Chapter 21

Prenatal Genetic Counseling in Congenital Anomalies

Mihaela Amelia Dobrescu, Florin Burada, Mihai Gabriel Cucu, Anca Lelia Riza, Gratiela Chelu, Razvan Mihail Plesea, Adela Cucu, Alina Liliana Cimpoeru and Mihai Ioana

Additional information is available at the end of the chapter

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Abstract

The impact of genetic variability on embryogenesis and fetus development established medical genetics as essential for the prevention of congenital anomalies, early detection and appropriate management. Advances in ultrasonography equipment and technique allow early detection of many congenital malformations. In addition, genetic testing can be performed in a prenatal setting on a variety of biological samples obtained by invasive and noninvasive procedures: chorionic villus sampling, amniocentesis, cordocentesis, or maternal blood collection (i.e., cell free fetal DNA). In the past, only a small percentage of congenital anomalies had a readily identifiable etiology; genetic diagnostic procedures can provide at least some of the answers for the remaining unsolved cases. Undoubtedly, the need for appropriate case management and counseling justifies the importance of uncovering the underlying genetic cause of birth defects. In this chapter, we will focus on genetic counseling in congenital anomalies, including isolated congenital anomalies and preimplantation genetic diagnosis. Genetic counseling provides information and support, assisting parents in making informed decisions. Through this process, parents learn about the risk of having a newborn with a congenital malformation and the nature of the disorder and its natural history, are advised on available testing for that particular case, and discuss options for risk management and family planning.

Keywords: congenital anomalies, genetic counseling

1. Rationale for prenatal genetic counseling

Congenital anomalies are a major cause of stillbirths and neonatal mortality. Taking into consideration that in 2004 WHO estimated an incidence of about 7% in newborns, congenital anomalies are a major cause of morbidity and mortality worldwide.

Congenital anomalies can be caused by *chromosome abnormalities, single-gene defects, multifactorial inheritance*, or *epigenetic or nongenetic factors*. It is notable that in up to 50% of all cases no apparent identifiable cause can be found. Any microscopically detectable autosomal imbalance, such as trisomy, duplication, deletion, or monosomy, will result in severe structural and developmental abnormality, most of which are lethal conditions. Single-gene defects have been associated with congenital abnormalities that might involve one or more organs and systems with or without an obvious underlying embryological relationship. Multifactorial inheritance accounts for the majority of congenital abnormalities, including isolated malformations, in which genetic factors can clearly be involved.

It should be noted that although malformations are always thought to be congenital, not all congenital abnormalities are "literally" malformations. Anomalies due to an intrinsic, genetic (chromosomal aberration and gene mutation), or multifactorial factor represent approximately 45% of all congenital abnormalities. These are considered primary congenital malformations. Anomalies resulting from the action of an extrinsic factor—chemical, physical, biological agents, and possibly maternal condition—add up 5% of the congenital anomalies identified and are considered secondary congenital anomalies. For the remaining 50% of these abnormalities, the cause is unknown and therefore cannot be included in this classification [1].

The impact of genetic variability on embryogenesis and fetus development established medical genetics as essential for the prevention of congenital anomalies, early detection, and appropriate management. In the past, when dealing with congenital malformations, medical professionals had to face two major issues: a late detection of the anomaly and the lack of an identifiable cause. The act of disease prevention back then was virtually impossible.

Though, in the last decade of rapidly progressing genomic technologies, genetic diagnosis tools became widely accessible, playing an important role in both clinical practice and research. The completion of the Human Genome Project has contributed greatly to our understanding of the molecular basis of genetic disorders.

The importance of determining the genetic cause of birth defects lies in the need for appropriate case management and genetic counseling. Genetic counseling is meant to assist parents in making informed decisions. Through counseling, parents learn about the risk of having a newborn with a congenital malformation and the nature of the disorder and its natural history, are advised on available testing for that particular case, and discuss options for risk management and family planning.

All attempts must be made to arrive at as precise a diagnosis as possible by evaluating gestational history for environmental factors, family history for genetic factors, and patient anatomy for clues to embryologic etiopathogenic mechanisms. Evaluating family history for genetic factors, gestational history for environmental factors, and patient phenotype for information on embryologic mechanisms is mandatory to arrive at as precise a diagnosis as possible.

Genetic counseling may be hampered by the inaccurate recording of the above mentioned and the inherent uncertainty in interpreting them. Given the incompleteness of available data and the difficulty in interpretation, genetic counseling has a demanding and potentially difficult mission.

1.1. Prenatal genetic counseling—when and how

Genetic counseling is a complex medical act, which aims to help families, individuals, and couples to better understand the familial, medical, psychological, and reproductive consequences of the genetic contribution to specific health conditions. It can be offered both pre- and postnatally.

Fortunately, most babies are born healthy. However, in some pregnancies, a risk for birth defects or other genetic problems may be identified. Geneticists and genetic counselors provide prenatal genetic counseling services for individuals, couples, or families with a concern about the health of their unborn baby.

Prenatal counselling manages cases with risks by understanding prenatal screening and testing options. Increased chance of having a child with a birth defect or genetic condition makes the genetic consultations a necessity. The purpose of genetic counseling is to allow informed decision-making by communicating accurate and complete information and presenting objective diagnostic and therapeutic options [2]. To achieve its goal, information transfer must be made in a clear but neutral way, using simple language, respecting ethical and cultural values.

Pretest counseling. At this stage, the couple will be informed on the objectives of the counseling session regarding the suspicion of congenital anomaly for the pregnancy.

The genetic counselor/geneticist will lay down the alternatives the couple has for following up the pregnancy and explain the possibility and alternatives for testing for identifying the cause of the congenital anomalies identified. The geneticist must take into consideration that accepting to be tested may be influenced by psychosocial factors, such as ethnicity, sociodemographic status, and the presence of the partner during the counseling session [3].

If the couple expresses the desire for prenatal diagnosis, the counselor must present the objectives, benefits, risks, limitations, costs, and alternatives for each of the available screening and/or diagnosis techniques. The patient has the right to accept or refuse a given recommendation. At all times, it must be clear that testing is optional.

The counseling must go beyond making an informed choice for testing and what this step entails, but also preparing the couple for possible outcomes dictated by a positive or negative result.

Posttest counseling. Posttest counseling must explain thoroughly the significance of the result, the meaning of a positive or negative result, and go over the limitations of each test. It must

also suggest other possible confirmatory or complementary tests or alternatives [2] and unconditionally support the patient's options, respecting the autonomy of his/her choice.

One of the most encumbering tasks of genetic counseling is presenting a family with the fact that their child has a genetic condition or birth defect. Most of the test results face the couple with a termination/no-termination decision.

As part of the informed decision-making process, the couple must be informed in detail on the clinical presentation and prognosis of the disorder identified. This is often problematic in chromosomal disorders: (1) genotypic variability—the phenotype will vary depending on the extent of the genetic defect and (2) phenotypic variability—the evolution of a case can vary greatly, even between carriers of the same type of anomaly.

1.2. "Why did it happen? Will it happen again? What can be done?"

These questions are perhaps among the most frequent during the counseling session and we will try to answer them briefly below. The probability reoccurrence is called "recurrence risk." Recurrence risk assessment and counseling is based on a combination of theoretic risk assessment and empiric data. Families and patients should be informed on the assumptions involved and the limitations of such estimates.

This chapter is focused on genetic counseling in congenital anomalies, caused by chromosomal, monogenic, or plurifactorial anomalies, as well as on preimplantation genetic diagnosis.

2. Genetic counseling in chromosomal congenital anomalies

Carrier and aneuploidy screening and diagnostic testing have expanded intensely over the past two decades [2], which is justifiable given the estimate of 5.3% of the neonates affected by a genetic disorder. Despite ultrasound and biochemistry reasons for recommending a prenatal diagnosis, genetic testing in pregnancy is optional. Decisions about undergoing testing should be expressed, consented, and based on individual patient's values and needs and guided by the geneticist during counseling sessions.

Congenital anomalies can be caused by chromosomal, monogenic, and multifactorial disorders [4]; out of which, chromosomal anomalies have a significant impact given their combined frequency of 1 in 153 pregnancies [5] and the reserved prognosis for many of them.

Aneuploidies are the most frequent chromosomal anomalies. Aneuploidies are numerical disorders (**Figure 1**)—the number of chromosomes differs to the normal state, called euploidy. Any of the chromosomes, autosomes, or heterosomes can be affected. Aneuploidies can be complete, involving the whole chromosome, or partial. From a single fertilized egg, more populations of cells of different genotypes can develop—this abnormal situation is called mosaicism. Due to their high incidence, three complete trisomies bear significance for the prenatal diagnosis: trisomy 21 (T21—Down syndrome), 18 (T18—Edwards syndrome), and 13 (T13—Patau syndrome).

