual, e.g. second-degree relatives (grandparents and aunts/uncles) and third-degree relatives (first cousins, great-grandparents, great-aunts, and great-uncles).
- All offspring of an affected individual whose partner is a non-carrier are obligate carriers.

Autosomal recessive inheritance



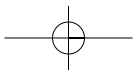
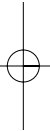
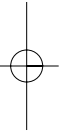


Expert adviser: Ian D. Young, Consultant Clinical Geneticist, Leicester, England.

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Communication skills

The genetics consultation

The success of any consultation depends on how well the patient and doctor communicate with each other. Time is limited so it is important to ensure that it is used as effectively as possible. It may be helpful to think of the consultation as divided into three separate phases:

- 1 establishing rapport and trust—building a relationship;
- 2 collecting data;
- 3 agreeing a plan of action (management plan).

Key skills

- 1 **Setting an agenda for the consultation.** Elicit the main issues at the outset of the consultation. Is the main issue finding a diagnosis, or determining whether an individual with a family history is themselves at risk of developing the condition, or reviewing the natural history if that is known? If the condition may have implications for future children, offer to discuss this. What do the family want to know?
- 2 **Determine the patients' perception.** What is their interpretation of the child's problems, or family history?
- 3 **Explain the genetic basis of the condition** if known or, if unknown, state whether you think it is likely to have a genetic basis or not. Check the family's understanding of the information you are giving as you go along. It is easier to change tack and alter the pitch of an explanation as you are going along.
- 4 **Assess the genetic risk to other family members.** Discuss whether or not there is a significant risk to other family members not present at the consultation and, if an appreciable risk exists, agree a strategy for offering genetic advice and investigation.

Breaking bad news

Geneticists are frequently called upon to give bad news to patients, whether it is a chorionic villus sampling (CVS) result indicating an affected fetus or an adverse result in a Huntington or *BRCA* predictive test, that the disorder just diagnosed has a progressive downhill course, or to tell parents that the disorder that has afflicted one of their children has a substantial recurrence risk.

When arranging prenatal or predictive tests careful plans should be laid for the giving of results. Care should be taken to ensure the following.

- The individual is aware of the possibility of an adverse result and has thought through how they

might handle this information and is prepared for this eventuality.

- The result is given by a member of staff well known to the individual, usually the person who has undertaken the pre-test counselling.
- The individual has a choice in how they receive the result and know when to expect the result, e.g. by telephone, in a clinic visit, or by letter.
- Ongoing support is offered following receipt of the test result.

Studies show that patients take in and retain very little of the information that is given after receiving a bad-news result. Aim to keep discussion simple and focused on the patient's needs.

Communicating a diagnosis (after Unique-rare chromosome disorder support group)

Diagnosis and genetic counselling should be given:

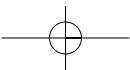
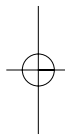
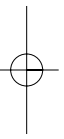
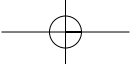
- in private, in person, and with both partners present, or with a supporter;
- with sensitivity, respect, compassion, understanding, and honesty;
- without being rushed and without jargon, using positive, sensitive language;
- with the contact details of relevant support groups;
- with the offer of a follow-up appointment to answer new questions and discuss new issues;
- with the offer of ongoing support to help the family cope and adjust.

Sometimes, it can be helpful to remind the family that, although knowledge of the diagnosis is new, the genetic condition has in fact been present since conception and has always been a part of their child's life.

Expert adviser: Tony Hope, Professor, Director of Ethox, Institute of Health Sciences, University of Oxford, Oxford, England.

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Confidentiality

Confidentiality is a major issue for all doctors. Medical geneticists must particularly be on their guard against the potential for breaching confidentiality when their advice is sought by different members of the same family.

The general duty to maintain the confidential nature of personal genetic information is, however, not an absolute one. The Human Genetics Commission note circumstances where it may be appropriate to disclose personal information. Wherever possible, this will be with the consent of the patient, and will be in the interest of the patient, of relatives, or of the wider public.

Disclosure

The Human Genetics Commission recognizes that, exceptionally, 'disclosure of sensitive personal genetic information without consent may be justified in rare cases where a patient refuses to consent to such disclosure but the benefit to other family members or the wider public substantially outweighs the need to respect confidentiality.'

If you decide to disclose confidential information you must be prepared to explain and justify your decision. In practice such cases are usually discussed within a professional forum such as a departmental meeting or with a group of consultant colleagues so that the subjective decision about the balance of interests is shared and agreed.

Children

In 1985, Gillick challenged the right of a doctor to prescribe contraception to a girl under the age of 16 years without obtaining the consent of the girl's parents. This became an important case in English law and Lord Scarman gave the following ruling in the House of Lords, 'As a matter of law the parental right to determine whether or not their minor child below the age of 16 will have medical treatment terminates if and when the child achieves sufficient understanding and intelligence to enable him to understand fully what is proposed.' It is a matter for a doctor to judge whether a child aged under 16 years is 'Gillick competent', i.e. is competent to make judgements about their own medical care. Furthermore, if a child is deemed 'Gillick competent' a doctor can only disclose information to the parent with the child's consent, regardless of parental responsibility.

In the non-Gillick competent child, authority must be given by whoever has parental responsibility under the provisions of the *Children's Act 1989*. In deciding whether to disclose information, the practitioner's overriding consideration must always be what is in the *best interests of the child*.

A child's biological parents both have parental responsibility if they were married at the time of the child's birth. In such circumstances a practitioner will normally disclose all information concerning a young child to either parent without the other's consent. When such parents are separated or divorced, information may still be disclosed to either parent irrespective of who has custody, unless a court has removed parental responsibility from one or other parent.

With parents who were unmarried at the time of the child's birth, only the mother automatically has legal parental responsibility. Her consent is therefore required before information may be disclosed to the father, unless he has been given parental responsibility either by agreement with the mother or by a court order.

Deceased patients

Seek consent from the next of kin. The Human Genetics Commission recognizes that 'There may be some clinical situations where genetic information about the dead is needed *in order to assess the risk to a living relative*. This information may be obtained by testing samples removed from an individual during life. The approach we favour is that a presumption should be made that the dead person would have consented in his or her lifetime to such testing and that this justifies post-mortem testing.'

Refusal of consent

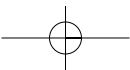
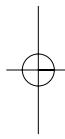
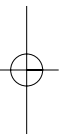
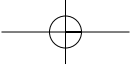
Whilst privacy and the right to refuse consent is an important proposition it is not an absolute principle and it can be overridden if the harm to others outweighs the importance to the individual concerned, e.g. if the refusal of consent is capricious or vindictive.

Useful websites: General Medical Council (GMC) <www.gmc-uk.org/standards/consent.htm>; Joint Committee on Consent and Confidentiality in Medical Genetics <www.bshg.org.uk/JCMG/jcmg.htm>.

Expert adviser: Martin Bobrow, Professor of Medical Genetics, University of Cambridge, Cambridge, England.

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Confirmation of diagnosis

See also 'Confirmation of diagnosis of cancer', page 440.

In order to provide precise genetic advice it is *essential* to have an accurate diagnosis. If the diagnosis in your patient has been made by others, and the patient and his/her family are referred to you for genetic advice, you will need to seek confirmation of the diagnosis. If you are asked to give advice to a relative, without the opportunity to see and assess the proband, you will need to confirm the diagnosis in the proband before giving definitive genetic advice. The diagnosis is of such fundamental importance that there may be medico-legal implications if it turns out that the given diagnosis was wrong and appropriate steps were not taken to substantiate it. Some diagnoses such as 'cystic fibrosis' tend to be fairly reliable, whereas others such as 'achondroplasia' are notoriously unreliable. Depending on the circumstances, various options are available.

- **Clinical assessment.** Some genetic disorders have specific clinical features that enable a rapid confirmation of diagnosis. Take a history of the main features/symptoms and briefly examine the patient to confirm that you agree with the clinical diagnosis, e.g. neurofibromatosis type 1 (NF1), tuberous sclerosis (TS), etc., before giving genetic advice. Where possible follow this up by seeking results of various key investigations that were instrumental in making the diagnosis, e.g. cranial magnetic resonance imaging (MRI) result, mutation result.
- **Laboratory findings.** Many genetic diagnoses depend on specific laboratory results. These may be the results of molecular genetic testing, e.g. Huntington disease (HD), fragile X (FRAXA) syndrome, myotonic dystrophy, or the results of biochemical investigations, e.g. Zellweger syndrome, phenylketonuria (PKU), etc., or histological assessment. Ensure that you have sight of the critical result(s) (or a copy of the result(s)) and that these are from a reliable source (e.g. an accredited laboratory) before giving definitive advice.
- **Radiological investigations.** Some genetic disorders, e.g. skeletal dysplasias, depend on radiological studies for diagnosis. Ensure that you see either the images or the

radiologist's report confirming the radiological findings before giving definitive genetic advice.

- **Death certificate.** For deceased relatives, the death certificate may lend some support to diagnosis. This is generally less reliable than laboratory results, but is helpful if, for example, hospital notes have been destroyed and it is otherwise difficult to obtain any confirmation of diagnosis.
- **Family photographs.** These are often helpful when determining familial involvement with a syndrome that has dysmorphic features, and when other avenues fail.

