

Genetic counselling

Genetic counselling is the process of advising individuals and families affected by or at risk of genetic disorders to help them understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. Genetic counselling may be described as the process through which individuals affected by, or at risk for a problem which may be genetic or hereditary, are informed of the consequences of the disorder, of the probability of suffering from or of transmitting it to their offspring, and of the potential means of treating or of avoiding the occurrence of the malformation or disease in question. Genetic counselling in common disorders is often given by the family doctor, the paediatrician or the obstetrician. However, with the recognition that thousands of problems have a major hereditary component, counselling is increasingly done in specialized centers which also provide the laboratory diagnostic tools which we hear so much about in our era.

Some 2-3% of infants are born with congenital malformations, the majority of which have at least a partially genetic basis. And if one considers the causes of illness in persons up to the age of 25 years or so, at least 5% of all individuals will suffer by adulthood from a malformation or disease with a major genetic component. (Baird et al., 1988). Thus, the comprehension and control of genetic disorders is, particularly with regard to the decline in mortality and morbidity from infectious disease, a major public health concern.

Four aspects are involved in giving genetic counselling:

1. *Arriving at a specific diagnosis:* this is often the most difficult, trying and time consuming part of the process, for the health care professionals as well as for the family (who are understandably more concerned with the care of their affected relative, than with the specific name of his or her disorder). However, without a correct diagnosis, counselling is at best incomplete and imprecise.
2. *Estimation of risks:* to develop the disorder and/or to transmit it to offspring.
3. *Practical aid:* this includes, for example, recommending doctors for specialized examinations or health care professionals for speech or educational therapy. It often implies as well the coordination of prenatal and other diagnostic tests.
4. *Supportive role:* this aspect is at least as important as the diagnostic question, for the great majority of genetic disorders cannot be cured or even satisfactorily treated. Although the genetic counselor cannot provide support for the family on a daily basis, he or she should be able to orient them towards those health professionals who can best serve them in this role. Accepting and learning to live with a genetic diagnosis is particularly difficult when

reproductive options are involved, and feelings of " guilt " may touch several generations and cause rifts in the family just at the time when solidarity is most needed.

Types of genetic disorders:

"Genetic" does not necessarily mean "hereditary". The first term implies simply that the genetic material, on a chromosomal or a gene level, contains one or more mutations which are the cause of the disorder. Once a mutation is present in a patient, particularly if it is constitutional (and thus present in all cells), it can of course be transmitted and thus becomes a hereditary disorder.

Genetic disorders are generally of four types:

1. *Chromosomal disorders*: affect some 1/200 live-born children (Robinson & Puck, 1967), and about 1/500 adults. Abnormalities of chromosome *number* are rarely inherited, although affected individuals who reproduce may transmit the extra chromosome to their offspring. Structural abnormalities, such as translocations in which two chromosomes exchange segments, may cause little or no effect in carriers, but predispose to reproductive problems such as miscarriage and infertility.
2. *Monogenic ("Mendelian") inheritance*: is the result of mutations in single genes, at specific gene "loci" We have some 50-100,000 individual genes, for several thousand of which monogenic disease has been described (McKusick, 1992). Some 1/300 individuals will suffer from a monogenic disease manifesting within the first two decades (Baird et al., 1988), but this figure may be as high as 1% if the lifetime probability of manifesting a monogenic disorder is considered. Four types of transmission are observed in monogenic disorders caused by nuclear genes: *autosomal dominant* (one mutated gene of the pair is sufficient to produce symptoms), *autosomal recessive* (the two alleles must be abnormal to cause the phenotype) and *X-linked*, which includes *recessive* (theoretically, only males suffer, given that they are " hemizygous " for the X chromosome) and, less frequently, *X-linked dominant* gene mutations (males more seriously affected than females). A few genes, involved particularly in sex determination and fertility, have been localized on the Y chromosome, the transmission of which is only from a father to his XY offspring.
3. *Polygenic or " multifactorial "*: although this causation is not " as genetic " as are monogenic and chromosomal disorders, the majority of malformations and of common familial disorders have this type of cause. Polygenic implies that the association of several different genes, each one slightly modified, is necessary to produce the disorder. Multifactorial causation means that both genetic and non-genetic (environmental, either pre- or postnatal) factors are associated to produce the pathology. Some 5-10% of the population will suffer either from a malformation or from a disease in which genetic factors are major.

4. *Mitochondrial disorders*: In recent years a "new" type of inheritance has been proven, that resulting from mutations in the mitochondrial genome. Each cell contains hundreds or thousands of mitochondria, each containing one or several circular chromosomes. These chromosomes can be deleted or suffer other types of mutations which interfere with cellular production of ATP, and thus of the energy vital for the cell/organ/organism; the symptoms depend on the tissues involved and on the proportion of mitochondria mutated, but involve first the central nervous system and the muscle, due to their large energy demands (Morris, 1990; Wallace, 1993). The incidence of mitochondrial mutations in human disease is still unknown. In many cases the mutation is "de novo" in an affected individual, but hereditary transmission is purely *maternal*, since, a fertilized egg's mitochondria originate from the maternal germ cell only.