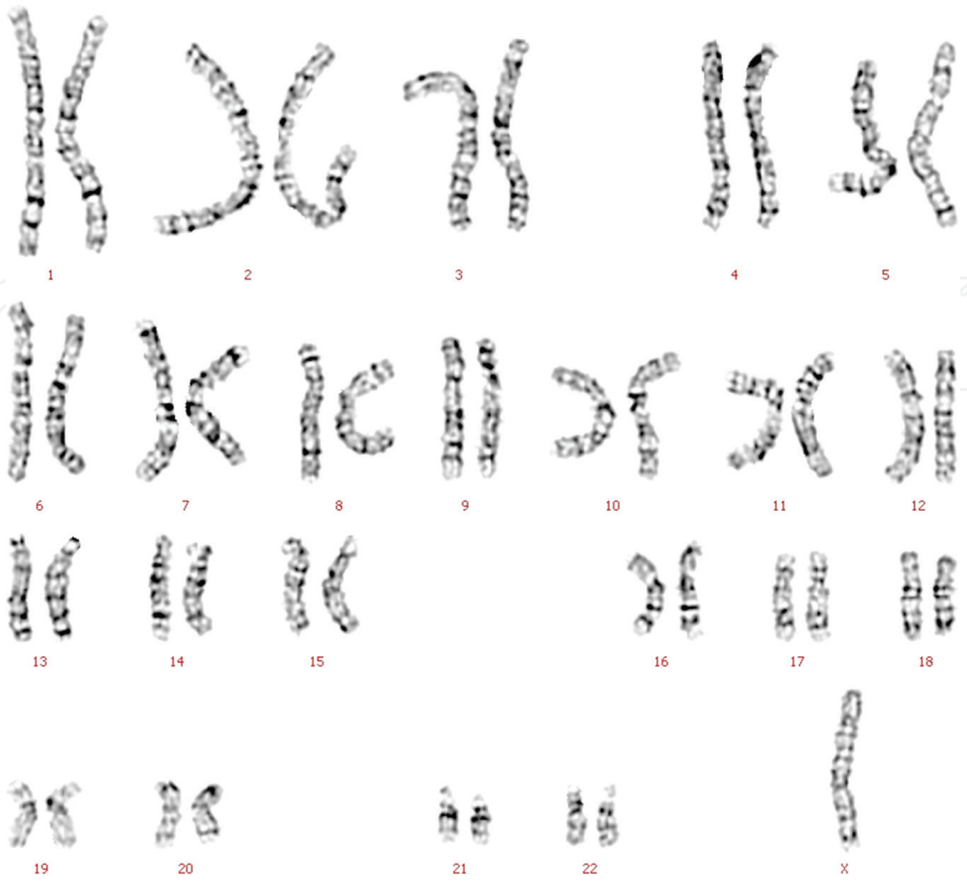

Figure 1. Karyotype 45,X—monosomy X.

Other chromosomal anomalies are structural, such as deletions, duplications, inversions, insertions, translocations, etc. (**Figures 2** and **3**). They are rare and require different diagnosis strategies, counseling, and management of the case.

Possible alternatives for screening ("Prenatal Biochemical and Ultrasound Markers in Chromosomal Anomalies") and diagnosis ("Genomic Testing for Prenatal Clinical Evaluation of Congenital Anomalies") are presented in detail in different chapters, due to their marked importance in genetic testing and counseling.

In the current section, we aim to cover several genetic counseling concepts in a few hypothetical situations of congenital anomaly with underlying chromosomal cause. Pre- and posttesting counseling are a prerequisite of all genetic counseling, but the genetic consult comprises also of a detailed assessment of medical history, psychosocial assessment, and family history, which we are not focusing on here [3, 6, 7].

The possible mechanism by which the chromosomal anomalies occur is usually due to errors in the cell division cycles: nondisjunction in the maternal meiotic division I, and, less frequently, paternal origin [8] or meiosis II [9].

The etiology is mostly unclear, but the probability of chromosomal anomalies increases with maternal age [4], and this is one of the most common etiological factors. Predisposition to

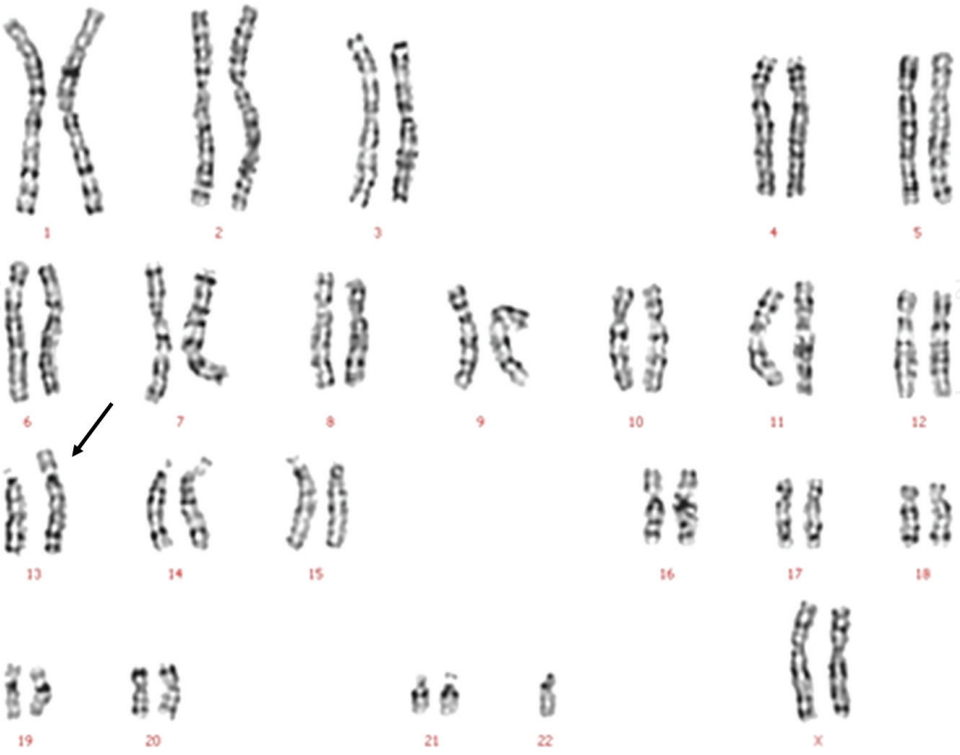

Figure 2. Karyotype 45,XX,rob(13;22)(q10;q10)—Robertsonian translocation.

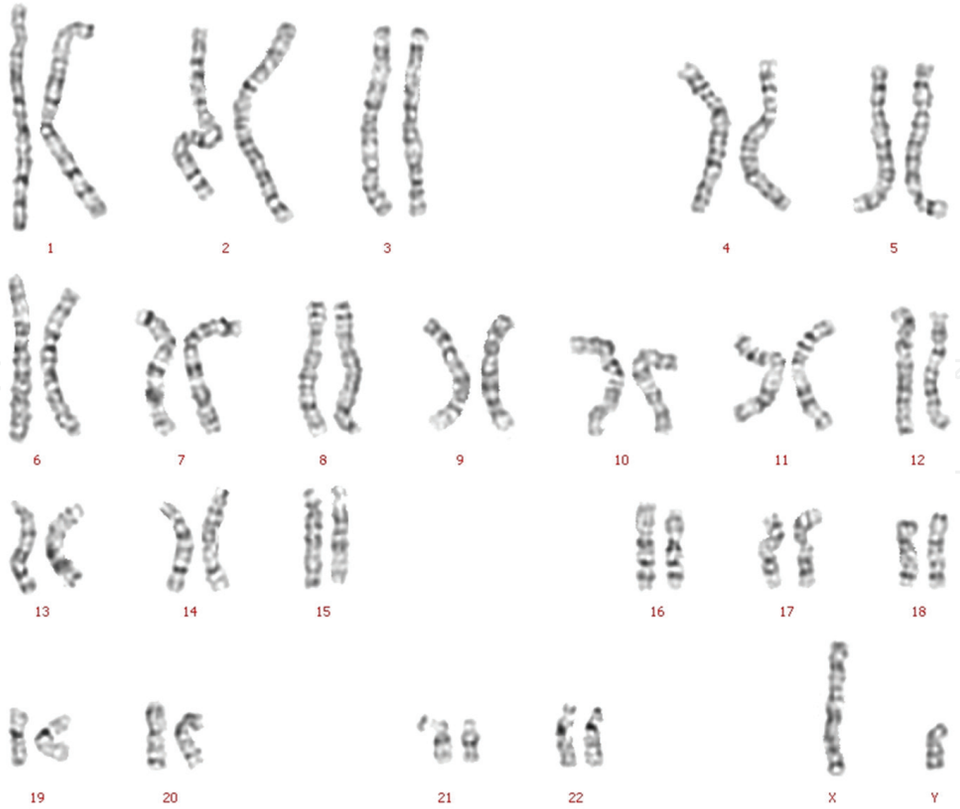

Figure 3. Karyotype 46,XY,t(1;15)(p36.3;q26.1)—reciprocal translocation.

oocyte aneuploidy is also seen in young women, gene expression alteration due to environmental factors and the influence of follicle-stimulating hormone (FSH) being possible culprits [10]. It is yet uncertain if the paternal age contributes to the risk of aneuploidy, if at all [11]. The contribution of different occupational or environmental factors is insufficiently documented.

Aneuploidies are most frequent causes of mental retardation and pregnancy loss [9]. It comes as no surprise that the chance of reoccurrence is one of the most relevant aspects of genetic counseling.