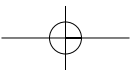
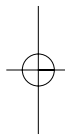
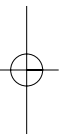
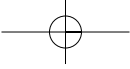
Seeking confirmation of diagnosis in relatives

When advice is sought about a family history (and the proband is not seen in clinic) it is usual practice to obtain consent from the proband (their parents/guardians) to approach their doctor/genetics department for confirmation of the diagnosis. Many departments have a standard form for obtaining consent from relatives in these circumstances. Taking the family history and talking about affected family members may be a sensitive area—ensure that there is adequate time for this as it is often crucial to the provision of accurate genetic advice. Sometimes the genetic disorder is not openly discussed in the family, and not all families are on good speaking terms, so it often takes a lot of sensitivity to get accurate information and even so it can be difficult on occasion to establish the diagnosis truly accurately. Under such circumstances you need to explain to the family the limits of the information that you have and document in the medical notes that you have done the best job possible under the circumstances. See also 'Confidentiality', page 12.

Expert adviser: Judith G. Hall, Professor of Pediatrics and Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada.

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Consent for genetic testing

Consent is the agreement to an action based on knowledge of what the action involves and its likely consequences.

Private genetic information about a person (e.g. whether they are affected with a genetic disorder) should generally not be obtained, held, or communicated without that person's free and informed consent (Human Genetics Commission 2002).

The nature and extent of information that is required in seeking consent for a genetic test depend on whether the test in question is likely to reveal sensitive genetic information—information that has special significance for the patient or for the patient's relatives (Human Genetics Commission 2002).

Genetic testing may reveal unexpected information, e.g. about misattributed parentage. The wider implications of testing should therefore be considered and discussed before a genetic test is done.

Points to consider when obtaining consent for genetic testing (Human Genetics Commission 2002)

See also 'Testing for genetic status', this chapter.

- What is the purpose of the test?
- Is there a clear explanation of the nature and treatment of the condition and the way in which it is inherited (if appropriate)?
- Is there a clear explanation of the test, or tests, to be carried out?
- What potential benefits might there be from having the test?
- What might be the potential disadvantages?
- Are there any alternatives to having the test that would achieve the same benefits? Does the test have to be done now or can it be delayed?
- Could the test have implications for the person's:
 - future health;
 - reproductive choices;
 - relatives;
 - family relationships (e.g. information about parentage);
 - present or future employment;
 - insurance prospects?
- What is the method of communication of the result to the patient and how long will it take from sampling to result?
- What are the arrangements for ensuring the confidentiality of the test result, e.g. arrangements for storing of test result in patient's individual medical record? Is any accompanying written information, particularly where this substitutes for face to face consultation, written in clear, simple, understandable language, objective and without bias?
- Is there an awareness of the patient's level of understanding/cultural beliefs/language?
- Would the person like further information or access to other sources of advice (e.g. the opportunity to talk to an independent counsellor or other persons who have faced the same choice)?
- What provision is there for post-test support?

Competence

Competence to make decisions depends on three broad capacities:

- the capacity for understanding and communication;
- the capacity for reasoning and deliberation;
- the capacity to develop and sustain a set of moral values.

Competent adult

A competent adult is a person who has reached 18 years of age and has the capacity to make medical decisions on his/her own behalf. To demonstrate that capacity an individual must be able to (British Medical Association and Law Society 1995):

- 1 understand in simple language what genetic testing is, its purpose, and why it is being proposed;
- 2 understand its principal benefits, risks, and alternatives;
- 3 understand in broad terms what the consequences would be of not undergoing genetic testing;
- 4 retain the information long enough to make an effective decision; and
- 5 make a free choice (i.e. free from pressure).

Incompetent adults

Adults with dementia or severe learning disability are often not competent to give consent to genetic testing (see criteria above). The Law Commission's (1995) recommendations include a proposal to consider the following:

- (1) The ascertainable past and present wishes and feelings of the person concerned and the factors which he or she would consider if able to do so;
- (2) The need to permit and encourage the person concerned to participate, or to improve his or her ability to participate, in anything done for and any decision affecting him or her;
- (3) If it is practicable and appropriate to consult them, the views as to that person's wishes and feelings and as to what would be in the best interests of that person of:
 - (i) Any person named by him or her as someone to be consulted;
 - (ii) Any person (such as a spouse, relative or friend or other person) engaged in caring for or interested in the person's welfare;
 - (iii) The donee of a continuing power of attorney granted by him or her;
 - (iv) Any manager appointed by the court; and
- (4) Whether the purpose for which any action or decision is required can be as effectively achieved in a manner less restrictive of the person's freedom of action.

The Law Commission (1995) recommends that 'it should be lawful to do anything for the personal welfare or health care of a person who is, or is reasonably believed to be, without capacity in relation to the matter in question if it is in all the circumstances reasonable for it to be done by the person who does it and it is in the best interests for that person'.

Young people

The *Family Law Reform Act 1969* enables children of 16 and over to consent to medical treatment and, by inference, genetic testing undertaken in a medical context. In such circumstances there is no legal requirement to obtain consent from the parent or guardian.

Children

For young children and babies, the parents (or those with parental responsibility) give or withhold consent on behalf of the child. Children under 16 years can truly consent to treatment only if they understand its nature, purpose, and risks (see 'Confidentiality', page 12 for further discussion).

In practice, as children grow older and if they express an interest, competence, and desire to be involved in decision-making, they should participate in such decisions. The parent and child may choose to both sign the consent form indicating their joint involvement in the decision-making process. Usually genetic tests that will have no impact on health care before adult life are deferred until the individual reaches an age when he/she is legally competent to make his/her own decisions regarding health care.

Children in care

When a child is the subject of a care order, the local authority acquires 'parental responsibility' under the *Children Act 1989*. The order does not, however, deprive

parents of their parental responsibility and they are not deprived of their ability to authorize or refuse treatment.

Useful websites: General Medical Council (GMC) <www.gmc-uk.org/standards/consent.htm>; Joint Committee on Consent and Confidentiality in Medical Genetics <www.bshg.org.uk/JCMG/jcmg.htm>.

Expert adviser: Martin Bobrow, Professor of Medical Genetics, University of Cambridge, Cambridge, England.

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The genetic code and mutations

DNA (deoxyribonucleic acid) contains four types of bases—two purines, adenine (A) and guanine (G), and two pyrimidines, cytosine (C) and thymine (T). RNA (ribonucleic acid) contains uracil (U) in place of thymine. The DNA double helix (Watson and Crick 1953) maintains a constant width and is faithfully replicated, because purines always face pyrimidines in the complementary A–T, and G–C base pairs. Thus it can: (1) serve as a template for replication that re-establishes the double helix and (2) open to be 'read' and 'copied' in the process of transcription for producing proteins.

Because there are more codons (61 plus 3 STOP codons) than there are amino acids (20), almost all amino acids are represented by more than one codon, i.e. the code is degenerate, particularly at the third base.

Triplet codons and their corresponding amino acids and STOP sequences

	T	C	A	G
	TTT = Phe	TCT = Ser	TAT = Tyr	TGT = Cys
T	TTC = Phe	TCC = Ser	TAC = Tyr	TGC = Cys
	TTA = Leu	TCA = Ser	TAA = STOP	TGA = STOP
	TTG = Leu	TCG = Ser	TAG = STOP	TGG = Trp
	CTT = Leu	CCT = Pro	CAT = His	CGT = Arg
C	CTC = Leu	CCC = Pro	CAC = His	CGC = Arg
	CTA = Leu	CCA = Pro	CAA = Gln	CGA = Arg
	CTG = Leu	CCG = Pro	CAG = Gln	CGG = Arg
	ATT = Ile	ACT = Thr	AAT = Asn	AGT = Ser
A	ATC = Ile	ACC = Thr	AAC = Asn	AGC = Ser
	ATA = Ile	ACA = Thr	AAA = Lys	AGA = Arg
	ATG = Met	ACG = Thr	AAG = Lys	AGG = Arg
	GTT = Val	GCT = Ala	GAT = Asp	GGT = Gly
G	GTC = Val	GCC = Ala	GAC = Asp	GGC = Gly
	GTA = Val	GCA = Ala	GAA = Glu	GGA = Gly
	GTG = Val	GCG = Ala	GAG = Glu	GGG = Gly

Amino acid	Characteristic
Alanine (A)	Neutral
Arginine (R)	Basic
Asparagine (N)	Polar
Aspartic acid (D)	Acidic
Cysteine (C)	Polar, forms disulphide cross-links
Glutamine (Q)	Polar
Glutamic acid (E)	Acidic
Glycine (G)	Small, neutral
Histidine (H)	Basic (weak)
Isoleucine (I)	Hydrophobic
Leucine (L)	Hydrophobic
Lysine (K)	Basic
Methionine (M)	Hydrophobic
Phenylalanine (F)	Hydrophobic, bulky
Proline (P)	Hydrophobic, helix-breaker
Serine (S)	Polar
Threonine (T)	Polar
Tryptophan (W)	Hydrophobic, bulky
Tyrosine (Y)	Polar, bulky
Valine (V)	Hydrophobic
Nonsense (X)	(Stop)

Physical basis of some mutations

Nucleotide substitutions

These are described by a number representing the nucleotide in the coding DNA sequence (cDNA), followed by a letter representing the original nucleotide (A, C, G, T) followed by > and the mutated nucleotide, e.g. in the β -globin gene (*HBB*) 17A>T means that adenine at nucleotide 17 is changed to thymine, while in the haemochromatosis gene (*HFE*) 845G>A means that guanine at nucleotide 845 is changed to adenine.