Who seeks genetic counselling?

In most genetics divisions patients can either come self-referred or be recommended by a physician. Currently, genetics has not evolved to a state of knowledge where couples come for "genetic screening" without a specific family history or increased risk for a genetic disorder for another reason. The day will probably come in the not too distant future when preconceptional or prenatal screening can be offered to the general population for a panel of different diseases. However, for the moment only several dozen of our 50,000-100,000 individual genes have been identified and their mutations defined. Testing for any one of these requires both technical competence and a considerable investment of time and money. The reasons for seeking genetic counselling can be divided into the following six categories:

1. *The individual (often hoping to be a parent) suffers himself form a genetic or potentially genetic disease.* This may be a (relatively unsevere) chromosomal disorder, a single gene condition (transmitted in a dominant, recessive or X-linked manner), or a "multifactorial" disorder, e.g. implying the combined effects of a genetic predisposition and unfavourable environmental factors (for example, diabetes or epilepsy).
2. *A close relative has a genetic disease,* and the individual who consults is worried either about his/her owns risk of developing the disease, or the risk that his offspring will suffer from the disorder.
3. *The individual is at increased genetic risk for a specific genetic disorder given his or her particular ethnic origin.* Each population has one or more genetic diseases, generally transmitted as autosomal recessive traits, which are particularly frequent within it, e.g. cystic fibrosis in white Europeans and sickle cell anaemia in Africans and Mediterranean populations. A similar situation may apply to couples who are *consanguineous* (blood

relatives), although there is no way of determining which specific genes or diseases are implied, unless this is indicated by a positive family history for a particular disorder.

4. *The individual or couple is having reproductive problems, e.g. infertility, repeated miscarriage, etc.* Such problems may have genetic, particularly chromosomal causes. The individual may be initially referred for a laboratory diagnostic test, with counselling differing markedly depending on the result of the analyses.
5. *The couple has already born a child or foetus with a malformation or genetic disorder.* In this situation the specific diagnosis may be known or not, and the risk of recurrence vary from less than 1% up to 50%.
6. *The couple requests counselling, concerning prenatal diagnosis, for such reasons as advanced parental ages.* Amniocentesis or chorionicentesis should be offered to women of 35 years and older, given their increased risk of bearing a child with a chromosomal anomaly. Counselling sessions for older parents, or for those requesting prenatal diagnosis because of anxiety (close contact with a handicapped individual, for example) are intended to provide information concerning the benefits and risks inherent to prenatal diagnostic techniques.

In all these situations, genetic counselling should be, in so far as is possible, impartial and nondirective. The goal is never to make a decision *for* the couple, whose familial, social, moral and religious situation is *different* from that of the counselor, but rather to provide them with the objective information which will allow them to make their own informed decisions.

What information is sought in genetic counselling?

Unless a *specific diagnosis* has already been proven, the first and foremost concern is to establish, if at all possible, the identity of the disorder. If and when this is done, the geneticist must often review the literature, as well as count on his own experience, in order to inform consultants as precisely as possible of the *etiology* of the problem. Of primary concern to the family is of course the *natural history of the genetic disease*, which includes prognosis and discussion of *potential treatments* and of practical guidelines in how to deal with these. Even if not an initial concern for those seeking counselling concerning a child recently born, the question of *recurrence risks* must be rapidly discussed, as well as possibilities for *prenatal diagnosis* if such is desired by the family. This in itself is often a difficult task, as necessary information about a particular disorder or diagnostic technique may be sparse, and couples may directly ask what the counselor for directive advice.

Steps of genetic counselling:

From the geneticist's point of view, and in order to more efficiently counsel a given family, it is preferable to obtain and review medical documents in advance, as well as to review recent literature

on the problem to be treated. Once a family arrives in the genetic clinic, the steps to be taken, depending on whether the specific diagnosis is established, can be summarized as follows:

1. *Obtaining a detailed family history*, which includes both sides of the family even if counselling has been requested for a dominant disorder affecting one parent. It is not rare that in taking such a history, other antecedents are revealed which also merit discussion.
2. *A review of medical and/ or pregnancy histories* is especially important when the diagnosis is not yet established, but also helps geneticists to learn more about etiologies and natural histories of certain disorders.
3. *A physical examination*, of the affected person, and sometimes of other family members, is often needed.
4. *Medical and/or laboratory exams* may be suggested. If a diagnosis has not been established these often include chromosome study, and may necessitate DNA analysis if the identity of the gene suspected to be involved is known. Other frequent suggestions include X-ray or ultrasound examinations, and various biochemical analyses. Once the diagnosis is known, medical tests aimed at evaluating health risks linked to the disorder may also be established.
5. *Genetic counselling* can only be given at the end of this process.

