REVIEW ARTICLE

Genetics of Birth Defects

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ABSTRACT

Congenital anomalies constitute a significant proportion of infant morbidity and mortality. In about 50 to 70%, the cause of the birth defect remains unknown. However, with continued advancements in technology and research, as the genes involved in various processes instrumental in programming early embryonic development are identified, the molecular basis of an increasing number of birth defect syndromes is being defined.

Keywords: Congenital malformations, Birth defect, Genetics.

INTRODUCTION

A birth defect is an abnormality of structure, function or metabolism present at birth that results in physical or mental disabilities or death. Thousands of different birth defects have been identified. It may be clinically obvious at birth or may be diagnosed only later in life. For example, neural tube defect is a structural birth defect clinically obvious at birth and thalassemia is a functional birth defect that may present clinically only in infancy or childhood. A few birth defects, like Huntington's disease, manifest only in adulthood. Serious birth defects are life-threatening or have the potential to cause lifelong mental, physical, visual or auditory disability.[1,2] The birth prevalence of all genetic birth defects collectively ranges from a high of 82 to a low of 39.7 per 1,000 live births worldwide.[3] Many of the highest birth prevalence rates are found among the world's poorest countries while many of the lowest rates are found among the world's wealthier countries, with the exception of countries where common recessive disorders and marriages between first cousins and other close relatives are common. According to the March of Dimes report,[3] five common serious birth defects of genetic or partially genetic origin in 2001 were: (1) Congenital heart defects (1,040,835 births); (2) neural tube defects (323,904 births); (3) the hemoglobin disorders, thalassemia and sickle cell disease (307,897 births); (4) Down syndrome (trisomy 21) (217,293 births); and (5) glucose-6-phosphate dehydrogenase (G6PD) deficiency (177,032 births). Collectively, these five conditions account for about 25% of all of birth defects of genetic or partially genetic origin.

Congenital birth defect affects 2 to 4% of all liveborn infants and 15 to 20% of stillbirths. Recognizing patterns of multiple congenital malformations may allow inferences to be made about the timing, mechanism, and etiology of structural developmental defects. Research on animal models is providing information about cellular interactions, migration and differentiation processes, and gives insight into the possible mechanisms underlying human malformations. Molecular studies are now identifying defects, such as submicroscopic chromosomal deletions and mutations in developmental genes as the underlying cause of some recognized syndromes. Diagnosing multiple congenital abnormality syndromes in children can be difficult and require great expertise to give correct advice about management, prognosis and risk of recurrence in the future pregnancies.

CAUSES OF BIRTH DEFECTS[3]

Genetic and environmental factors, or a combination of these factors, can cause birth defects. However, the causes of about 70% of birth defects are unknown.[1] Hence causes can be divided broadly into two groups:

1. Genetic and partially genetic causes, originating mostly before conception (preconception)
2. Causes developing after conception, but before birth (post-conception)

Preconceptional Causes

Most of the birth defects originate prior to conception and are due to abnormalities of chromosomes and genes. Multifactorial defects occur due to a combination of genes and environmental factors. Genetic abnormalities can either be inherited or occur as an isolated event in a particular pregnancy.

The three main categories in preconceptional causes are:

Chromosomal Abnormalities

Chromosomal abnormalities are due to changes in the number or structure of chromosomes from the normal state resulting in

a gain or loss of genetic material. Chromosomal abnormalities usually are caused by an error that occurred when an egg or sperm cell was developing. Because of the error, a baby can be born with too many or too few chromosomes, or with one or more chromosomes that are broken or rearranged. These abnormalities account for approximately 6% of birth defects in industrialized countries.[4]

Examples include:

- Trisomies are the commonest form of chromosomal aneuploidies. Presence of an extra chromosome is known as trisomy. Down Syndrome is the most common cause of mental retardation and occurs due to an extra chromosome 21 (Fig. 1). Affected children have varying degrees of intellectual disabilities, characteristic facial features and, often, heart defects and other problems. Affected babies with trisomies 18 and 13 have multiple birth defects and often die in the first months of life. The trisomies result from failure of separation of one of the pairs of homologous chromosomes during anaphase of maternal meiosis 1, known as *nondisjunction*. Nondisjunction can also occur in early phase of postzygotic mitosis giving rise to mosaicism. The cause of nondisjunction is uncertain but aging effect on primary oocyte has been postulated from observations of increased incidence of Down syndrome babies in mothers of advanced maternal age.
- Sex chromosome abnormalities (missing or extra copies of the sex chromosomes, X and Y). These disorders affect sexual development and may cause infertility, growth abnormalities and behavioral and learning problems. However, most affected individuals live fairly normal lives. Examples include Turner syndrome (Fig. 2) (in which all or part of an X-chromosome is missing) and Klinefelter syndrome (in which there is one or more extra X-chromosomes).