If this results in an amino acid substitution the mutation is termed a *missense mutation*. In protein annotation this is written with a number representing the amino acid in the translated protein product, the first letter preceding the number being the wild-type amino acid, and the letter after being the altered amino acid, e.g. in sickle cell disease E6V (glutamic acid at amino acid 6 is changed to valine); in *HFE*, C282Y (cysteine at amino acid 282 is changed to tyrosine) and H63D (histidine at amino acid 63 is changed to aspartic acid). If the nucleotide substitution does not alter the genetic code it is termed a *silent* or *synonymous substitution*, but note this could still cause problems by affecting splicing, etc.

Most *splice site mutations* occur in introns. Mutations in introns are referred to by the nearest nucleotide in an exon, e.g. in *CFTR* 621+1G>T, the first nucleotide (G) in the intron 3' to nucleotide 621 in the cDNA is replaced by T and, in 1717–1G>A, the last nucleotide (G) in the intron 5' to nucleotide 1717 in the cDNA is replaced by A.

Nucleotide deletions and insertions

The nucleotide number is followed by del/ins and the letter for the relevant nucleotide, e.g. 394delT means the nucleotide T at position 394 in the cDNA is deleted. 3905–3906insT means a T is inserted after nucleotide 3905 in the cDNA. Insertions/deletions involving single nucleotides or pairs of nucleotides cause a shift in the reading frame (*frameshift mutation*) and usually result in protein truncation.

In protein annotation, the term delta or a small triangle is used to denote a deletion, e.g. in *CFTR*, the $\Delta F508$ mutation means a deletion of phenylalanine at amino acid 508 resulting from a three-nucleotide deletion. Although this particular terminology is not current, it is still in widespread use.

Types of mutation and assessment of their significance

Some mutations, e.g. $\Delta F508$, are well known and clearly pathogenic and their interpretation is straightforward. On the other hand, interpreting the clinical significance of a newly identified 'private mutation' can be very difficult and, unless it is a truncating mutation, you are strongly advised to discuss the situation with a clinical molecular geneticist before using the result in clinical practice, e.g. in predictive or prenatal testing.

Missense mutations

A mutation that results in an altered amino acid sequence in the encoded protein is termed a missense mutation. Not all missense mutations are pathogenic as the nature of the amino acid change and its precise location in the three-dimensional protein structure will determine whether

there is any effect on protein function. The following factors increase the likelihood that a missense mutation is pathogenic.

- It is a *de novo* change in the gene of interest (i.e. not present in either parent), or it segregates with the disease in the family.
- It causes a significant alteration in the predicted protein conformation, e.g. a hydrophobic amino acid is substituted for a polar one, or it occurs at a key site in the protein (e.g. a binding site).
- It has been reported previously on several occasions in a database of mutations for the gene in question.
- It is not present at significant levels in the general population. Some 'missense mutations' are in reality polymorphisms. It is necessary to look at control data in the unaffected population to evaluate significance.

Truncating mutations

Mutations that result in protein truncation are nearly always pathogenic. They include single nucleotide substitutions that encode STOP codons (*nonsense mutations*), frameshift mutations in which the reading frame is lost, and also large deletions/insertions.

Splice-site mutations

Splicing is the process by which the introns are removed from the primary transcript, and the exons are joined together. A splice acceptor site is the junction between the dinucleotide AG at the end of an intron and the start of the next exon. A splice donor site is the junction between the end of an exon and the dinucleotide GT at the start of the next intron.

Some genes have alternative splice variants, where a single gene gives rise to more than one mRNA sequence that may have different tissue distributions. Mutations may abolish a splice acceptor or donor site or impair the efficiency of splicing resulting in abnormal ratios of splice variants.

Triplet repeat mutations

A mutation caused by an increase above threshold in the number of copies of a tandemly repeated trinucleotide, e.g. (CTG)_n in myotonic dystrophy, (CAG)_n in SCA2.

Mechanisms by which mutations exert their effect on phenotype

Loss-of-function mutation ('inactivating' mutation). This term includes nucleotide substitutions that

introduce a stop codon, out-of-frame deletions resulting in a truncated protein, or specific mutations that cause loss of function of the protein by disturbing the conformation or charge of a site critical in the interaction of the protein with other molecules. Most mutations in recessively inherited disease are loss-of-function.

Gain-of-function mutation ('activating' mutation).

These mutations are site-specific and usually result in constitutive activation of a specific protein function. In achondroplasia, where *FGFR3* is a bone growth-suppressing gene, two common mutations, 1138G > A and 1138G > C, both encoding G380R account for 98% of mutations in affected individuals. When *FGFR3* is mutated at this site its normal signalling function is partially constitutively activated (i.e. activated even in the absence of bound fibroblast growth factor (FGF)) resulting in increased inhibition of growth of cartilage cells.

Dominant-negative mutation. This is a mutation in one copy of a gene resulting in a mutant protein that has not only lost its own function, but also prevents the heterozygously produced wild-type protein of the same gene from functioning normally. It commonly acts by producing an altered polypeptide (subunit) that prevents or impairs the assembly of a multimeric protein, e.g. assembly of collagen triple helices in osteogenesis imperfecta (OI).

Haploinsufficiency arises when the normal phenotype requires the protein product of two alleles, and reduction of 50% of gene product as a result of loss-of-function mutations results in an abnormal phenotype.

Expert adviser: A.O.M. Wilkie, Nuffield Professor of Pathology and Honorary Consultant in Clinical Genetics, Oxford University, Oxford, England.

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Genomic imprinting

Genomic imprinting is a genetic mechanism by which genes are *selectively expressed* from the *maternal or paternal homologue* of a chromosome. Imprinting invokes a variety of mechanisms that distinguish the maternal and paternal homologue and affect the chromatin structures that determine transcriptionally silent and active states. The inactive

allele is epigenetically marked by histone modification, cytosine methylation, or both. The imprint is maintained throughout the life of the organism. Imprints once established are erased during the early development of the male and female germ cells and then reset prior to germ cell maturation.

Map of known human genomic imprinting sites

Chromosome location	Gene	Maternally/paternally expressed gene	Disease association	
1	1p31.2	ARH1/NOEY2	Paternally expressed	
	1p36.32	p73	Maternally expressed	
6	6q24.2	HYMA1	Paternally expressed	
	6q24.2	ZAC/PLAGL1	Paternally expressed	Transient neonatal diabetes
	6q25.3	M6P/IGFR2	Biallelic expression with maternally methylated IC	
7	7q21.3	PEG10	Paternally expressed	
	7q32.2	COPG2	Maternally expressed	
	7q32.2	PEG1/MEST	Paternally expressed	Russell-Silver syndrome
	7q32.2	PEG1/IAS	Paternally expressed	
11	11p15.5	H19	Maternally expressed	
			Paternally methylated IC	
	11p15.5	IGF2	Paternally expressed	Beckwith-Wiedemann syndrome
	11p15.5	IGF2-AS	Paternally expressed	
	11p15.5	INS	Paternally expressed	
	11p15.5	ASCL2	Maternally expressed	
	11p15.5	TRPM5	Paternally expressed	
	11p15.5	KCNQ1	Maternally expressed	
			Maternally methylated IC	
	11p15.5	KCNQ1 QT1	Paternally expressed	
	11p15.5	p57kip2/CDKN1C	Maternally expressed	
	11p15.5	SCL22A1/IITM	Maternally expressed	
	11p15.5	ZNF215	Maternally expressed	
14	14q32	DLK1	Paternally expressed	
			Paternally methylated IC	
		MEG3	Maternally expressed	
15	15q11-q13	MKRN3	Paternally expressed	
	15q11-q13	MAGEL2	Paternally expressed	
	15q11-q13	NDN	Paternally expressed	
	15q11-q13		Maternally methylated IC	
	15q11-q13	SNRPN	Paternally expressed	Prader-Willi syndrome
	15q11-q13	UBE3A	Maternally expressed	Angelman syndrome
	15q11-q13	ATP10C	Maternally expressed	
	15q11-q13	GABRB3	Paternally expressed	
18	18q21.1	ELONGIN A3	Maternally expressed	
19	19q13.43	PEG3/ZIM2	Paternally expressed	
20	20q13.32	GNAS1-AS	Maternally expressed	
	20q13.32	GNAS	Maternal and paternal transcripts distinctly expressed depending on promoter usage or alternate splicing	Albright hereditary osteodystrophy
X	Xq13.2	XIST		

In humans about 50 genes are known to be imprinted, i.e. differentially expressed according to their origin in either the oocytes or spermatozoa. These imprinted genes have roles in growth and development as well as in tumour suppression.

Imprinted genes cause disease when the maternal/paternal gene that is usually expressed is mutated, silenced, or deleted such that there is no functional copy (since the other homologue is transcriptionally silent) or when, in the case of a paternally expressed gene, the organism has two maternal homologues as a consequence of uniparental disomy or vice versa.

Imprinting centre (IC). One mechanism involves an IC that seems to control the resetting of a cluster of closely linked imprinted genes during transmission through the opposite sex. Imprinting centres are differentially (paternally or maternally) methylated. Deletion of an imprinting centre, can cause disordered imprinting of several genes in

a chromosomal domain, e.g. in Prader–Willi or Angelman syndrome.

Uniparental disomy (UPD) describes the karyotype of a euploid cell or organism in which one of the chromosome pairs has been inherited exclusively from one parent. If two identical homologues are inherited this is called *isodisomy*; if non-identical homologues are inherited the term *heterodisomy* is used. This occurs when non-disjunction during meiosis in one parent leads to formation of a disomic gamete. A trisomic zygote is formed and trisomic rescue with loss of the chromosome from the other parent occurs. If UPD occurs in an imprinted region this may cause disease.

Expert adviser: Eamonn Maher, Professor of Medical Genetics, University of Birmingham, Birmingham, England.