(a) Complete chromosomal, especially autosomal trisomies, when parents are not carriers of translocations

Recurrence risk in the absence of parent translocations follows the empirical risk—the risk measured in the general population, generally evaluated around 1% for the most common trisomy [12] and increases with age for trisomy 21. For other trisomies, the recurrence risk seems lower. Recurrence rates are rather difficult to estimate in sexual aneuploidies. Subjects with Down syndrome are generally infertile, but they have a significant risk of aneuploidy recurrence in their offspring [13].

(b) Chromosomal trisomies with one of the parents being a carrier of a chromosome 21 translocation

Down syndrome translocations are present in less than 4% of the cases. Translocations can occur de novo. For transmitted translocations, the recurrence risk depended on the affected parent: for instance, depending on the involved translocated chromosomes, if the mother is the balanced carrier, the risk is to that of the father, without any known reason for the discrepancy. A balanced translocation t(21,21) has 100% recurrence risk [14].

(c) Mosaicism

Generally, mosaicism cases have the lowest frequency contributions to the total of the trisomies. Mosaicism can occur de novo in the offspring, but parental germ line mosaicism contributes to the recurrence risk [15]. Reduced mosaic [16], meaning low percentage of modified cell lines, or partial trisomy [17], equivalent with duplication, generally has a better prognosis by comparison with a homogenous complete trisomy, but this is not a rule [18].

The couple must be informed that there is no prophylaxis or treatment to correct the aneuploidy, but genetic counseling can provide the support for medically informed decisions to guide the management of the case.

If the couple wishes to keep a pregnancy with chromosomal disorder, they must be informed on the obstetrical complications that may arise, the life expectancy, and the natural history of the disease neonatally and into adulthood.

A trisomy prenatal case, especially 13 or 18, may present with different obstetrical challenges: miscarriage and stillbirth are more frequent than compared to the general population. Structural anomalies of the fetuses lead to a negative prognosis after birth and low life expectancy [19].

Screening and diagnosis limitations for trisomy 13 lead to underdiagnosis of this aneuploidy. Genetic counseling should bring into discussion the viable fetuses in the second trimester (60% of the cases), when life expectancy is very hard to predict and there is no longer the alternative to terminate the pregnancy. It is crucial to inform the parents on the neonatal procedures for resuscitation, possibilities to correct certain defects so that the couple is prepared to face the trauma of having a child with lethal defect [20].

For trisomy 18, only 10% of the neonates survive longer than 1 year. Diagnosing this trisomy though genetic testing is essential for decision-making during the neonatal life, where critical emergency interventions and choosing invasive treatments are often required [21].

Trisomy 21 has a life expectancy of almost 60 years. Following up, the patient asks for collaborations with multiple medical specialties: cardiological, ENT, ophthalmology, endocrinology, to assess possible complications. During their pediatric life, other interventions are generally symptomatic and similar to their euploid peers [22]. The parents must be prepared though through genetic counseling for the possible difficulties due to motor and cognitive delay. Support in the patient's lifestyle can also come from nongovernmental associations and patient support groups, e.g., Down Syndrome International (https://ds-int.org/down-syndrome-your-country).

3. Congenital anomalies in monogenic diseases

Very often, genetic congenital anomalies are part of the clinical presentation of monogenic diseases; 7.5% of isolated or syndromic congenital anomalies are caused by monogenic disorders. Congenital anomalies can become obvious prenatally or at birth, and at times, they are noticeable only in later development, but in all cases, it happens between conception and birth.

The diagnosis of a monogenic disease is often established based on a conclusive family history, clinical examination, and pedigree pattern and confirmed through genetic testing.

With a known diagnosis, the risk of recurrence will be estimated according to the inheritance pattern of the disease. When definite diagnosis is not available, all attempts should be made to associate the clinical picture with a specific disease. If successful, precise genetic counseling can be offered. Situations when diagnosis cannot be demonstrated before birth are difficult to manage—the counselor will advise the couple when there is a lack of crucial medical information.

Should screening identify congenital anomalies during intrauterine life, couples will be faced with a pressing situation, as anomaly finding does not necessarily imply certain diagnosis. In this case, establishing the diagnosis should be aimed for whenever possible, as the first step in genetic counseling.

There are situations with a known diagnosis and known disease-causing mutation that allow prenatal diagnosis testing. Prenatal invasive diagnosis for monogenic disease running in the family, depending on its severity, should and will be recommended. If diagnosis can be readily

established, then the recurrence risk can be calculated. Probability of inheritance based on Mendel's principles and conditional probability (also known as Bayesian analysis, based on Bayes' theorem on probability) are used to calculate genetic risk [1].

The risk of expressing a monogenic disease is dependent not only on the pattern of inheritance, but also on other factors such as the incidence of the disease, the presence of other affected members, the penetrance and variable expressivity, ethnicity, and the influence of environmental factors.

3.1. Autosomal dominant inheritance

An autosomal dominant disease is a condition expressed in both heterozygous, carrying one copy, and homozygous individuals, carrying two copies one from each parent. The disease is caused by a single gene defect located on an autosome. The affected individuals are usually heterozygous, and the homozygous genotype is associated with more severe features or can be lethal. Females and males exhibit the trait in approximately equal proportions and severity of clinical signs is similar between the two sexes. Both sexes are equally likely to transmit the mutation to their offspring. Mostly, the affected offsprings are descendants of an affected heterozygous and a normal parent. On average, half of the children will be heterozygous and express the disease and half will not. Rarely, homozygous are seen in autosomal dominant diseases. This status can be due to a higher frequency of a gene with mild effects, late onset (e.g. Huntington disease) or when both parents are affected (e.g. achondroplasia). Unusually, an affected homozygous parent will transmit the disease to all of his children. On the pedigree, a vertical transmission pattern is observed (**Figure 4**), and the disease phenotype is usually seen in one generation after another. The disease does not skip generations: if an individual has an autosomal disease, in most of the cases, one parent must also have it [1, 2].

Frequently, autosomal dominant disorders involve different organs and systems of the body; however, dominant conditions affecting one organ have been described (e.g., congenital cataract). The capacity of a single gene to affect unrelated organs is called *pleiotropy* (e.g., Marfan syndrome can affect the skeletal, ocular, and cardiovascular systems; some affected individuals have all features, whereas others may have almost none). In addition, the clinical features in autosomal dominant disorders can show remarkable variation between patients, even between the members of the same family. This difference between individuals is referred to as *variable expressivity* (e.g., in autosomal dominant polycystic kidney disease, some affected individuals develop renal failure in early adulthood, whereas others have just a few renal cysts that do not significantly influence renal function). Occasionally, the heterozygous and homozygous individuals express identical phenotype (complete dominance) [2, 23].

Sometimes, a dominant mutation is inherited, but the condition it determines is not expressed. In these cases, the gene has *reduced (incomplete)penetrance.* The term penetrance is used in monogenic inheritance to indicate the probability of a gene to influence the phenotype. A number of autosomal dominant diseases show an incomplete penetrance (e.g., polydactyly), meaning that a person has the mutation but shows no evidence of a disease. A gene is *completely penetrant* if each individual who inherited the mutation expresses clinical features (e.g., neurofibromatosis type I) [3].

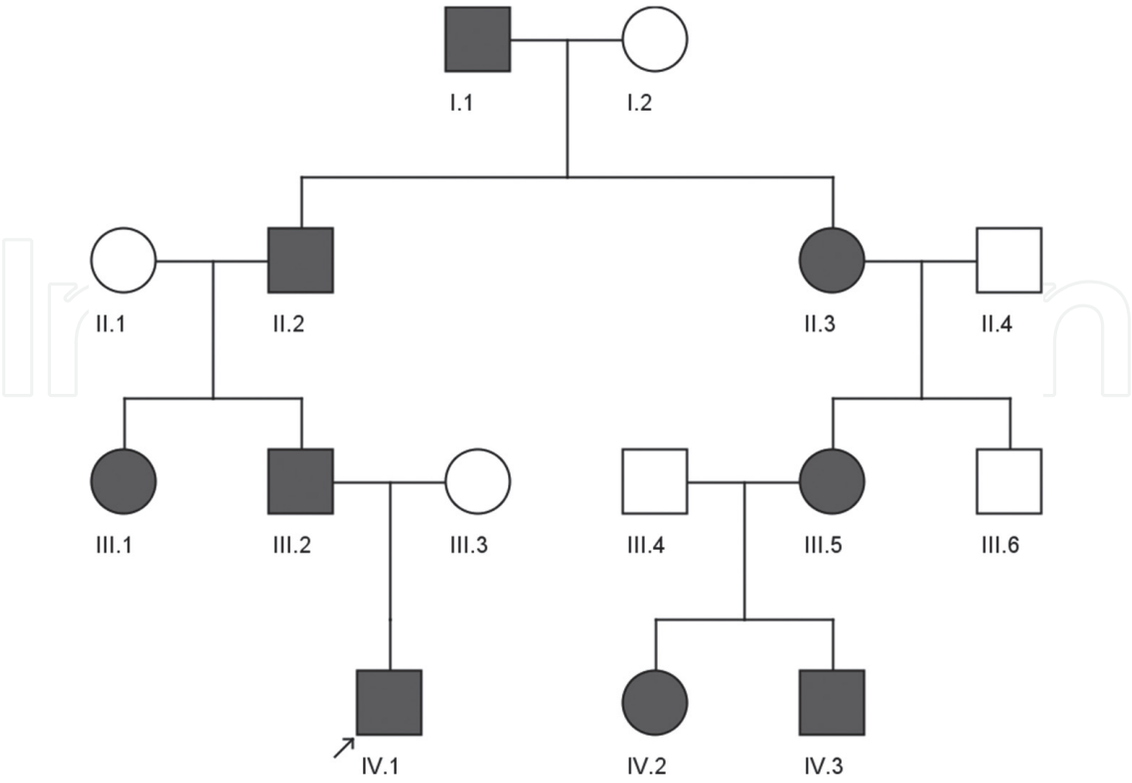

Figure 4. Autosomal dominant inheritance.

