

B. Genetic counseling and prenatal diagnosis

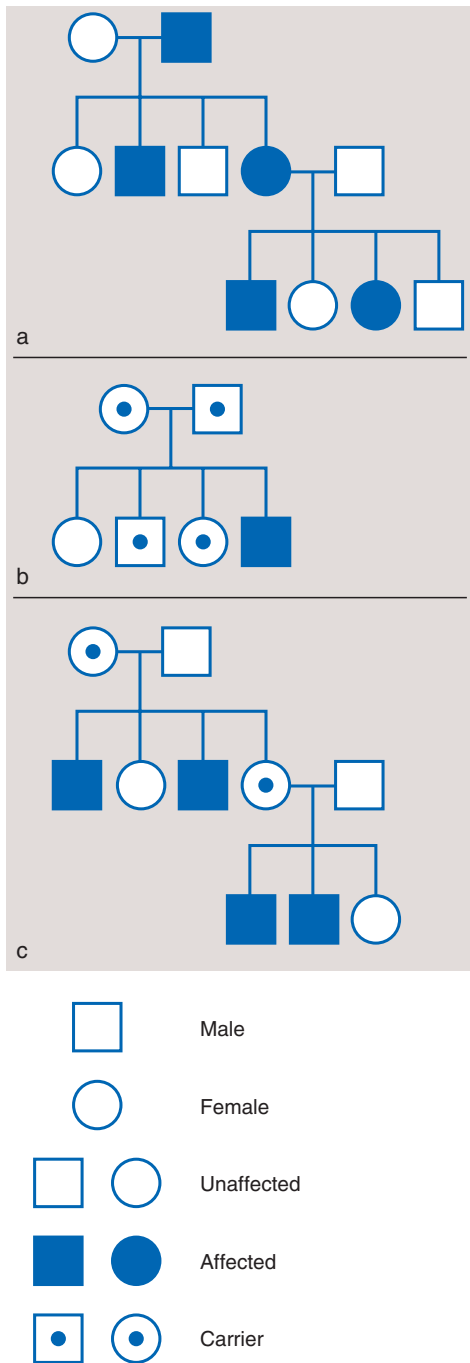


Fig. 29.1 Examples of inheritance patterns.
 a: Autosomal dominant inheritance (AD). b: Autosomal recessive inheritance (AR). c: X-linked recessive inheritance (XR).

Outline

- Genetic counseling is important in dermatological practice. Estimation of genetic risks requires accuracy.
- Prenatal diagnosis (PND) may be chosen for severe genodermatoses. It is essential that PND be based on ethical considerations.

1. Genetic counseling

Genetic counseling is the process whereby a patient or family receives advice on the prognosis of a disease, the risk of occurrence, inheritance, prevention and treatment.

Such counseling was first introduced in the U.S. and Europe in the 1940s. Because neither carrier diagnosis nor fetal diagnosis was possible at that time, the recipients of the counseling used to have only two choices: terminate the pregnancy, or accept the risks of continuing it. Recent advances in molecular biology, clarification of responsible genes for genodermatoses, and technical improvements have made it possible to perform PND on carriers and fetuses. Accordingly, the process and details of genetic counseling have been greatly changing.

For genetic counseling, accurate diagnosis of the disease is essential. Careful family history-taking, physical examinations, and evaluation of inheritance patterns are necessary, and the penetration rate of the disease should be discussed thoroughly each case (Fig. 29.1).

2. Estimation of genetic risk

Newborns with relatively severe inherited disorders account for approximately 2% of all pregnancies. A pregnancy with 10% or greater risk of severe genetic abnormality is considered highly risky.

Estimating genetic risk, i.e., the risk of a fetus being affected by a genetic disease, is one of the most important parts of genetic counseling. Monogenic diseases are caused by abnormality in a single gene and are inherited as Mendel's law of segregations. Genetic risk can be estimated mathematically as a probability of severe genetic abnormality. Autosomal dominant, recessive and X-linked inheritance are monogenic inheritances.