Reference

<www.geneimprint.com>.

Mitochondrial inheritance

Mitochondrial DNA (mtDNA) has unique genetic features that distinguish it from nuclear DNA, which follows a Mendelian pattern of inheritance. The mtDNA genome of humans is a double-stranded circular DNA, 16.6 kb in length and encoding 13 proteins (all subunits of respiratory chain complexes), two ribosomal RNAs, and 22 transfer RNAs. There are no introns and, except for the D loop region that is involved in the initiation of DNA replication and transcription, most of the mitochondrial genome is coding sequence. Mitochondria typically contain several copies of mtDNA and a typical human somatic cell can contain up to 1000 mitochondria (i.e. 5000–10 000 copies of mtDNA) representing >1% of the cell's total DNA. Mature oocytes contain a staggering ~100 000 copies of mtDNA, whereas sperm contain ~100.

The organs most often affected in mitochondrial disorders are highly energy-demanding tissues, such as the central nervous system (CNS), skeletal and cardiac muscle, pancreatic islets, liver, and kidney.

Aspects of mitochondrial inheritance

Maternal inheritance. Mitochondrial DNA (mtDNA) is exclusively maternally inherited with very rare exceptions (Schwartz and Vissing 2002). Paternal mitochondria enter the egg on fertilization where they constitute a miniscule fraction (0.1%) of the total mitochondria. The paternal mitochondria and their mtDNA are rapidly eliminated early in embryogenesis. For the purposes of genetic counselling the risk of paternal inheritance is essentially zero.

Homoplasmy is the existence of only one mtDNA type in the same cell, tissue, or individual, e.g. mitochondria containing only mtDNA carrying the A1555G sequence sensorineural deafness sequence.

Heteroplasmy is the existence of more than one mtDNA type in the same cell, tissue, or individual, e.g. mitochondria containing a mixture of mtDNA carrying the MELAS 3243 point mutation and mtDNA with the wild-type sequence. In mitochondrial disorders, because of the thousands of mitochondria in each cell, there are often variable percentages of mutant and wild-type mtDNAs between different cells and especially between different tissues. The different mtDNAs can vary between 0 and 100%.

Threshold effect. For some mtDNA mutations there is a relatively narrow threshold below which mitochondrial function is normal, but above which mitochondrial function is greatly impaired. For some mtDNA mutations, e.g. the 8993 mutation seen in neuropathy/ataxia/retinitis pigmentosa (NARP) syndrome and some patients with Leigh syndrome, the severity of clinical symptoms increases sharply above a threshold mutant load.

Mitochondrial bottleneck. A high variation in mutant load is sometimes seen in the offspring of heteroplasmic women. This is at variance with expectation based on random distribution of mutant and wild-type mtDNA in

the cell. The bottleneck hypothesis states that the number of mtDNAs during oogenesis is either relatively small or that only a few mtDNAs are used as templates for amplification. Brown *et al.* (2001) measured the mutant mtDNA load in 82 oocytes from a woman harbouring the MELAS (mitochondrial myopathy–encephalopathy–lactic acidosis–stroke-like episodes) A3242G mutation who had an 18% mutant load in her skeletal muscle. The mutant load in oocytes ranged from 0 to 45% and the mean within individual oocytes was similar to that in the mother.

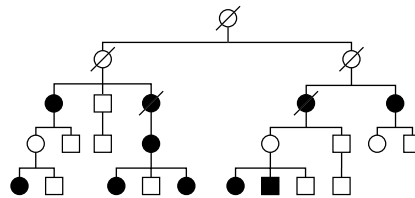
Tissue variation. In heteroplasmic disorders, the distribution of mutant load in tissues is often not uniform. In some tissues the level of mutant mtDNA changes successively with time, for instance falling in blood and accumulating in non-dividing cells such as muscle.

Selection. Preferential accumulation of mutant mtDNA in affected tissues appears to explain their progressive nature (Poulton *et al.* 2003). However, in some cell lines, e.g. blood, cells with high mutant loads appear to be selected against and the mutant load may fall over time.

Mutation rate. Human mtDNA has a mutation rate 10–20 times that of nuclear DNA, probably due to replication repair systems that are less stringent than those in the nucleus. This has been exploited in a study of the migration of human populations (Sykes 2001).

Typical family tree

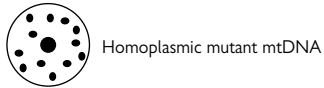
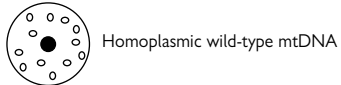
Mitochondrial inheritance



A typical family tree showing mitochondrial inheritance. Offspring of females in the maternal line are at risk; males do not transmit the condition.

Genetic advice

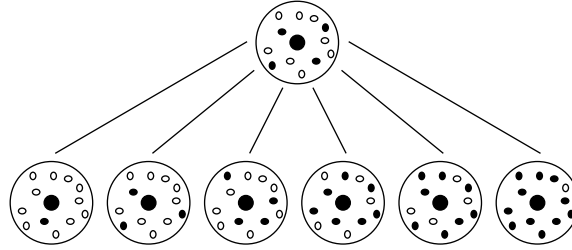
- Inheritance is matrilineal, i.e. the condition can only be transmitted by females in the maternal line.
- Males do not transmit mitochondrially inherited disorders with extremely rare exceptions (Schwartz and Vissing 2002).
- Typically a mitochondrially inherited condition can affect both sexes.
- Point mutations are commonly maternally inherited, whilst deletions and duplications are most often sporadic but see advice for specific mitochondrial disorders page 384.
- If the mother is heteroplasmic for a mutation, the proportion of mutant mtDNA in her offspring can vary considerably.

Mitochondrial inheritance**Homoplasmy****Heteroplasmy**

Mother



Oocytes



Offspring



NB. Correlation between phenotypic severity and level of mutant mtDNA is poor in many mitochondrial diseases.

Expert adviser: Joanna Poulton, Professor of Mitochondrial Genetics, University of Oxford, Oxford, England.

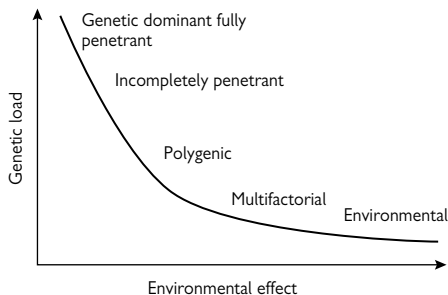
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Multifactorial inheritance

From a clinical perspective there is a continuous spectrum of disease from, at the one end, disorders that are strictly genetic and caused by fully penetrant mutations with minimal contribution from the environment to, at the other extreme, those caused predominantly by environmental factors (e.g. teratogens) with minimal contribution from genetic factors. Between these two extremes lie the incompletely penetrant, and the polygenic disorders, creating a smooth transition from strictly genetic to multifactorial illnesses (Bomprezzi *et al.* 2003).



The progression from strictly genetic to strictly environmental causation in the aetiology of disease.

Genes and environment in the aetiology of disease (Bomprezzi *et al.* 2003)

Common birth defects such as cleft lip/palate, congenital dislocation of the hip, congenital heart disease, and neural tube defect do not generally follow a Mendelian pattern of inheritance. Nevertheless, a tendency for these conditions to cluster in families, more than would be expected by chance, is observed. The same is true for schizophrenia, ischaemic heart disease, and type 1 diabetes. Many of these conditions probably depend on a mixture of major and minor genetic determinants, together with environmental factors. This is termed multifactorial inheritance. Diseases inherited in this manner are termed complex diseases. Multifactorial inheritance may involve a small number of loci (oligogenic), many loci (polygenic), or a single major locus with a polygenic background.

In multifactorial inheritance, disease occurrence is attributable to the interaction of the environment with alleles at many loci interspersed throughout the genome. The mapping and identification of these genes is difficult because the disease-associated alleles occur almost as commonly in patients as in healthy individuals; even the highest-risk genotypes confer only modest risk of disease (Todd 1999).

Terminology

Polygenic traits are governed by the simultaneous action of many (>3) gene loci.

Oligogenic traits are governed by the simultaneous action of a few (e.g. 3) gene loci.

Digenic traits are governed by the simultaneous action of two gene loci.

Monogenic traits are governed by the individual action of a single gene (as in classical Mendelian disorders).

Modifier gene is a gene whose expression can influence a phenotype resulting from mutation at another locus.

Linkage is a physical relationship between a locus/loci and a trait/disease that lie on the same chromosome at a genetic distance of <50 centimorgans (cM).

Association is a statistical relationship between an allele(s) and a trait/disease.

Lambda (λ) is the ratio of the frequency of a multifactorial disease in the relative of an affected person compared with its rate in the general population, e.g. in sib pair studies λ_s is the ratio of the frequency of the disease in siblings compared with that in the general population. λ_s is a measure of relative risk and hence of disease heritability.

Aspects of multifactorial inheritance

Complex traits. Traits such as intelligence, behavioural traits, height, and weight approximate to a normal distribution in the general population. A large number of genes are involved in determining these characteristics together with environmental factors. For example, factors influencing height include parental height, nutrition, and chronic illness.

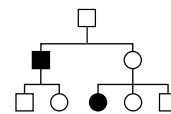
Falconer's polygenic threshold model. This is based on the assumption that liability to a condition is multifactorial and follows a normal distribution in the population and that the disease occurs when a particular threshold value is exceeded. The normal distribution for liability is shifted in close relatives of an affected individual; hence a greater proportion of them will exceed the critical threshold value and be affected (see figure at the end of this article). For first-degree relatives the expected incidence approximates to the square-root of the population incidence.