Often, known autosomal dominant conditions are seen in a person without an affected parent. The condition seems to be isolated and no clinical features are detected among other family members. In these cases, the disease can be attributed to a *"de novo" mutation* and the recurrence risk for siblings is very low. The mutation is found only in a gamete and the mutated gene is transmitted by one of the healthy parents. The percent of cases caused by de novo mutations is influenced by the severity of clinical features or the capability of reproduction. Osteogenesis imperfecta type II is exclusively caused by new mutations, the condition being perinatally lethal. Also, more than 80% of cases with achondroplasia are due to new mutations, and the proportion is significantly lower in polycystic kidney disease. In this case, it is important to know the family history to distinguish isolated cases and rule out incomplete penetrance or variation in expression. The detection of a specific mutation in a proband allows direct testing of the parents to exclude a disease with expression variability. Also, the detection of a specific mutation can help predict the severity of clinical features in some diseases [24].

Germline mosaicism is another mechanism documented in a number of autosomal dominant diseases such as tuberous sclerosis or osteogenesis imperfecta. Germline mosaicism, also known as gonadal mosaicism, is a condition in which the precursor (germ line) cells to egg and sperm cells are a mixture (mosaic) of two or more genetically different cell lines [1, 2]. The parents do not exhibit any clinical features because the somatic cells are not affected; only a proportion of eggs or sperm cells are carriers of the mutation. Two or more children are affected when there is no family history of disease. This condition is associated with increased recurrence risk for future offspring of a mosaic parent. Because mutation is a rare event, it is unlikely that this would be due to multiple mutations in the same family.

3.2. Autosomal recessive inheritance

An autosomal recessive disease is a condition expressed only in homozygous individuals with both mutant alleles. The parents of such homozygotes must be at least heterozygous for the disease allele and are usually referred to as carriers for that disorder (**Figure 5**). In most cases, the *loss-of-function* mutation is a process in which mutant allele reduces or removes the function of an enzyme. In the heterozygous state, the normal allele can compensate the mutant one, and in homozygotes or compound homozygotes with both mutant alleles, the disease occurs [1, 2, 4].

When two carrier parents of the mutant allele are matting, there is a 50% chance for each of them to transmit either the wild-type or the mutant allele. Thus, each of them has a 50% chance to transmit the mutant allele and further 25% of offspring may be homozygous affected. This also means that 50% of the cases the offspring will get one wild-type allele and one mutant allele, resulting in a carrier. If a parent is affected by a recessive disorder and the other is heterozygous there is a 50% chance that the disorder will be transmitted to children, depending on which allele the partner contributes with. All children are carriers when a parent is affected by an autosomal recessive disorder and the other is homozygous wild-type [1, 4].

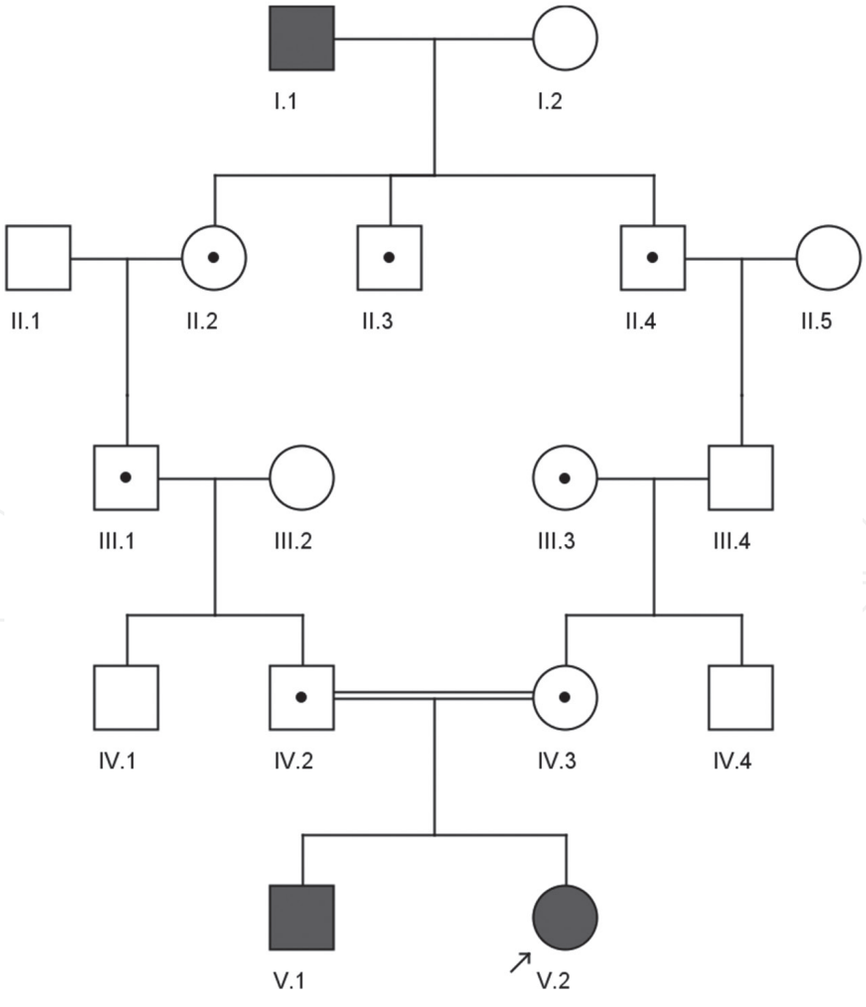

Figure 5. Autosomal recessive inheritance.

Consanguinity is referred to as a couple who have at least a common ancestor, meaning that they are relatives. Finding out that an individual with a genetic disorder is the result of a consanguineous couple is strong evidence for a recessive condition, although not certainty, because there is a greater chance that the parents would have inherited the mutant allele from their common ancestor and passed it down, than the possibility of finding a similar mutation in two unrelated individuals in the general population. In fact, this is true for very rare mutations (e.g., alkaptonuria or xeroderma pigmentosum). In contrast for common autosomal recessive disorders (e.g., cystic fibrosis), the incidence in general population is not significantly lower than in consanguineous marriages. Meaning that the rarer the mutation is in the general population, the more likely that the parents are related (consanguinity) [5].

There are specific recessive disorders for which it is not uncommon that two affected individuals will have children together. Such is the case for individuals with deafness or visual impairment who will benefit from the same social facilities or will be educated together. If the disorder is caused by the same mutation, then all their children would be affected; however, there are studies that show that normal children are born from these couples. The most common explanation is that the parents are homozygous for different genes, both causing deafness, and so the children are heterozygous for both mutations, also known as double heterozygote. This type of genetic heterogeneity is called *locus heterogeneity.* Heterogeneity can also be found in the same locus, as it would be the case of an affected individual who is heterozygote for both alleles, making him/her a *compound heterozygote*. Most affected individuals with recessive autosomal inherited disorders are compound heterozygotes, unless that specific mutation is rather common in the general population (as is the case with cystic fibrosis), or he/she is the result of a consanguinity marriage [1].

Another method of assessing recurrence risk is by calculating the genotype frequency, knowing the allele frequency. This is not as straightforward as it would seem because there is the matter of allele distribution in heterozygotes and homozygotes. This can be done by using the *Hardy-Weinberg Law*, but the population used on has to meet some criteria such as: (a) the population is large and the mattings are random; (b) there is no significant rate of new mutations; (c) there is no selection for any genotype; and (d) there is no significant migration disturbing the endogenous population allele frequency [6].

The presence of both homologous from a pair or chromosomal regions in an offspring coming from the same parent is called *uniparental disomy*. The uniparental disomy can be caused by an error in meiosis resulting in two different chromosomes coming from the same parent, which is called heterodisomy, or by an error in meiosis II, which will result in identical chromosomes transmitted from the same parent called isodisomy. This abnormality has been reported to be a rare cause for cystic fibrosis, in families where only one parent is heterozygote and the offspring takes both homologous chromosomes with the mutant allele from that parent [1, 4].

3.3. Sex-linked inheritance

This type of inheritance is linked to the genes found on the sex chromosomes. Inheritance patterns for the genes found on X chromosome relates to X-linked inheritance, while for the genes located on Y chromosomes, it is called holandric or Y-linked inheritance. The genes positioned on the X and Y chromosomes are unequally transmitted to males and females.

X-inactivation is a normal process, which appears in the early development of the embryo. The result is that most of the genes on one of the two X chromosomes in females are inactivated in each cell, ensuring the fact that, similar to males, females have only one functional X chromosome. One of the two chromosomes is randomly inactivated, meaning that approximately half of the cells in females have a functional X chromosome of maternal origin and the other half have the paternal one functional. This process interferes with both dominant and recessive X-linked inheritance as detailed below [5].