The process of genetic counselling has changed dramatically over the past 25 years. Instead of being based on purely clinical findings, the identity of many disorders can be proven because their genic or chromosomal basis is known. The availability of an ever-increasing number of laboratory tests allows more accurate diagnosis, and often gives the opportunity for pre-symptomatic or prenatal diagnosis to family members who prefer to use it. However, it must not be overlooked that the availability of such tests also poses psychological and ethical questions which are difficult to resolve. A sub-speciality of medical genetics has thus evolved which examines the individual's and the society's means and ways of resolving such questions (Wertz and Fletcher, 1989).

The training of individuals competent to give genetic counselling has been formalized in a number of European countries, as was done in the United States and Canada a number of years ago through their respective Boards of Medical Genetics. Medical doctors with post-graduate training in medical genetics depend heavily on cytogeneticists and molecular geneticists for diagnosis, as well as, increasingly, on genetics "associates" (master's degree geneticists and nurse specialists) and Ph.D. medical geneticists to help both with the initial work-up and with follow-up of families. As genetics has become a bona fide speciality in itself, with training programs developing for health professionals at various levels. Most training is done in university medical genetics departments.

Services offered by genetics centers:

To provide both, diagnostic counselling and follow-up services, close ties must be established with such hospital departments as paediatrics and obstetrics and access to specialized diagnostic services and to medical library facilities is essential. However, a number of services are best offered within one unit:

1. Clinical diagnosis and genetic counselling.
2. Chromosomal analysis: both postnatal and prenatal diagnostics.
3. DNA extraction and banking.
4. DNA analysis.
5. Prenatal diagnostic services.

Prenatal genetics

Prenatal genetics involves services for women either during or prior to a pregnancy.

General indications for referral to genetic counselling in the preconception or prenatal setting may include, but are not limited to.^[57]

- Advanced maternal age (35 years old or older at time of delivery)
- Advanced paternal age
- Current pregnancy with anomalies identified by ultrasound (e.g. increased nuchal translucency measurements)
- Current pregnancy with an abnormal genetic screening test or test result
- Current pregnancy with risk of or concern for maternal exposures, such as medications, radiation, drugs/alcohol, or infections
- Consanguineous union (cousins or otherwise blood related)
- Family history of an inherited genetic condition or chromosome abnormality
- Genetic carrier screening for recessive and/or X-linked diseases
- History of a previous child with a birth defect, developmental delay, or other genetic condition
- History of infertility, multiple unexplained miscarriages or cases of unexplained infant deaths
- Molecular test for single gene disorder

Prenatal genetic counselling may help with the decision-making process by walking patients through examples of what some people might do in similar situations, and their rationale for choosing that option. Decisions made by patients are affected by factors including timing, accuracy of information provided by tests, and risk and benefits of the tests. This discussion enables patients to place the information and circumstances into the context of their own lives, and in the context of their own values.^[74] They may choose to undergo non-invasive screening (e.g. ultrasound, triple screen, cell-free foetal DNA screening) or invasive diagnostic testing (amniocentesis or chorionic villus sampling).

Invasive diagnostic tests possess a small risk of miscarriage (1–2%) but provide more definitive results. Testing is offered to provide a definitive answer regarding the presence of a certain genetic condition or chromosomal abnormality.

Short Note:

Amniocentesis:

During pregnancy, the fetus is surrounded by amniotic fluid, a substance much like water. Amniotic fluid contains live fetal cells and other substances, such as alpha-fetoprotein (AFP). These substances provide important information about your baby's health before birth.

Amniocentesis is a prenatal test in which a small amount of amniotic fluid is removed from the sac surrounding the fetus for testing. The sample of amniotic fluid (less than one ounce) is removed through a fine needle inserted into the uterus through the abdomen, under ultrasound guidance. The fluid is then sent to a laboratory for analysis. Different tests can be performed on a sample of amniotic fluid, depending on the genetic risk and indication for the test.

Amniocentesis does not detect all birth defects, but it can be used to detect the following conditions if the parents have a significant genetic risk:

- Down syndrome
- Sickle cell disease
- Cystic fibrosis
- Muscular dystrophy
- Tay-Sachs and similar diseases

Amniocentesis can detect certain neural tube defects (diseases where the brain and spinal column don't develop properly), such as spina bifida and anencephaly.

Because ultrasound is performed at the time of amniocentesis, it may detect birth defects that are not detected by amniocentesis (such as cleft palate, cleft lip, club foot, or heart defects). There are some birth defects, however, that will not be detected by either amniocentesis or ultrasound.

If you are having an amniocentesis, you may ask to find out the baby's sex; amniocentesis is the most accurate way to determine the baby's gender before birth. However, you may already know the baby's gender from an earlier ultrasound or genetic test.