For a condition affecting 1/1000 individuals (0.1%), the risk to sibs, parents, and children is ~1/30 (3%), falling to 1/100 (1%) for second-degree relatives, and close to population risk for third-degree relatives. This is fairly close to the figures observed for neural tube defects and cleft palate.

Gender predisposition. For most multifactorial disorders males or females have a greater frequency. If the disorder does occur in the less likely gender then there is a greater recurrence risk implying more genes and/or environmental factors are present in that family.

Typical family tree

Multifactorial inheritance



Genetic advice

This is based on *empiric data*. Refer to the individual tables of data for specific conditions.

Several general principles affect the risk.

- **Relationship to the affected individual.** The risk is greatest amongst close relatives and decreases rapidly with increasing distance of relationship (see above).
- **Severity of the disorder in the proband.** The risks to relatives are greater if the proband is severely affected, than if the proband is only mildly affected. The average liability in the siblings of affected individuals will be greater (further right-shifted) in such families (see figure at the end of this article).

- **The number of affected individuals in the family.** If there are two or more close relatives affected, then risks for other relatives are increased. If there are several affected close relatives, the possibility of an autosomal dominant (AD) disorder with incomplete penetrance should be carefully considered.

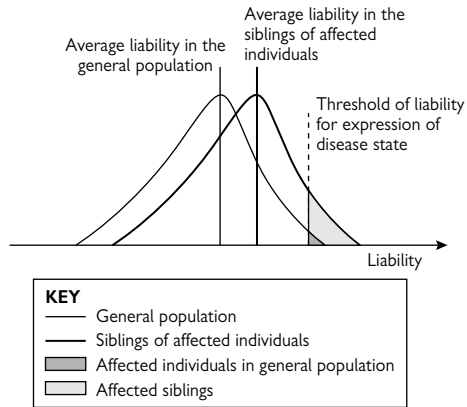


Figure showing the distribution of liability to a multifactorial trait/disease.

Expert adviser: Ian D. Young, Consultant Clinical Geneticist, Leicester, England.

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Reproductive options

After a genetic disorder that has a significant sibling or offspring recurrence risk is diagnosed, many families are faced with a difficult choice about future pregnancies. It may be helpful for them to be introduced to the range of reproductive options available to them for future pregnancies. This is not always easy as such decisions are very personal. It may help to introduce the topic by explaining that some of the choices available may include options that they would not consider choosing.

Accepting the risk of another affected child. For some families this will be their option of choice; for others an option they cannot bear to contemplate.

Electing against further pregnancies. The burden of caring for a child with a severe genetic disorder may be such that the family feel that they do not wish to extend their family because all of their energy is channelled into caring for their existing child(ren).

Adoption. Although this process can be frustrating and lengthy, some couples are successful in locating a baby or child to join their family. (Some couples may choose to adopt another affected child as in achondroplasia and Down syndrome.)

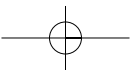
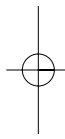
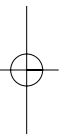
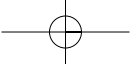
Donor gamete. AID (artificial insemination by donor) is an option that can be used to minimize the risk of recurrence of an autosomal recessive (AR) disorder for which both parents are carriers, or to evade the risk of a dominant disorder present in the father, or the risk of unbalanced products of a balanced translocation present in the father. A donor ovum can also be used to minimize the risk of recurrence of an AR disorder and has the advantage that both parents play a biological role in bringing the baby into the world—technically this is much more demanding and the shortage of donor ova means that, in practice, AID is usually the more pragmatic option. A donor ovum is also an option to avoid the risk of a dominant disorder present in the mother, or a mitochondrial encoded disorder carried by the mother, or the risk of unbalanced products of a balanced translocation present in the mother.

Prenatal diagnosis. For many couples facing a high risk of recurrence for a serious disorder this is the option of choice, but for others (particularly those with religious or moral objections to termination of pregnancy) it is ethically unacceptable. Prenatal diagnosis by chorionic villus sampling (CVS) or amniocentesis is possible for cytogenetic disorders, monogenic disorders in which the pathogenic mutation is known, and the great majority of biochemical disorders. Prenatal diagnosis by ultrasound can be used in many conditions causing major structural malformations.

Pre-implantation genetic diagnosis (PGD). At first sight this seems the most attractive option to many couples. In reality, PGD is only available in a very few specialist centres and for a few severe genetic diseases (predominantly those in which single-cell diagnosis is technically feasible, e.g. fluorescent *in situ* hybridization (FISH)-diagnosable conditions such as chromosome translocations or trisomies, or where there is a commonly occurring mutation such as the exon 7, 8 deletion in spinal muscular atrophy (SMA)). PGD entails ovarian hyperstimulation (and its attendant risks), egg retrieval, *in vitro* fertilization, embryo biopsy, and implantation of screened embryos. For single gene disorders, a pregnancy rate of 21% per egg retrieval and 25% per embryo transfer procedure has been reported. The costs are often prohibitive (e.g. in the UK approximate current costs are £3500 for a first cycle plus the cost of the drugs (£800–£1200)). There are only limited data on safety and there may be unforeseen risks. See 'Assisted reproductive technology: *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), and pre-implantation genetic diagnosis (PGD)' page 568.

Adopt-out or foster-out an affected child. If the family does not feel they can care for another affected child, but also have religious or other objections to contraception and prenatal diagnosis, this option may need to be considered.

Useful websites: British Association for Adoption and Fostering <www.baaf.org.uk>.



Testing for genetic status

The great expansion in the number of disease genes that are cloned and for which mutation analysis is available has led to a growth in the demand for genetic testing.

Genetic testing has some distinct differences from routine clinical investigation.

- The results are permanent for the individual concerned.
- The results may have important implications for other family members, usually offspring, but sometimes siblings or parents.
- Occasionally, some forms of genetic testing, e.g. linkage or testing of parents to confirm carrier status for an autosomal recessive (AR) condition present in the child, may reveal unwanted information about paternity.

These issues need to be carefully thought through before embarking on genetic testing. Particular issues arise with regard to genetic testing of children and monozygotic (MZ) twins and these are discussed further below.

Genetic testing for diagnostic indications

In this situation genetic testing is used as a diagnostic tool, e.g. in a preterm neonate with meconium ileus in whom sweat testing is not feasible molecular genetic testing for cystic fibrosis (CF) may enable a specific diagnosis of CF to be made and appropriate management to be instigated. Similarly, in a young boy presenting with delayed walking and a high creatine kinase (CK) level, genetic testing for Duchenne muscular dystrophy (DMD) may enable a specific diagnosis to be reached without the need to resort to an invasive test (muscle biopsy).

There are very few situations in which this is inappropriate in adults or in children, but those involved in the decision-making should be mindful that it does have genetic as well as therapeutic implications.

Genetic testing to confirm or refine an existing clinical diagnosis

In this situation there is a pre-existing clinical diagnosis and genetic testing serves to confirm and refine the diagnosis (but rarely to alter it). For example, an individual with tall stature, pectus carinatum, dilated aortic root, and dislocated lenses has a clinical diagnosis of Marfan syndrome (MFS). If a fibrillin mutation (*FBN1*) is identified on genetic testing this confirms the clinical diagnosis. For a child with sensorineural deafness diagnosed by audiometry the finding of homozygosity for the del 35G mutation in connexin 26 serves to further refine the clinical diagnosis. In hereditary motor and sensory neuropathies (HMSN) the finding of a duplication of *PMP22* serves to refine the diagnosis from HMSN type 1 to HMSN type 1A. There are very few situations in which this is inappropriate in adults or in children.

Predictive testing for disorders in which clinical management is affected by the test results

Examples of such disorders are familial adenomatous polyposis (FAP) and von Hippel–Lindau syndrome (VHL).

These are disorders where effective screening and/or treatments are available and yet where the burden of screening is sufficiently high that 'at risk' individuals may prefer to determine their risk in order to avoid unnecessary screening.

Testing should be offered in the context of a clinic consultation at which the following are discussed:

- 1 the natural history of the condition;
- 2 the implications of a 'high risk' result;

- 3 the screening programme/treatment available to individuals with a 'high risk' result (usually also available to 'at risk' individuals who elect not to discover their genetic status);
- 4 the possible implications of the test result for other family members;
- 5 the possibility that genetic testing may have implications for financial arrangements (e.g. mortgages, pensions, and insurance)—the patient may wish to take further advice from an independent financial adviser.

If the individual wishes to proceed with genetic testing *written consent* for predictive testing should usually be obtained, the expected time-scale for results should be discussed, and arrangements made for the giving of the results (e.g. letter, phone call, clinic appointment).

Predictive testing for disorders in which clinical management is not affected by the test result

Examples are Huntington disease (HD) and spinocerebellar ataxia (SCA).

Predictive testing for HD is usually only offered as part of a structured programme. There are usually a series of three or more meetings between the individual at risk and a geneticist/genetic counsellor to explore the reasons why they wish to have the test and to discuss possible outcomes and future management. Most programmes follow similar guidelines.