3.3.1. X-linked dominant inheritance

X-linked dominant inheritance is caused by a dominant mutant allele located on the X chromosome. Hemizygous males and both homozygous and heterozygous females are affected. Males are more likely to be severely affected given the fact that in females one of the X chromosomes will be inactivated (X-inactivation), unless the females are homozygous for that allele.

Affected heterozygote offsprings of both sexes have a 50% chance to inherit the mutant allele from an affected mother, which is similar in the autosomal dominant inheritance too (**Figure 6**). The difference between the autosomal and X-linked dominant inheritance refers to affected males. All daughters of an affected male will also be affected by inheriting the X chromosome with the mutant allele, whereas male offsprings will inherit the Y chromosome, thus avoiding the disorder. Affected females are twice more frequent than affected males, although females tend to have milder phenotypic manifestations. One example of an X-linked dominant inheritance disorder is the hypophosphatemic rickets [1, 2, 4].

In some cases, affected males with an X-linked dominant disorder are rarely seen, for example, Rett syndrome and incontinentia pigmenti. This is due to the fact that the presence of the mutant allele in male hemizygotes will result in an early embryonic development stop. In other cases, it seems that only females are affected because males are "speared." An example of a disorder that spares male hemizygotes is X-linked females—limited epilepsy and cognitive impairment. Females appear to be healthy at birth, yet they develop the affection from the second year of life, while males are unaffected their whole life. This disorder is caused by a loss of functional mechanism in the protocadherin gene 19, which is expressed in the neurons. The explanation for this particular case would be that random X-inactivation makes a mosaic expression of this gene in the cells of the central nervous system, which disrupts communications between neurons. In males, the brain is spared this miscommunication between neurons by seemingly a different protocadherin, which compensates the loss of the first [6].

3.3.2. X-linked recessive inheritance

X-linked recessive inheritance is caused by a recessive mutant gene located on the X chromosome. Almost all affected individuals are males (hemizygotes), while homozygotes affected females are rarely seen. The clinical features seen in females are mainly due to non-random X-inactivation [4].

All daughters of an affected male (hemizygous) will be carriers (heterozygotes) for a specific disorder, whereas the sons will inherit the Y chromosomes from the father and thus will be

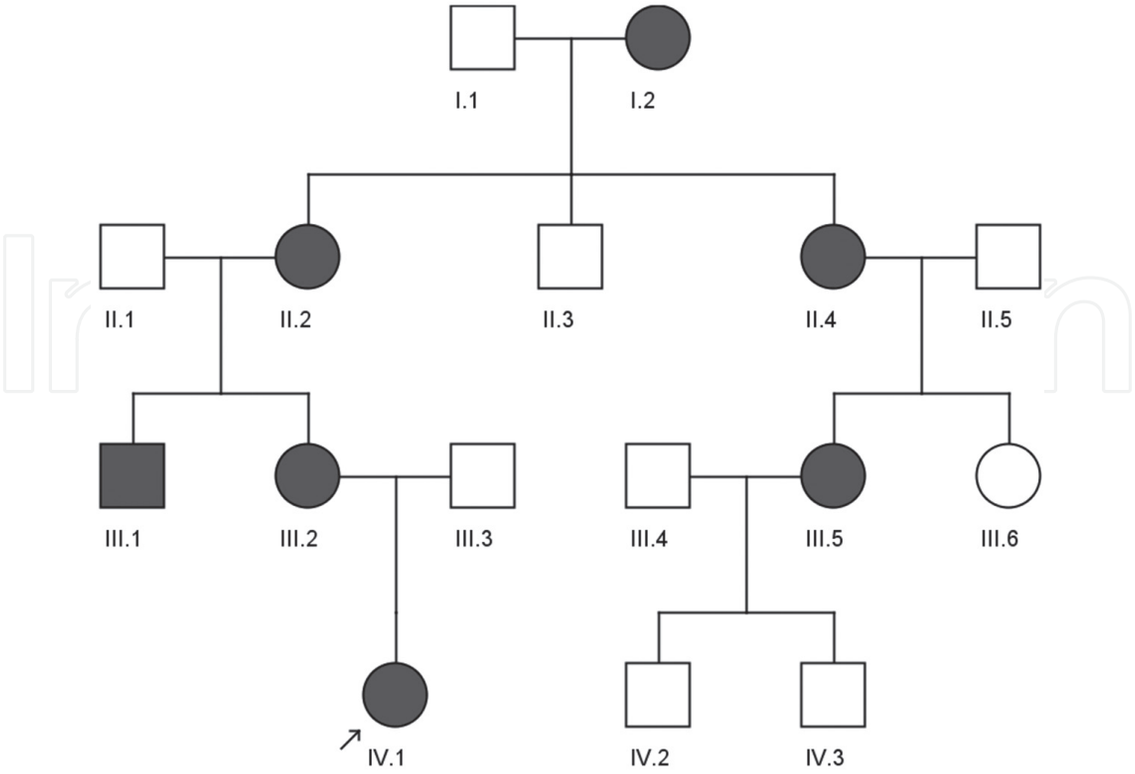

Figure 6. X-linked dominant inheritance.

unaffected by the disorder. For a female carrying the mutation, there is a 50% chance to transmit the mutant X chromosome to the offspring, as a result 50% of the daughters will be carriers and 50% of the sons will be affected (**Figure 7**). For a female to be affected means to inherit the mutant allele from each parent, which is very unlikely to happen, or another option is the presence of only one X chromosome (monosomy X) on which the mutation is present, making her a hemizygous for the allele, like in the case of males. A commonly known X-linked recessive disorder is hemophilia A caused by deficiency of factor VIII, a protein involved in clotting [1, 2, 6].

Sometimes, the females can express the phenotype. The most common situation is represented by a carrier female showing phenotypic features, phenomenon known as *manifesting heterozygote.* This manifestation is due to X-inactivation, which is not random anymore; rather, it has become unbalanced or skewed. The skewed X-inactivation can be both advantageous when the inactivated X chromosome in all or most cell lines and tissues is the one with the mutation and deleterious when inactivation occurs on the X chromosome containing the wild-type allele. This unbalance can be created through chance alone by selecting mostly one of the X chromosomes, rather than the other, or through different mechanisms like cytogenetic abnormalities (translocation) or removal of the cells containing the mutant allele [6].

The *germline mosaicism (gonadal mosaicism)* is an important mechanism in assessment of X-linked recessive inheritance risk and it was also seen in autosomal dominant inheritance. Because both male and female gametogenesis can be affected, it should be taken into account when the recurrence risk is assessed in apparently sporadically appeared X-linked disorders like Duchenne muscular dystrophy [1].

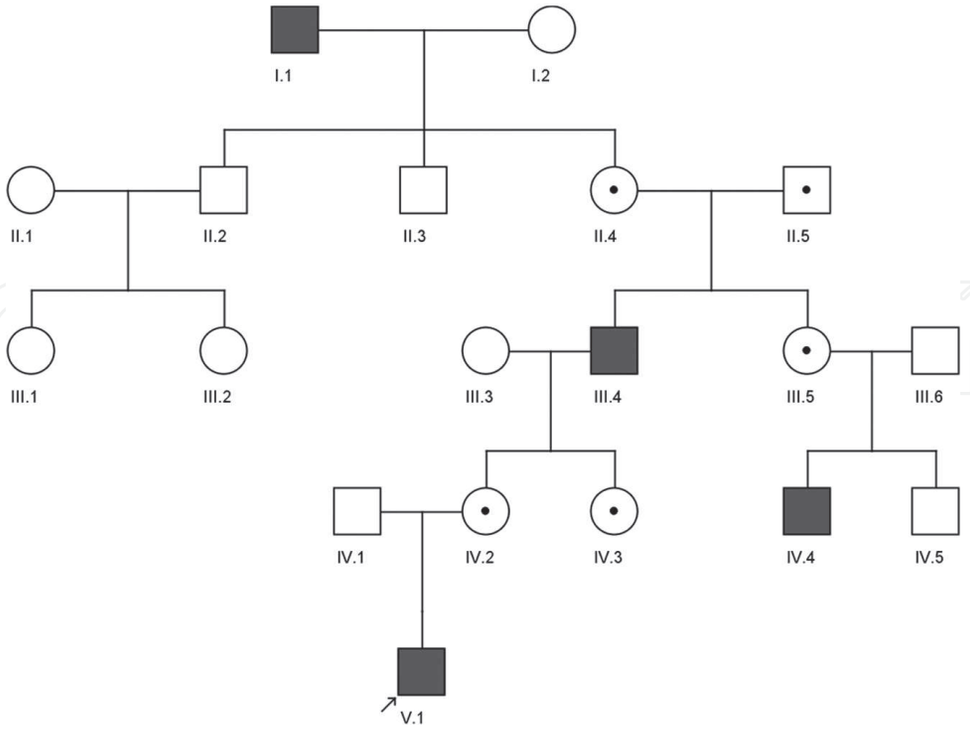

Figure 7. X-linked recessive inheritance.