In multifactorial diseases and many cases of congenital or chromosomal abnormality, the risk calculated statistically based on family history is used (empirical genetic risk). However, it is impossible to accurately calculate genetic risk in many cases.

3. Prenatal diagnosis and its ethics ★

Prenatal diagnosis (PND) and medical genetics have a long history of association and improvement. In the 1970s, diagnosis based on amniotic fluid played a central role in PND. Then diagnosis of metabolic anomaly from cultured cells collected from amniotic fluid became possible. In the 1980s, improvements in ultrasonography made it possible to perform villus sampling and fetal tissue biopsy of skin and other fetal materials for PND.

Before PND became common, some patients and parents whose first child had been affected with a genetic disease would choose to terminate the pregnancy. For example, if a child with an autosomal recessive inherited disease was born to healthy parents, it was clear that the parents were carriers of the disease. In this case, the risk of the second child being affected by the same disease would be 25%. Many parents were afraid of those odds, choosing to terminate the pregnancy after long suffering (Fig. 29.2).

In cases with a PND that does identify a fetus as being affected by a genetic disease, the parents are likely to terminate the pregnancy. This means PND can influence life-or-death choices. For this reason, the decision of whether PND should be conducted should be carefully justified. It is necessary for the hospital ethics committee to discuss the appropriateness of PND in each case. The final decision regarding the confirmation of pregnancy should be left to the parents.

Of the numerous genetic skin diseases, the only ones for which PND is indicated are those severe enough to cause serious morbidity or mortality. Providing accurate and proper PND to clients is an important part of dermatology. The genetic skin diseases for which PND is common include severe subtypes of epidermolysis bullosa and ichthyosis (particularly harlequin ichthyosis).

4. Prenatal diagnosis in practice

When the clients are considering whether to terminate a pregnancy, PND must be made by the 21st week of pregnancy so that artificial abortion can be performed as early as possible to reduce the physical and emotional burden on the parents. DNA-based PND is widely used in the early stages of pregnancy, in the 10th to 14th week.

PND of genodermatoses used to be conducted by fetal skin biopsy in the 19th week of pregnancy in most cases. When genetic mutation has been identified in a family, PND is now commonly made from fetal DNA, which is possible in the earlier stages of pregnancy.

Common techniques for sampling fetal DNA are chorionic villus sampling, which can be performed from the 10th week of pregnancy onward, and amniocentesis, which is possible from the 13th week onward. It is essential to enlist the cooperation of a skilled gynecologist.

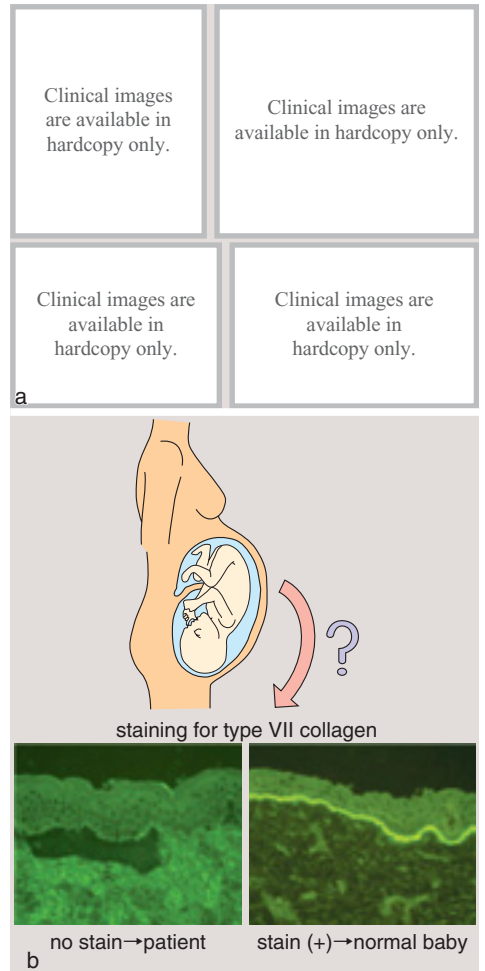


Fig. 29.2 Prenatal diagnosis. a: Examples of an autosomal recessive inherited disease (Hallopeau-Siemens recessive dystrophic epidermolysis bullosa (RDEB)). b: It is possible to make prenatal diagnosis of Hallopeau-Siemens RDEB by embryonic skin biopsy in the 19th week of pregnancy. If type VII collagen is found in the epidermal basement membrane, the embryo is normal.