- The predictive programme extends over a period of months and includes a discussion of all points 1–5 raised above. Individuals are free to withdraw at any time.
- A 'supporter' (often a partner or friend) is nominated by the patient who attends all of the clinic visits and makes an ongoing commitment to support the individual undergoing testing.
- If the individual wishes to proceed with genetic testing, *written consent* for predictive testing should be obtained and the expected time-scale for results should be discussed. A clinic visit for the result is usually arranged so that this can be given in person by a member of the team known to the patient. (Alternative arrangements for giving the result may be considered in some circumstances, e.g. letter, phone call.)
- Testing for dominant disorders in individuals at 25% risk (in which the result may reveal the status of an individual in a previous generation) is only undertaken in exceptional cases in which every effort has been made to provide genetic counselling to the individual at 50% risk.
- Testing is not generally undertaken within 6 months of the individual first becoming aware of the diagnosis in the family

Formal programmes are less common for other dominantly inherited disorders for which there is no very effective treatment but, in general, a broadly similar approach is adopted in which individuals are discouraged from making a rushed decision about testing and encouraged to reflect on both the advantages and disadvantages and optimum timing of testing for them as individuals. Generally, this type of testing is not available to children/minors.

Testing for carrier status

Examples are in cases involving cystic fibrosis (CF) or chromosome translocations.

In general, testing for carrier status has potential implications for reproduction but not for the health of the individual being tested. Having explained the reproductive

consequences if the individual is found to be a carrier it is reasonable to arrange testing for adults or younger adults who are able to give consent for themselves (Gillick competent) if this is requested.

Genetic testing of children

The best interests of the child need to direct genetic testing. In general, predictive genetic testing of children is only undertaken when the potential benefit of testing can reasonably be viewed as outweighing the disadvantages of testing (particularly removing the child's autonomy, when more mature, to be involved in decisions affecting his/her own future and the risk of stigmatization). It is usually undertaken when the child is at significant risk for a genetic disorder for which screening is burdensome and effective treatment is possible, e.g. retinoblastoma, FAP, and VHL. Please refer to the websites listed at the end of this section for a thorough discussion of the ethical, legal, and psychological issues.

The principal conclusions from the American Medical Association (1996) policy document are these.

- 1 When a child is at risk for a genetic condition for which preventative or other therapeutic measures are available, genetic testing should be offered or, in some cases, required.
- 2 When a child is at risk for a genetic condition with paediatric onset for which preventive therapeutic measures are not available, parents generally should have discretion to decide whether the child should undergo genetic testing.
- 3 When a child is at risk for a genetic condition with adult onset for which preventive or effective therapeutic measures are not available, genetic testing of children generally should not be performed. Families should still be informed of the existence of tests and given the opportunity to discuss the reasons why the tests are generally not offered for children.
- 4 Genetic testing for carrier status should be deferred until the child either reaches maturity or needs to make reproductive decisions or, in the case of children too immature to make the reproductive decisions, reproductive decisions need to be made for the child.
- 5 Genetic testing of children for the benefit of a family member should not be performed unless testing is necessary to prevent substantial harm to the family member.

Adoption

When a child is being considered for adoption the same guidelines for genetic testing should be followed as for other children.

The American Society of Human Genetics and the American College of Medical Genetics (1995) recommend the following.

- 1 All genetic testing of newborns and children in the adoption process should be consistent with the tests performed on all children of a similar age for the purposes of diagnosis or of identifying appropriate prevention strategies.
- 2 Because the primary justification for genetic testing of any child is a timely medical benefit to the child, genetic testing of newborns and children in the adoption process should be limited to testing for conditions that manifest themselves during childhood or for which preventive measures or therapies may be undertaken during childhood.
- 3 In the adoption process, it is not appropriate to test newborns and children for the purpose of detecting genetic variations of or predispositions to physical, mental, or behavioural traits within the normal range.

Testing for genetic status in MZ twins

Genetic testing of MZ twins raises special ethical issues, particularly with respect to predictive testing. Where possible, try to ascertain that both twins wish to proceed with predictive testing and arrange for them to proceed through the predictive testing process simultaneously (perhaps with parallel consultations). When a diagnostic test is contemplated in one twin, this may potentially be a predictive test for the other twin and that factor needs careful consideration and forethought. Usually, in the rare situation where one twin wishes to proceed with genetic testing and the other does not, the rights of the twin to seek a genetic test for him or herself as an individual will prevail (provided the test in question is part of routinely available health care to which other individuals would normally be entitled).

Paternity

Some genetic tests have the potential to reveal non-paternity. Unless this potential is recognized and discussed in advance of testing, a test result revealing non-paternity raises serious ethical dilemmas. (See Lucassen and Parker (2001) for a thorough discussion of this issue.)

In practice the geneticist should try to foresee situations where tests could potentially disclose non-paternity and include discussion of this topic in the pre-test counselling. Occasionally, unusual genetic mechanisms suggest non-paternity, e.g. *de novo* deletion of the SMN gene in spinal muscular atrophy (SMA), but more thorough analysis reveals parentage to be true.

Examples of genetic tests that may inadvertently reveal misattributed parentage include:

- analysis of triplet repeat size (alleles are often highly polymorphic), e.g. tests for myotonic dystrophy, HD, etc.;
- carrier testing where both mutations have been defined in the affected child;
- linkage-based tests where haplotypes are determined for different family members—when these results are collated discrepancies may be seen.

NB. In all these cases, it is imperative to consider that genetic mutation can also lead to discrepant findings in families.

Useful websites: British Society for Human Genetics 'Testing children' <www.bsng.org>; Canadian Paediatric Society 'Guidelines for genetic testing of healthy children' <www.cps.ca>; American Medical Association 'Testing children for genetic status' <www.ama-assn.org>; The American Society of Human Genetics (ASHG) and the American College of Medical Genetics (ACMG) 'Genetic testing in adoption' <www.faseb.org/genetics/acmg/p01-36.htm>.

Expert adviser: Martin Bobrow, Professor of Medical Genetics, University of Cambridge, Cambridge, England.

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Useful resources

One of the frustrations in writing this handbook has been the brevity with which each topic can be discussed. Whilst this has been necessary in order to try to include the myriad of conditions that may be encountered in a general genetics clinic, we hope that we have included sufficient detail to enable the reader to make progress towards a diagnosis. Once a precise diagnosis is achieved, there is a wealth of sources from which further information can be obtained. Listed below is a selection of sources that we find particularly useful.

General

Books

- Cassidy SB, Allanson JE (eds.). *Management of genetic syndromes*, 2nd edn, Wiley, New York, 2004.
- Harper PS. *Practical genetic counselling*, 6th edn, revised reprint. Arnold, London, 2004.
- Rimoin DL, Connor JM, Pyeritz RE, Korf BR. *Emery and Rimoin's principles and practice of medical genetics*, 4th edn. Churchill Livingstone, Edinburgh, 2002.
- Strachan M, Read AP. *Human molecular genetics*, 3rd edn. Garland Science, Philadelphia, 2003.
- Young ID. *Introduction to risk calculation in genetic counselling*, 2nd edn. Oxford University Press, Oxford, 1999.

Databases/websites

Pubmed <www.ncbi.nlm.nih.gov/PubMed>.

Support groups

- Contact a Family (UK) <www.cafamily.org.uk>.
- National Organization for Rare Disorders (US) <www.raredisease.org>.

Monogenic disorders

Databases/websites

- Ensemble genome browser <www.ensembl.org>.
- Geneclincs <www.geneclincs.org>.
- Genew: Human Gene Nomenclature Database <www.genec1.ac.uk>.
- Online Mendelian Inheritance in Man (OMIM) <www.ncbi.nlm.nih.gov>.
- The Frequency of Inherited Disorders Database (FIDD) <http://archive.uwcm.ac.uk/uwcm/mg/fidd>

Dysmorphology

Books

- Aase JM. *Diagnostic dysmorphology*. Plenum Medical, New York, 1990.
- Epstein CJ, Erickson RP, Wynshaw-Boris A (eds.). *Inborn errors of development—the molecular basis of clinical disorders of morphogenesis*. Oxford University Press, Oxford, 2004.
- Gorlin RJ, Cohen MM, Hennekam RCM (eds.). *Syndromes of the head and neck*, 4th edn. Oxford University Press, Oxford, 1990.
- Hall JG, Froster-Iskenius I, Allanson J. *Handbook of physical measurement*. Oxford University Press, Oxford, 1989.
- Jones KL (ed.). *Smith's recognizable patterns of human malformations*, 5th edn. W.B. Saunders, Philadelphia, 1997.
- Sadler TW. *Langman's medical embryology*, 8th edn. Lippincott Williams & Wilkins, Philadelphia, 2000.
- Stevenson RE, Hall JG, Goodman RM (eds.). *Human malformations and related anomalies*. Oxford University Press, Oxford, 2003.

Databases/websites

- POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations) version 5.5 Melbourne: The Murdoch Research Institute, 2001 <www.possum.net.au>.
- Winter RM, Baraitser M (eds.) London Dysmorphology Database 2003 <www.1mdatabases.com>.

Chromosomes

Book

- Gardner RJM, Sutherland GR. *Chromosome abnormalities and genetic counselling*, Oxford Monographs on Medical Genetics no. 31, 3rd edn. Oxford University Press, New York, 2004.

Databases/websites

- Schinzel A. *Human cytogenetic database and catalogue of chromosome aberrations in man*, 2nd edn. Oxford University Press, Oxford, 2004.

Cancer

Book

- Hodgson SV, Maher ER. *A practical guide to human cancer genetics*, 2nd edn. Cambridge University Press, Cambridge, 1999.

Neurogenetics

Books

- Baraitser M. *The genetics of neurological disorders*, 3rd edn, Oxford Monographs on Medical Genetics no. 34. Oxford University Press, Oxford, 1997.
- Dubowitz V. *Muscle disorders in childhood*, 2nd edn. W.B. Saunders, Philadelphia, 2000.