3.3.3. Y-linked inheritance

Y-linked inheritance also known as holandric inheritance is caused by genes located on the Y chromosome. This is a rather straightforward type of inheritance as only males have Y chromosome, meaning that a male will transmit the mutant allele and thus the disorder to all his male descendants and none of his female ones.

4. Genetic counseling in multifactorial congenital anomalies

Multifactorial heredity describes a trait whose manifestations are determined by the activity of one or more genes in combination with environmental factors that can trigger, accelerate, or exacerbate the pathological process. Multifactorial diseases present a specific familial disposition, the incidence for close relatives of the affected individual being about 2–4%, unlike diseases determined by the mutations of a single gene (25–50%) [7].

These types of pathologies are classified into two main categories: (1) common diseases of adulthood (coronary disease, hypertension, diabetes, asthma, schizophrenia, etc.), having a prevalence of around 1–5%, and (2) isolated congenital abnormalities of the childhood (e.g. neural tube defects, cleft lip and anterior palate, congenital anomalies of the heart, varus equina), with an incidence of approximately 1–8% in newborns [25].

Congenital anomalies, also referred to as congenital abnormalities, congenital malformations, congenital disorders, or birth defects, are conditions of prenatal origin that describe developmental

disorders of the embryo and fetus, potentially impacting its health and development [26]. There is a wide array of anomalies including structural and functional conditions that can fall under these headings [3].

Congenital anomalies are affecting 1–6% of pregnancies worldwide, making them a leading cause of morbidity and mortality in early life [8, 9, 27, 28]. In high-income countries, a quarter of the infant deaths is due to these anomalies [10, 29, 30]. Mortality in children under 5 years old escalates to 3.3 million [28].

These anomalies can occur in isolation (isolated congenital anomalies) or as a group of defects (multiple congenital anomalies). However, there is no generally accepted system of classification, or even an agreed definition of what constitutes a congenital anomaly [3].

Improvements in the sensitivity and availability of prenatal screening have helped decrease the number of children born with congenital anomalies [8, 31]. Even so, when the event arises, the diagnosis and the discussions around pregnancy termination create significant emotional distress [32]. Moreover, parents who have lost a child to a congenital anomaly or families with a preexisting condition will be very concerned about the risk of recurrence in future pregnancies [11].

The role of genetic counseling is to provide guidance and support to the families being affected by these conditions [12, 24], yet the etiology of most congenital anomalies is multifactorial or unknown [33] and so an exact evaluation of the recurrence risk is hard to make for most anomaly groups and subtypes. There are a few population-based studies that offer some information concerning the recurrence risk [13, 14, 34]. All three studies conducted in the 1990s found that a congenital anomaly has twice the risk of occurrence in a future pregnancy if it has already been present, and the risk rises 5- to 12-fold if the same anomaly is present in the subsequent pregnancy [13, 14, 34]. These studies have also limitations, due to small sample size, lack or outdated classification, rendering them less useful. There is also more accurate data available in a recent article [3] that shows that for similar anomalies the recurrence risk for isolated congenital anomalies is 20-fold higher, while for dissimilar anomalies, the recurrence risk is 1.3-fold higher. Also, it was concluded in the article that the absolute recurrence risk varies between 1 in 20 and 1 in 30 [3].

General recurrence risk. Under these conditions, a number of general principles must be respected for genetic counseling. The empirical risk represents a medium risk for the respective disease in the population of which the proband (index case) is, and so it is possible that in the studied family the average risk is not the same as the real risk.

The overall empirical risk of recurrent fracture or progression for isolated congenital malformations with a frequency of 1–1000 newborns is about 2.5% for common diseases; at a frequency of 1–100, the risk is about 10%.

The risk of recurrence of the condition is influenced by a number of factors:

- The degree of kinship with the proband (index case). The risk of recurrence to first-degree relatives is much higher than for other people in the family; for example, the descendants and siblings of a proband with oral cleft have a risk of 3.15 and 2.79%, respectively, and the second- and third-degree relatives have much lower risks, 0.47 and 0.27%, respectively.

- The presence of a more severe condition in the proband. If the proband has a unilateral oral cleft, the risk to siblings is 1.9%, and if the proband has bilateral oral cleft, the risk rises to 6.6%.
- The presence in the family of several affected individuals. In the case of labia, if two siblings are affected, the risk for the next birth is 10%; if a parent and child are affected, then the risk for another affected child is 14%.
- Sex of the proband. The risk increases if in the family there are sick individuals of a certain sex at which the illness is normally less frequent (i.e., developmental dysplasia of the hip in boys and pyloric stenosis in girls).
- Consanguinity increases the risk of recurrence because the risk genes are inherited from both sides.

If for certain isolated congenital anomalies there is no information on the empirical risk in a given population, the risks may be recalculated based on the population frequency and the severity of the condition, as well as the number of affected individuals.

Recurrence risks per pathology. Regarding *congenital anomalies of the heart*, the recurrence risk is greater on the horizontal line (brotherhood) than on the vertical line for first-degree relatives and it revolves around 2–4%, whereas for second-degree relatives, the risk is reduced, becoming similar to that of the general population [35]. On the other hand, though, if the affected parent is the mother, the recurrence risk is significantly higher than the one for which the father would have been the carrier of the anomaly.

Cleft lip when associated or not with anterior palate represents the most common facial congenital anomaly, being present in over 20% of the cases and also having a positive family history.

At birth, the fact that the child has an affected mother and that she has another affected child increases the prevalence. The recurrence risk for patients that have first-degree relatives with this disease is 32 times greater than in the general population for cleft lip and anterior palate and 56 times greater for anterior palate alone, even though patients with cleft lip have a high familial recurrence of almost 4%.

In regard to *neural tube defects*, recent studies have pointed that if the proband would be the first affected child in the family then the recurrence risk for the following children would be 3.15%, whereas for the second affected sibling, the risk for recurrence would be around 10–11.76%. Some studies also showed that the risk is higher for female children and for the first and last siblings of a mother.

Congenital hip dislocation has a 5% recurrence risk if an affected sibling is already present. An increased risk of male probing according to sex ratio (8 males per 1 affected female) is encountered in people affected by this congenital anomaly.

Varus equina seems to be twice as frequent in girls as in boys, while in families that have one child with this condition, the occurrence risk for the following children is 30 times higher than that of the general population being approximately 7.3%.

The indirect setting, based on family history, of an increased individual risk of the disease will allow for the direct determination by molecular tests of genetic risk factors, possibly specific medical actions of early diagnosis.

To summarize, genetic counseling in isolated congenital anomalies relies on information gathered from population-based studies, on new and future discoveries related to the etiology of these disorders, and other factors such as the degree of kinship with the proband, presence of a more severe condition, more than one individual affected in the same family, or consanguinity for calculating the recurrence risk for the respective condition.

Genetic counseling is about guidance and support for the patient and the patient's family, so a great deal of attention must also be directed toward careful wording when explaining the risk and decisions that need to be made.

5. Preimplantation genetic diagnosis (PGD)

Preimplantation genetic diagnosis is a multistep procedure that analyzes the genetic material from a single or several cells, with the purpose to avoid a pregnancy affected by a specific disease. The biological samples were obtained during assisted reproductive treatment (ART) by the biopsy of oocyte polar bodies or embryos. PGD requires a multidisciplinary and highly experienced team in ART and genomic evaluation at single-cell level [15, 16].

Indications for PGD. Usually, PGD is provided to couples at risk of conceiving abnormal offspring with monogenic or chromosomal disorders. Thus, PGD is suitable for couples where one member is affected by a dominant disorder or both are known carriers of mutant alleles for a recessive disease, or one of them carries a balanced chromosome rearrangement that predisposes him/her to transmit and unbalanced chromosomal abnormality, often deletion or duplication [16, 17]. The presence of a gene mutation or chromosomal abnormality in a member or members of a family must be identified before PGD to allow the detection of a particular genetic abnormality before implantation and further the transmission of a specific disorder to children. Only normal embryos are transferred to the uterus to initiate the pregnancy knowing that the embryo is not a carrier for a specific abnormality, thus decreasing the risk of having an offspring affected by a specific genetic disorder. Many of these diseases are associated with an early death or severe mental and congenital abnormalities. The monogenic diseases diagnosed through PGD include autosomal recessive conditions (e.g., β-thalassemia, cystic fibrosis, spinal muscular atrophy, and sickle cell disease), autosomal dominant conditions (Huntington's disease, myotonic dystrophy, and Charcot-Marie-Tooth disease), or X-linked recessive conditions (fragile X syndrome, Duchenne muscular dystrophy, and hemophilia) [18].

PGD is also available to help parents in creating embryos that are human leucocyte antigen (HLA) compatible with a child affected by a severe blood disease, thus the selected sibling serving as a donor. PGD is an appropriate choice for carrier couples who also have infertility problems and plan to use assisted reproductive treatment anyway or for couples with an ethical or religious objection to pregnancy termination. PGD can also be used for the detection of a variety of cancer predispositions (e.g., familial breast cancer) [19, 20].

Biopsy procedures and genetic analysis technique. Genetic testing can be performed using biological samples obtained by one of the following: polar body, cleavage-stage embryo, or blastocyst biopsy [15, 16].