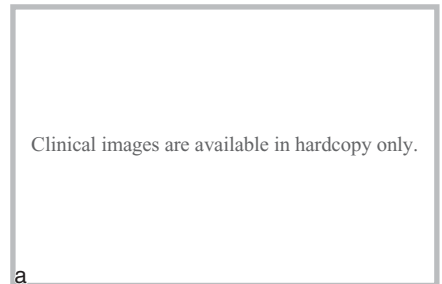


Fig. 29.3-1 Embryonic skin biopsy is available from the 19th week of pregnancy onward. a: The position of the embryo is confirmed by ultrasound scan, and then the skin biopsy site is determined.

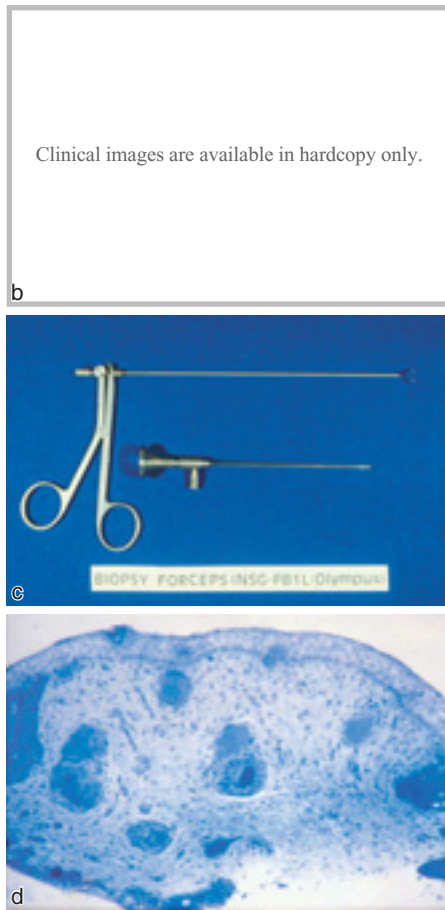


Fig. 29.3-2 Embryonic skin biopsy is available from the 19th week of pregnancy onward.

b: Skin biopsy. c: Devices used for embryonic skin biopsy. d: Electron microscopy of biopsied embryonic skin (low magnification).

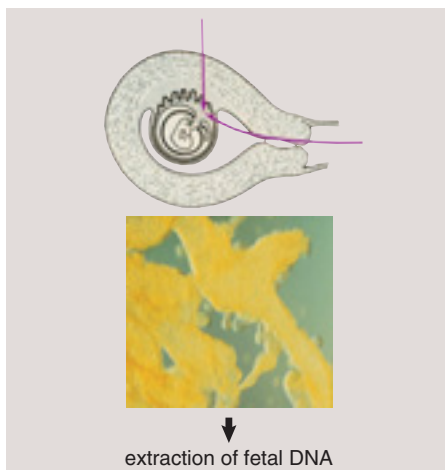


Fig. 29.4 Biopsy of the chorionic villus is performed in about the 10th week of pregnancy.

1) Fetal skin biopsy

Fetal skin biopsy is useful when the causative gene of a genodermatosis is unknown or there is an unidentified genetic mutation in the family. The biopsy can be performed from the 19th week of pregnancy onward, when the fetal skin has formed completely. A punch biopsy of fetal skin 1 mm to 2 mm in diameter is removed with biopsy forceps while confirming the position of the fetus using ultrasound (**Figs. 29.3-1** and **29.3-2**). The phenotypic change in fetal skin is examined by electron microscopy and immunohistochemistry.