Databases/websites

- Baraitser M, Winter R. London Neurogenetics Database (CD). European Neuro Muscular Centre <www.enmc.org>.

Skin

Book

- Sybert V. *Genetic skin disorders*, Oxford Monographs on Medical Genetics no. 33. Oxford University Press, Oxford, 1997.

Ear

Book

- Toriello HV, Reardon W, Gorlin RJ. *Hereditary hearing loss and its syndromes*, 2nd edn, Oxford Monographs on Medical Genetics. Oxford University Press, New York, 2004.

Eye

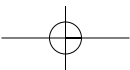
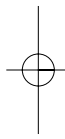
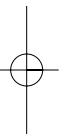
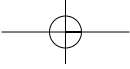
Books

- Moore, A (ed.). *Paediatric ophthalmology*, Fundamentals of Clinical Ophthalmology Series. BMJ Books, London, 2000.
- Traboulsi EI (ed.). *Genetic diseases of the eye*, Oxford Monographs on Medical Genetics. Oxford University Press, New York, 1999.

Metabolic

Books

- Clarke JTR. *A clinical guide to inherited metabolic diseases*, 2nd edn. Cambridge University Press, Cambridge, 2002.
- Scriver CR, Beaudet AL, Sly WS, Valle D (eds.). *The metabolic and molecular bases of inherited disease*, 8th edn. McGraw-Hill, New York, 2001.



X-linked dominant (XLD) inheritance

XLD disorders are encoded on the X chromosome. An XLD disorder manifests very severely in males, often leading to spontaneous loss or neonatal death of affected male pregnancies. Typical examples include incontinentia pigmenti (IP) due to mutations in *NEMO*, Rett syndrome due to mutations in *MECP2*, oral-facial-digital syndrome type 1 (OFD-1) due to mutations in *CXORF5*, and otopalatodigital syndrome types 1 and 2 (OPD-1 and OPD-2) due to mutations in *FMNA* (filamin A).

An **X-linked semi-dominant disorder** manifests severely in males who are hemizygotes, and mildly or sub-clinically in females who have two X chromosomes (one normal and one mutated copy). Examples include Coffin-Lowry syndrome and X-linked hereditary motor and sensory neuropathy (X-HMSN) where a proportion of heterozygotes manifests features of the disorder. Where the disorder manifests only infrequently or not at all in heterozygotes it is said to follow X-linked recessive (XLR) inheritance (see the eponymous section, page 34).

Recombination between the X and Y chromosomes is limited to the **pseudoautosomal region (PAR)** and is necessary for proper segregation of the sex chromosomes during spermatogenesis. Cross-over between the sex chromosomes during male meiosis is restricted to the terminal pseudoautosomal pairing regions PAR1, a 2.6 Mb region on Xp/Yp, and PAR2, a 320 kb region on Xq/Yq. Genes in the PARs escape X-inactivation and exhibit pseudoautosomal inheritance. Genes encoded in PAR1 include *SHOX* which has an important role in growth. Under normal circumstances, the *SHOX* genes on both Xpters of a female are active, as are the *SHOX* genes on Xpter and Ypter in a male and hence the severity of the phenotype is not sex-dependent. Mutations in *SHOX* therefore show **pseudo-autosomal inheritance** rather than X-linked semi-dominant inheritance. Deletions or mutations causing haploinsufficiency of *SHOX* are a common cause of idiopathic short stature (4/56 cases ie ~7% in Morizio's series) and also cause Leri-Weill syndrome. Individuals homozygous for the deletion or homozygous or compound heterozygotes for inactivating mutations have the more severe Langer mesomelic dysplasia.

Aspects of X-linked dominant inheritance

Skewed X-inactivation. If there is complete skewing, the ratio is 100:0; often an intermediate value is found. Values <80:20 fall within values expected from normal variation in X-inactivation patterns in the general population; values >80:20 are suggestive of X-inactivation due to a selection bias due to a deleterious X-linked recessive (XLR) mutation, but are seen in ~9% of normal females (see 'X-linked recessive inheritance', page 34). This selection bias may not operate equally in all tissues and so variable degrees of skewing may be observed in different tissues.

Degree of manifestation in heterozygotes. Unfavourable skewing of X-inactivation in key tissues may be a major factor in determining the expression of an XLD disorder in heterozygotes. Skewing towards the X without the mutation may result in minimal features and it may not be clinically recognized that the individual is a heterozygote (and recurrence may be attributed erroneously to germline mosaicism).

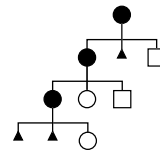
Distribution of features in heterozygotes. The distribution of features in a female is a reflection of the X-inactivation pattern in specific tissues. Asymmetry is an

important feature and this is well illustrated in X-linked chondrodysplasia punctata (XLCDP) where the limbs are shortened but not symmetrically. The skin lesions of IP are streaky and may follow the lines of Blaschko.

Germline mosaicism. As with XLR disorders, the risk of germline mosaicism needs to be considered. For example, in Rett syndrome it is recommended that mothers and sisters of affected girls are tested for an *MECP2* mutation identified in the proband.

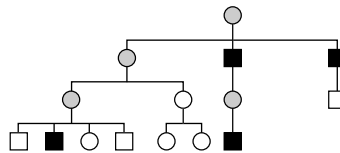
Typical family trees

X-linked dominant inheritance



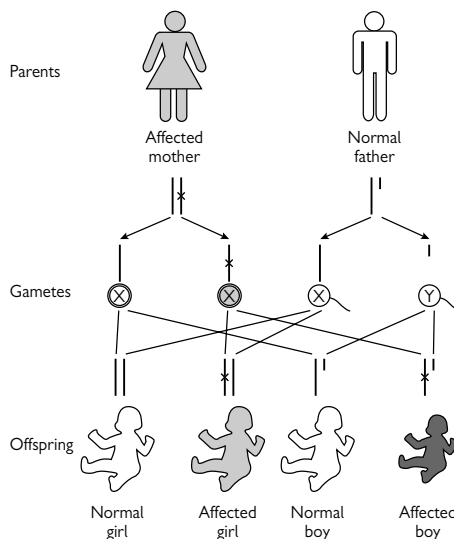
A typical family tree showing X-linked dominant inheritance. The condition is manifest in female heterozygotes and male hemizygotes. Many of these conditions cause spontaneous loss of affected male pregnancies.

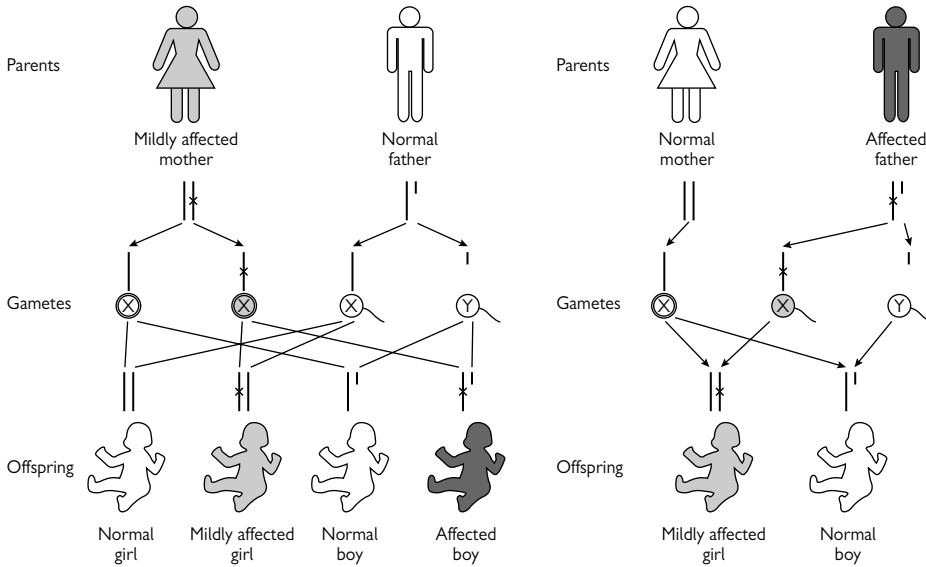
X-linked semi-dominant inheritance



A typical family tree showing X-linked semi-dominant inheritance. The condition is expressed severely in males and mildly in females. For a mildly affected female, on average, 50% of her sons will be severely affected and 50% of her daughters will be mildly affected. Daughters of an affected male are mildly affected and none of his sons inherit the condition.

X-linked dominant inheritance



X-linked semi-dominant inheritance**Genetic advice**

- Males carrying the mutation are severely affected, often leading to spontaneous loss or neonatal death of affected male pregnancies in XLD conditions.
- Female heterozygotes are affected but have less severe features than males.
- The degree to which females express the disorder is largely governed by X-inactivation patterns.
- When a heterozygous affected female has a pregnancy there are four genetic possibilities at conception, each equally likely. These are: a normal daughter; an affected daughter; a normal son; and a severely affected son, e.g. X-linked hypophosphatasia (vitamin-D resistant rickets) where affected males are viable. For many XLD disorders, e.g. IP, affected males are typically lost in early pregnancy so at birth there are three possibilities: a normal daughter; an affected daughter; a normal son.
- When an affected male has a child, all of his daughters will inherit the mutation and none of his sons will be affected.
- The family tree shows no male-to-male transmission.
- If the mother of an affected female with a presumed *de novo* mutation does not herself carry the mutation in her blood, female siblings of the proband should still be offered carrier testing by mutation detection because of the small possibility of germline mosaicism in the parent.