Polar body biopsy. First and second polar bodies are haploid cells produced in the first and, respectively, second meiotic division of oogenesis. The genetic evaluation of both polar bodies is required to precisely establish the genetic status of the oocyte. Because polar bodies are not a part of the zygote, this technique is mainly performed in some countries where embryo biopsy is unauthorized by law. Polar body analysis only provides data about mutations or aneuploidies of maternal origins. The chromosome abnormalities occurring postmeiotically (e.g., mosaicism and polyploidy), limited amount of genetic material, and doubling the number of samples for analysis have made the need to perform this type of biopsy questionable [36, 21].

Cleavage-stage embryo biopsy. Cleavage-stage biopsy is usually performed on day 3 when early embryo consists of approximately 6–10 cells. At this stage, the cells are still totipotent and are not yet adhering to one another, allowing the extraction of a single blastomere for genetic testing. Limited amount of genetic material and high rates of mosaicism observed in early embryos can lead to misdiagnosis at this stage. The biopsy of two blastomeres was associated with deleterious effects on embryo development and is recommended to be avoided [22, 37].

Blastocyst biopsy. The embryo reaches the blastocyst stage on day 5 or 6 after fertilization. The blastocyst contains about 100 cells and comprises the outer trophectoderm and inner cell mass. During blastocyst biopsy, 5–10 trophectoderm cells are retrieved; thus, more material for genetic diagnosis is available. The ethical and safety considerations related to early embryo biopsy are overcome somewhat because the trophectoderm cells will differentiate into trophoblast cells and further go on to form placenta and other extraembryonic tissues, and not participate to form the embryo [15, 23]. Recent studies showed that this type of biopsy has no effect on reproductive capacity of a blastocyst [16, 24]. However, only about 40–50% of preimplantation embryos will reach this stage in vitro. Because the time to obtain a genetic diagnosis is very limited to perform a fresh embryo transfer, mostly frozen embryo transfer is performed after vitrification [15, 16, 36].

Genetic analysis techniques. After the biological material is available for biopsy, the genetic analysis can be performed. The evaluation is based on only a single cell or very limited genetic material. For fresh embryo transfer, the genetic diagnosis must be done within 24–36 h. The single-gene mutations are detected using molecular genetic methods (PCR, PCR-multiplex, RTqPCR, whole genome amplification, or even next-generation sequencing) and chromosomal abnormalities (e.g., translocation and aneuploidies) by cytogenetic techniques (FISH, array CGH, and SNP array) [16, 25].

The embryo testing using genetic methods with the aim to detect *de novo* chromosomal aneuploidies is known as preimplantation genetic screening (PGS) [26]. PGS analyzes whether a single cell or a small number of cells biopsied from a preimplantation embryo is euploid before transferring it to the uterus. PGS is not PGD, being mainly offered to couples with advanced maternal age, recurrent implantation failure or recurrent miscarriages, and other conditions associated with high risk for aneuploid embryos in order to increase the success rate of IVF (~30%). PGS can be performed using FISH, multiplex quantitative PCR, or chromosomal microarrays [16, 27, 28].

Genetic counseling. A clinical genetic consultation provided by a geneticist with practice in ART is required to the couples before starting PGD treatment. Its purpose is to confirm the genetic diagnosis, to evaluate the reproductive status of the couple, and to provide information about the disease, mode of inheritance, recurrence risk, genetic testing, and reproductive options, including PGD [38].

Genetic counseling by a qualified geneticist or a certified genetic counselor is recommended to the couples to receive support and appropriate information in a nondirective manner and with no pressure, allowing them to make the best choice. Family history, reason for PGD, what is PGD, alternative reproductive options and side effects of treatment, the limitations of testing, success rates (about 30%), and possible outcome options should be discussed, including an unsuccessful cycle [29, 30].

Also, a multiple birth should be considered when ART is used. Thus, the couple should understand and consider the physical, psychological, and financial impact of treatment [31].

An important part of genetic counseling is to establish the reason for choosing PGD. In most cases, the couples choose PGD to avoid termination of pregnancy due to a genetic disease or to know earliest that the pregnancy is unaffected by a specific genetic abnormality [17]. Other reasons for PGD include a previously affected child or a loss of a child, recurrent abortions, or infertility. When parents are carriers for a recessive disorder, more embryos may be carriers for a mutant allele. The couple must be informed about the genetic status of the embryos and in the absence of a clinical feature in carriers, these can be considered for transfer to increase the number of available embryos. The issue of genetic testing of children for carrier status should be discussed prior to offering prenatal diagnosis to confirm the PGD result.

Sex selection is not allowed by law in many countries, while in others, it is allowed. Except some recessive X-linked disorders where females may have a mild phenotype, in these cases, the female embryos should be excluded for transfer, and the parents should be able to choose not to know the sex of their embryos.

After implantation, a new contact with a geneticist is required. Occasionally, when PGD is used, a misdiagnosis can occur; therefore, prenatal diagnosis should be offered. Prenatal diagnosis requires an invasive testing (chorionic villus sampling and amniocentesis) associated with the risk of losing the pregnancy, and many of them may refuse the confirmatory test [29].

The postnatal confirmatory diagnosis from blood is in contrast to recommendations for testing in childhood, which specify that unless there are clinical benefits to testing minors, testing for carrier or late disease conditions should be delayed until the child is old enough to understand the implications and be part of the decision making. In most cases, a successful PGD cycle will result in an ongoing pregnancy and a healthy live born infant. However, a follow-up after birth is recommended.

6. Ethical considerations

Biomedical ethics is based on applying various principles in order to create a framework of moral analysis that allows the practitioner to make an optimal decision in agreement with the patients' wishes/needs and their point of view.

Medical genetics is one of the medical fields in which, from the very beginning, sensitive ethical issues have been raised; their importance subsequently became more and more undeniable due to technological advances and discoveries in the field (see Human Genome Project, Next Generation Sequence, and Whole Genome/Exome Sequencing).

Of all the areas of genetics, prenatal diagnosis raises the most fervent debates and, consequently, ethical dilemmas. It is one of the chapters that are hard to fit in an accurate guide for the clinician, sufficient enough to use and make sure he has done or said what is needed to ensure that the health of the patient and family is protected.

The particularity of this field is derived from the existence of two entities whose rights must be taken into account: on one hand, the "patient," the unborn fetus at different stages of development at the time of the diagnosis request, and on the other hand, the mother/couple requesting the diagnosis. Although the phrase"on one hand and … on the other side" might seem inappropriate, it still reflects reality, because not always the rights of the patient are on the same side as those of the parents. And here lies the first dilemma: autonomy vs. benefit.

6.1. Ethical principles and prenatal counseling

In order to improve medical practice in medical genetics and implicitly in prenatal genetic diagnosis, a set of essential ethical principles was developed to support a clinical decision [32, 35]:

1. Respecting the autonomy of a person referring to the right of a patient to make his/her own decision without any constraint but at the same time informed by a genetic counseling in a nonlinear and impartial manner, without prejudices.
2. The "do not harm" obligation and the "doing good" duty reflect on the degree of necessity of the two desires. Obviously, it is desirable to do well (benefit), but in this process, it is much more important to avoid mistakes before getting the right benefit (e.g., presymptomatic testing for early-onset diseases) [33].
3. Confidentiality protects the patient's genetic data from various other parts. The data could be provided only with the patient's consent and only if the doctor considers them relevant. However, the doctor may not respect confidentiality if the genetic data are relevant for the relatives and the patient is not able to properly inform them about familial medical conditions.
4. Equal access to patients for care and treatment: this concept is the most difficult to apply due to the insufficient resources.

Prenatal diagnosis (PD), and here we will only refer to invasive PD, involves a genetic test that allows the diagnosis of a fetus with a serious genetic disorder (and there is an issue of what "serious" means in the opinion of specialists), followed by communication of the data to parents. The purpose of prenatal genetic testing is exclusively medical and testing criteria should be clearly established [34].

When PD is recommended, the couple will be informed, regardless of their perspective on abortion because sometimes it can be useful for psychological and medical training for the

birth of a child with a congenital anomaly [34]. However, PD is a voluntary decision of the couple who will decide if the suspected condition requires diagnosis testing or termination of the pregnancy.

The distinctiveness of PD consists in this one-sided decision of the pregnant woman whose sentence affects both herself and the unborn child; if a woman is able to make an independent and well-considered decision, she must have the necessary knowledge to act in the context that PD does not only give information about a potential termination of a pregnancy but also it provides information that will prepare the parents for the birth of an affected child.

For this purpose, pretesting counseling is vital, and it will determine not only the risk of the fetus being affected, but also the chances of it being normal, it will inform about the conditions that can be diagnosed and their consequences not only on the fetus but also on the care/treatment options. Furthermore, it will also provide counseling regarding the limits of the test, the possibility of an irrelevant or unexpected result, and the couple's options after testing.

If a PD is established, the physician should discuss with the pregnant woman about all the possible aspects of the clinical features, including the heterogeneity of the clinical manifestations. The informed choice of the pregnant woman/couple in the diagnosis of a fetus with congenital malformations will be respected and protected without prejudice, giving importance and priority to the family and sociocultural background in which the couple and the future malformed child will spend their lives.