2) Chorionic villus sampling and amniocentesis

These tests are conducted when a causative genetic mutation has been identified in a family. In chorionic villus sampling, which can be conducted from the 10th week of pregnancy onward, fetal placental villi are collected. In amniocentesis, which can be performed from the 13th week of pregnancy onward, fetal cells are collected from amniotic fluid. Fetal DNA is extracted from the specimen and investigation is made for genetic mutation (**Fig. 29.4**). The diagnosis of the fetus is determined by direct sequencing of fetal DNA, restriction enzyme digestion, and allele-specific oligonucleotide hybridization.

5. Prospects in prenatal diagnosis

In recent years, pre-implantation genetic diagnosis has been introduced for genetic diseases such as cystic fibrosis. In such diagnosis, 1 or 2 cells are taken from an in-vitro fertilized egg when it is at the stage of 4 or 8 cells, and investigation is made of the target genetic mutation using nested PCR (polymerase chain reaction). Only fertilized eggs without the mutation are selected for artificial implantation: This can prevent the need for artificial abortion. Problems remain in pre-implantation genetic diagnosis, such as those of ethics, low success rate, procedural safety, physical burden on the mother, and cost. There are few opportunities for clinical application of pre-implantation genetic diagnosis other than for the skin diseases that are reported in skin fragility syndrome and epidermolysis bullosa.

It has recently been clarified that fetal cells exist in the blood of women in their 8th to 11th week of pregnancy. Special techniques have made the selection of fetal cells possible. PND has been successfully made in certain diseases by DNA extracted from fetus-derived cells to determine the genetic pattern. It is expected that minimally invasive, accurate and safe PND of genodermatoses will one day be available.

C. New treatments for genodermatoses

Techniques for diagnoses and PND of genodermatoses have significantly improved; however, there are no specifically effective treatments for these conditions. Diseases whose causative genes have been identified are theoretically targets for gene therapies (Figs. 29.5 and 29.6). Such therapies consist of replacement therapy and gene expression inhibition therapy.

For example, recessive dystrophic epidermolysis bullosa is caused by genetic mutation in type VII collagen and lack of anchoring fibrils, a structural component of the epidermal basement membrane. For treatment of genodermatoses, transplantation of autologous cultured epidermal or dermal sheets has come into use. However, it has little effectiveness, because the cells of the patients have genetic mutation and are unable to produce normal type VII collagen. Therefore, studies have focused on transplanting the patient's cultured cells that have been supplied with the normal type VII collagen gene and on applying type VII collagen cDNA directly to the patient's skin (Fig. 29.5). New techniques are being studied, such as allogenic bone marrow transplantation, in which bone marrow stem cells are differentiated to epidermal stem cells to cure genodermatoses.

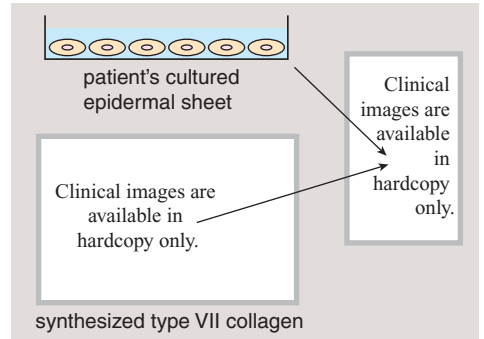


Fig. 29.5 Example of a newly improved treatment method.

Synthetic type VII collagen is injected into the skin ulcer of a patient with recessive dystrophic epidermolysis bullosa. In this condition, genetic mutation prevents the patient from producing type VII collagen. Epidermal sheet cultured from the patient's own skin is grafted over the injected site.



Fig. 29.6 Type XVII collagen knockout mouse, a model animal for epidermolysis bullosa.

This mouse can survive and can be used in therapeutic experiments (adapted from; Nishie W, et al. Humanization of autoantigen. *Nat Med* 2007;13: 378-83).