- Males who are born with features of a severe and normally lethal XLD condition should have a karyotype to exclude Klinefelter syndrome.
- Females with unusually severe features of an XLD or an X-linked semi-dominant disorder may have this as a consequence of:
 - highly unfavourably skewed X-inactivation;
 - Turner syndrome, where the girl is a hemizygote;
 - X-autosome translocation.

Hence a karyotype is indicated in these circumstances.

Expert adviser: Ian D. Young, Consultant Clinical Geneticist, Leicester, England.

References

- Morizio E, Stuppia L *et al.* Deletion of the SHOX gene in patients with short stature of unknown cause. *Am J Med Genet A* 2003; **119**: 293–96.
- Shears DJ, Guillen-Navaro E, *et al.* Pseudodominant inheritance of Langer mesomelic dysplasia caused by a SHOX homeobox missense mutation. *Am J Med Genet* 2002; **110**: 153–7.
- Shi Q, Spriggs E, *et al.* Recombination between the X and Y chromosomes is limited to the pseudoautosomal region and is necessary for proper segregation of the sex chromosomes during spermatogenesis. *Am J Hum Genet* 2002; **71**: 254–61.
- Strachan T, Read AP. *Human molecular genetics*, 3rd edn. Garland Science, Philadelphia, 2003.
- Young ID. *Introduction to risk calculation in genetic counselling*, 2nd edn. Oxford University Press, 1999.

X-linked recessive (XLR) inheritance

XLR disorders are encoded on the X chromosome. An XLR disorder manifests in males who are hemizygotes, but generally not in carrier females who have two X chromosomes (one normal and one mutated copy). Some X-linked disorders are almost never expressed in females, e.g. alpha-thalassaemia/mental retardation syndrome (ATRX). In some disorders females have symptoms infrequently, e.g. Duchenne muscular dystrophy (DMD)/Becker muscular dystrophy (BMD), whereas for others, e.g. X-linked hereditary motor and sensory neuropathy (X-HMSN) and fragile X syndrome (FRAXA), manifestation in female carriers is fairly common but is usually less severe than in affected males. Disorders in which heterozygotes commonly manifest, e.g. X-HMSN and Coffin–Lowry syndrome, may be said to follow **X-linked semi-dominant inheritance** (see 'X-linked dominant (XLD) inheritance', page 32).

X-inactivation is the process by which dosage compensation of X-linked genes in females is achieved by the transcriptional silencing of one of the two X chromosomes during early development (from day 9 post-fertilization when the inner cell mass of the blastocyst contains 64 cells). As a result of X-inactivation heterozygous females are mosaic for X-linked gene expression, with one population of cells expressing genes from the maternal X chromosome and the other population expressing genes from the paternal X chromosome (Nance 1964). The early events in X-inactivation are under the control of the X-chromosome inactivation centre (Xic). The *XIST* gene in the Xic at Xq13.2 is the only gene transcribed exclusively from the inactive X-chromosome and is known to play an essential role in the initiation of X-inactivation. Initiation of X-inactivation involves a counting step in which the number of X chromosomes in the cell is counted relative to cell ploidy so that only a single X chromosome is functional per diploid adult cell.

X-inactivation pattern	Frequency (%) of skewed X-inactivation in normal female controls (Plenge et al. 1999)
≥90:10	3
≥80:20	9
≥70:30	30

X inactivation in the embryo is a random process, with ~50% of cells containing the maternal X inactive and ~50% of cells containing the paternal X inactive. Significant deviation from a 50:50 inactivation pattern is occasionally observed among normal females in the population, a phenomenon referred to as **skewed X-inactivation** (see table). Skewing of X-inactivation is a feature of some X-linked disorders. In extra-embryonic tissues, e.g. placenta, there is imprinted inactivation of the paternal X-chromosome.

X-inactivation patterns may be assessed by comparing the ratio of the two alleles at a highly polymorphic site, e.g. the CA repeat in the androgen receptor gene, in a non-methylation-sensitive assay with the ratio of the same alleles in a methylation-sensitive assay. Usually the ratio approximates to 50%.

Aspects of XLR inheritance

Skewed X-inactivation. If there is complete skewing, the ratio is 100:0; often an intermediate value is found.

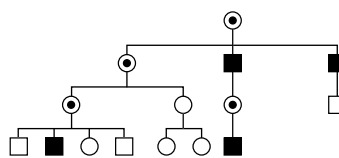
Values <80:20 fall within values expected from normal variation in X-inactivation patterns in the general population; values >80:20 are suggestive of X-inactivation due to a selection bias due to a deleterious XLR mutation, but are seen in ~9% of normal females (see above). This selection bias may not operate equally in all tissues and so variable degrees of skewing may be observed in different tissues. Maternal X-inactivation skewing may be used to suggest that a sporadic affected male has an X-linked disorder.

Manifesting carriers. Unfavourable skewing of X-inactivation in key tissues may be a major factor in determining whether or not an XLR disorder is expressed in heterozygotes. As noted above, the penetrance in heterozygotes shows wide variation between different XLR disorders.

Germline mosaicism. A number of XLR disorders have substantial germline mosaicism risks—most notably DMD/BMD. For the mother of an affected boy with a known mutation that is not present in the mother's genomic DNA, there is a suggested 1 in 5 (20%) risk to a future son who inherits the same X chromosome as his affected brother (i.e. there is an overall 5% risk to future pregnancies). For androgen insensitivity syndrome (AIS) this risk is much smaller, but nevertheless germline mosaicism has been observed.

Typical family tree

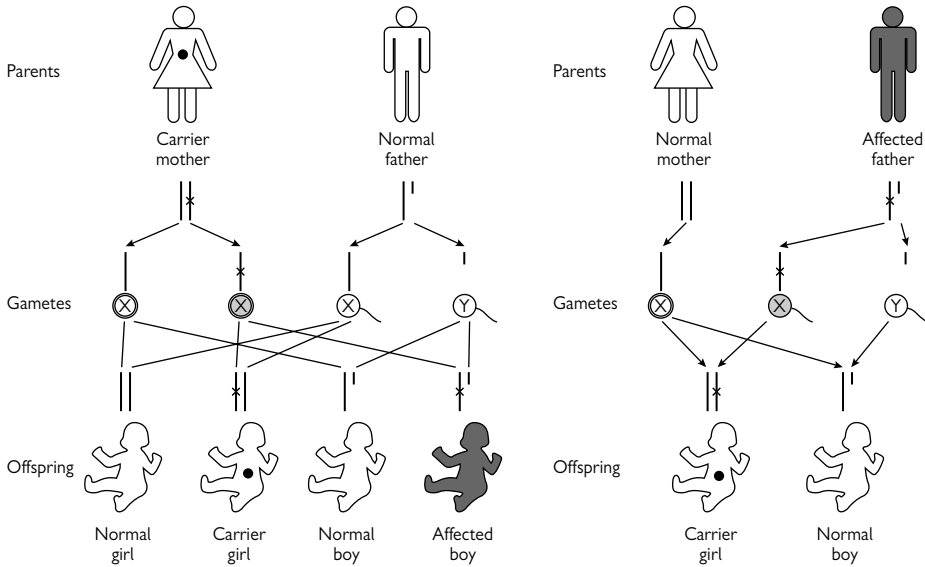
X-linked recessive inheritance



A typical family tree showing X-linked recessive inheritance. The condition is expressed in males, but not in females. For a carrier female, on average, 50% of her sons will be affected and 50% of her daughters will be carriers. All daughters of an affected male are obligate carriers and none of his sons inherit the condition.

Genetic advice

- Males carrying the mutation are severely affected; females carrying the mutation are generally either unaffected or more mildly affected than males.
- The degree to which females express the disorder is largely governed by X-inactivation patterns.
- When a carrier female has a pregnancy there are four possible outcomes, each equally likely. These are: a normal daughter; a carrier daughter; a normal son; an affected son. Another way of expressing this is that in a female pregnancy there is a 50% chance of a carrier daughter; in a male pregnancy there is a 50% chance of an affected son.
- When an affected male fathers a pregnancy, all of his daughters will be carriers and none of his sons will be affected.
- The family tree shows no male-to-male transmission.
- Even if the proband is the only affected member, it is generally more likely that the mother is a carrier than that the proband has the condition as the result of a *de novo* mutation. For XLR conditions where reproductive fitness is zero, there is a two-thirds chance that the mother is a mutation carrier and a one-third chance that the mutation is *de novo* for an apparently sporadic case.

X-linked recessive inheritance

- If the mother of a sporadic case with a presumed *de novo* mutation does not herself carry the mutation in her blood, female siblings of the proband should still be offered carrier testing by mutation detection because of the small possibility of germline mosaicism in the mother.
- Females with unusually severe features of an XLR disorder may have this as a consequence of:
 - highly unfavourably skewed X-inactivation;
 - Turner syndrome, where the girl is a hemizygote;
 - X-autosome translocation.
 Hence a karyotype is indicated in these circumstances.

Expert adviser: Ian D. Young, Consultant Clinical Geneticist, Leicester, England.

References

- Nance WE. Genetic tests with a sex-linked marker: glucose-6-phosphate dehydrogenase. *Cold Spring Harbor Symp Quant Biol* 1964; **29**: 415–52.
- Plenge RM, Tranebjaerg L, et al. Evidence that mutations in the X-linked DDP gene cause incompletely penetrant and variable skewed X inactivation. *Am J Hum Genet* 1999; **64**: 759–67.
- Strachan T, Read AP. *Human molecular genetics*, 3rd edn. Garland Science, Philadelphia, 2003.
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