In the case of PD without medical indication, when the testing is only based on pregnancy/couple's anxiety, it will be done but with a low priority in allocating resources compared to PD associated with medical reasons. The practice of PD testing with the intention of selecting the child's sex (except for X-linked diseases) is not permitted, as well as the testing of paternity (excepting the pregnancy after an incest or rape) [34].

Particularly, the evolution of technology with the implementation of NGS in PD complicates the ethical aspects because, although genetic diagnosis has been improved, the method has some limitations, some of them common with those of the usual methods of PD [35]:

1. Diagnosing a disease for which there is no treatment.
2. Neither the severity of the clinical manifestations nor the progression of the disease can always be predicted only by conducting a genetic test.
3. There are not yet genetic tests established for all genetic diseases.
4. The results require a complex interpretation because the test provides a lot of data.
5. No test is 100% safe; the safety is dependent on the disease and the used method.
6. Laboratory errors sometimes do occur.
7. Not all pathogenic variants could be detected and interpreted.
8. The cost of the method is very expensive and not all the patients have financial resources.

In conclusion, ethical aspects surrounding PD are multiple and demanding for both the physician and parents, but using the qualified knowledge of a professional, exposed with much tact and patience, the couple will correctly understand the implications of the problem and their possible solutions/the lack of solutions and will take the best decision based on these aspects and according to their own convictions.

Author details

Mihaela Amelia Dobrescu*, Florin Burada*, Mihai Gabriel Cucu, Anca Lelia Riza, Gratiela Chelu, Razvan Mihail Plesea, Adela Cucu, Alina Liliana Cimpoeru and Mihai Ioana

*Address all correspondence to: amelia_dobrescu@yahoo.com and florinburada2000@yahoo.com

Medical Genetics Regional Center (CRGM), Dolj, Human Genomics Laboratory, University of Medicine and Pharmacy of Craiova, Craiova, Romania

References

[1] Covic Mircea SD, Ionel S. Genetica Medicala. 2 ed. Romania, Iasi: Polirom; 2011. pp. 515-523

[2] Fonda Allen J, Stoll K, Bernhardt BA. Pre- and post-test genetic counseling for chromosomal and Mendelian disorders. Seminars in Perinatology. 2016 Feb;**40**(1):44-55

[3] Handbook of Genetic Counseling/Trisomy 18—Wikibooks, open books for an open world

[4] Wieacker P, Steinhard J. The Prenatal Diagnosis of Genetic Diseases. Deutsches Ärzteblatt International. 2010;**107**(48):857-62

[5] Verma IC, Puri RD. Global burden of genetic disease and the role of genetic screening. Seminars in Fetal & Neonatal Medicine. 2015 Oct;**20**(5):354-363

[6] Handbook of Genetic Counseling/Trisomy 13—Advanced Maternal Age—Occupational Exposures—Wikibooks, open books for an open world

[7] Handbook of Genetic Counseling/Down Syndrome—Trisomy 21-1—Wikibooks, open books for an open world

[8] Ioannou D, Tempest HG. Meiotic nondisjunction: Insights into the origin and significance of aneuploidy in human spermatozoa. Advances in Experimental Medicine and Biology. 2015;**868**:1-21

[9] Griffin DK. The incidence, origin, and etiology of aneuploidy. In: Jeon KW, editor. International Review of Cytology. Academic Press; 1996. pp. 263-296

[10] Vialard F, Boitrelle F, Molina-Gomes D, Selva J. Predisposition to aneuploidy in the oocyte. Cytogenetic and Genome Research [Article]. Switzerland; 2011;**133**(2-4):127-135

[11] Fonseka KGL, Griffin DK. Is there a paternal age effect for aneuploidy? Cytogenetic and Genome Research. [Article]. 2011;**133**(2-4):280-291

[12] Cereda A, Carey JC. The trisomy 18 syndrome. Orphanet Journal of Rare Diseases. 2012 Oct;**7**:81

[13] Bijanzadeh M. The recurrence risk of genetic complex diseases. Journal of Research in Medical Sciences. 2017;**22**:32

[14] Selikowitz M. Down Syndrome. Oxford: OUP; 2008

[15] Uehara S, Yaegashi N, Maeda T, Hoshi N, Fujimoto S, Fujimori K, et al. Risk of recurrence of fetal chromosomal aberrations: Analysis of trisomy 21, trisomy 18, trisomy 13, and 45,X in 1,076 Japanese mothers. Journal of Obstetrics and Gynaecology Research. 1999;**25**(6):373-379

[16] Chen CP, Wang LK, Chern SR, Chen YN, Chen SW, Wu PS, et al. Mosaic trisomy 17 at amniocentesis: Prenatal diagnosis, molecular genetic analysis, and literature review. Taiwanese journal of Obstetrics & Gynecology. 2016 Oct;**55**(5):712-717

[17] Bregand-White J, Saller DN, Clemens M, Surti U, Yatsenko SA, Rajkovic A. Genotype-phenotype correlation and pregnancy outcomes of partial trisomy 14q: A systematic review. American Journal of Medical Genetics Part A. 2016 Sep;**170**(9):2365-2371

[18] Baty BJ, Blackburn BL, Carey JC. Natural history of trisomy 18 and trisomy 13: I. Growth, physical assessment, medical histories, survival, and recurrence risk. American Journal of Medical Genetics. 1994;**49**(2):175-188

[19] Dotters-Katz SK, Kuller JA, Grace MR, Laifer SA, Strauss RA. Management considerations for ongoing pregnancies complicated by trisomy 13 and 18. Obstetrical & Gynecological Survey. 2016 May;**71**(5):295-300

[20] Pawelec M, Dzugalik M, Pietras J, Belza L, Latkowski L. Medical and ethical considerations related to viable fetuses with trisomy 13 in the 36th week of pregnancy—A review of the literature. Advances in Clinical and Experimental Medicine. 2015 Sep-Oct;**24**(5):911-921

[21] Rosa RF, Rosa RC, Zen PR, Graziadio C, Paskulin GA. Trisomy 18: Review of the clinical, etiologic, prognostic, and ethical aspects. Revista Paulista de Pediatria. 2013 Jan-Mar;**31**(1):111-120

[22] Ranweiler R. Assessment and care of the newborn with down syndrome. Advances in Neonatal Care. 2009 Feb;**9**(1):17-24; Quiz 5-6

[23] Bradley S, James T. Medical Genetics: An Integrated Approach. 1st ed. McGraw-Hill Education/Medical; 2014

[24] Harper PS. Practical Genetic Counselling. 7th ed. UK: CRC Press; 2010

[25] Covic Mircea SD, Ionel S. Genetica Medicala. 2 ed. Romania, Iasi: Polirom; 2011. pp. 677-680

[26] DeSilva M, Munoz FM, Mcmillan M, Kawai AT, Marshall H, Macartney KK, et al. Congenital anomalies: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. Netherlands; 2016;**34**(49):6015-6026

[27] CfDC, Prevention. Update on overall prevalence of major birth defects—Atlanta, Georgia, 1978-2005. Morbidity and Mortality Weekly Report. 2008 Jan;**57**(1):1-5

[28] Christianson A, Howson CP, Modell B. March of Dimes: Global report on birth defects, the hidden toll of dying and disabled children. 2005

[29] Oakley L, Maconochie N, Doyle P, Dattani N, Moser K. Multivariate analysis of infant death in England and Wales in 2005-06, with focus on socio-economic status and deprivation. Health Statistics Quarterly. London, England: the Stationery Office; c1999-2009;**42**(1):22-39

[30] World Health Organization. Birth defects. Sixty-Third World Health Assembly Provisional Agenda Item. 2010;**11**:32-33

[31] Boyd PA, Devigan C, Khoshnood B, Loane M, Garne E, Dolk H, et al. Survey of prenatal screening policies in Europe for structural malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome. BJOG : An International Journal of Obstetrics and Gynaecology. 2008 May;**115**(6):689-696

[32] Asplin N, Wessel H, Marions L, Georgsson Öhman S. Pregnancy termination due to fetal anomaly: Women's reactions, satisfaction and experiences of care. Midwifery. 2014 Jun;**30**(6):620-627

[33] World Health Organization, Prevention CfDCa. Birth Defects Surveillance Training: Facilitator's Guide. 2015

[34] Basso O, Olsen J, Christensen K. Recurrence risk of congenital anomalies—The impact of paternal, social, and environmental factors: A population-based study in Denmark. American Journal of Epidemiology. Oxford University Press for the Johns Hopkins Bloomberg School of Public Health; 1999 Sep;**150**(6):598-604

[35] Covic M, Stefanescu D, Sandovici I, Gorduza VE. Genetica Medicala. III ed. Polirom; 2017. pp. 636-655

[36] Xu K, Montag M. New perspectives on embryo biopsy: Not how, but when and why? Seminars in Reproductive Medicine. United States; 2012 Aug;**30**(4):259-266

[37] Goossens V, De Rycke M, De Vos A, Staessen C, Michiels A, Verpoest W, et al. Diagnostic efficiency, embryonic development and clinical outcome after the biopsy of one or two blastomeres for preimplantation genetic diagnosis. Human Reproduction. 2008 Mar;**23**(3):481-492

[38] Technology PCotSfAR, Medicine PCotASfR. Preimplantation genetic testing: A practice committee opinion. Fertility and Sterility. 2007 Dec;**88**(6):1497-1504

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