Fig. 1: Down syndrome

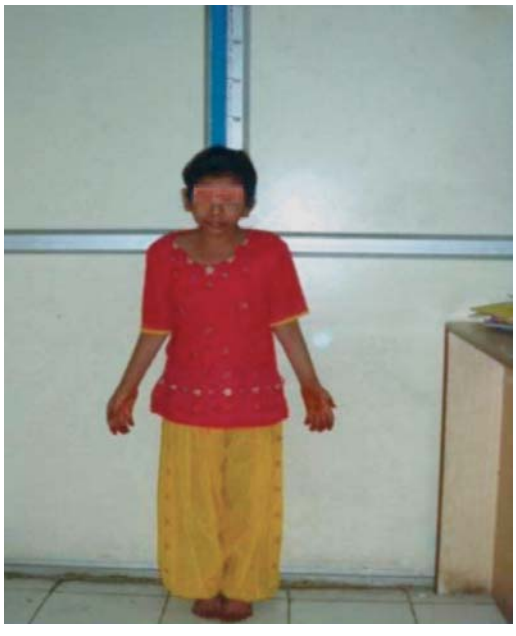


Fig. 2: Turner syndrome

Single Gene Defects

Single gene defects are caused by alterations in gene structure, called mutations, resulting in abnormal cell functioning. A mutation in a single gene can cause birth defects. Every human being has about 20,000 to 25,000 genes that determine traits like eye and hair color. Genes are packaged into each of the 46 chromosomes inside our cells and direct the growth, development and functioning of every system in the body. A child gets half its genes from each parent. More than 7,000 single gene defects have been described.[5] All single gene defects combined account for an estimated 7.5% of all birth defects in industrialized countries.[4] Mutations in the family of fibroblast growth factor receptor genes have been found in various skeletal dysplasias (achondroplasia, hypochondroplasia and thanatophoric dysplasia) as well as in a number of craniosynostosis syndromes like Pfeiffer and Apert syndrome. Other examples include mutations in the *PAX3* gene in Waardenberg syndrome type I, *PAX6* gene in aniridia type II, and *SOX9* gene in campomelic dysplasia.

Autosomal dominant (Fig. 3): A person can inherit a genetic disease when one parent (who may or may not have the disease) passes on a single faulty gene. This is called dominant inheritance. Each child of a parent with the mutant gene has a 50% chance of inheriting the disorder. Examples include:

- Achondroplasia (a form of dwarfism)
- Marfan syndrome (a connective-tissue disease).

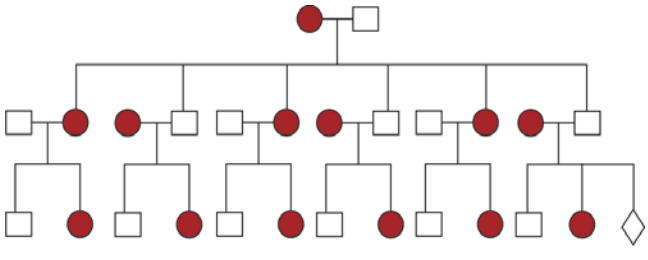


Fig. 3: Autosomal dominant pedigree

Autosomal recessive (Fig. 4): Other genetic diseases are inherited when both parents are carriers (means they do not have the disease but carry an abnormality in the same gene).They can pass the mutant gene on to a child. This is called recessive inheritance. Each child of carrier couple has a 25% chance of inheriting the disorder. Examples include:

- Tay-Sachs disease (a nervous system disorder)
- Cystic fibrosis (a serious disorder of lungs and other organs).

X-linked (Fig. 5): It is another form of inheritance in which males can inherit a genetic disease from a mother who carries an abnormal gene. Each son of a mother who carries an abnormal gene has a 50% chance of inheriting the disorder. Daughters usually do not inherit the disorder but they may be carriers like their mother. Examples include:

- Hemophilia (a blood-clotting disorder)
- Duchenne muscular dystrophy (progressive muscle weakness).

Multifactorial Disorders

Approximately 20-30% of all birth defects, a number of which are lethal.[4] Some birth defects appear to be caused by a combination of genes and environmental exposures. This is called multifactorial inheritance. Multifactorial defects occur due to a combination of genes that puts the fetus at risk in the presence of specific environmental factors. These defects are numerous and are usually malformations of a single organ system or limb. Some of the examples are congenital heart disease, neural tube defects, cleft lip and/or cleft palate, clubfoot, and developmental dysplasia of the hip.

It can also be the cause of the many common systemic diseases with a genetic predisposition presenting later in life. Examples are hypertension, diabetes, stroke, mental disorders and cancer.

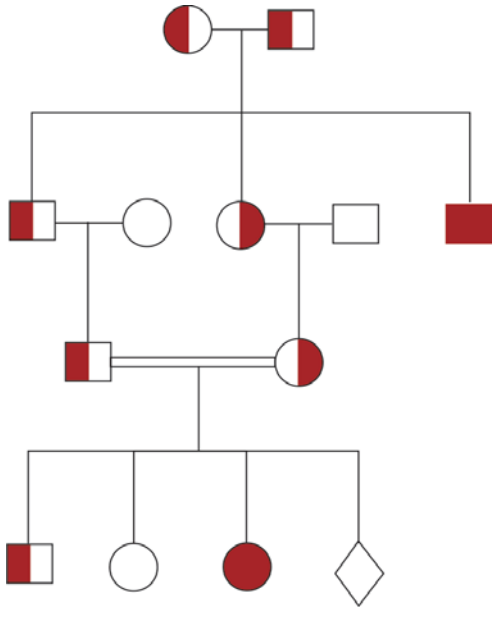


Fig. 4: Autosomal recessive pedigree

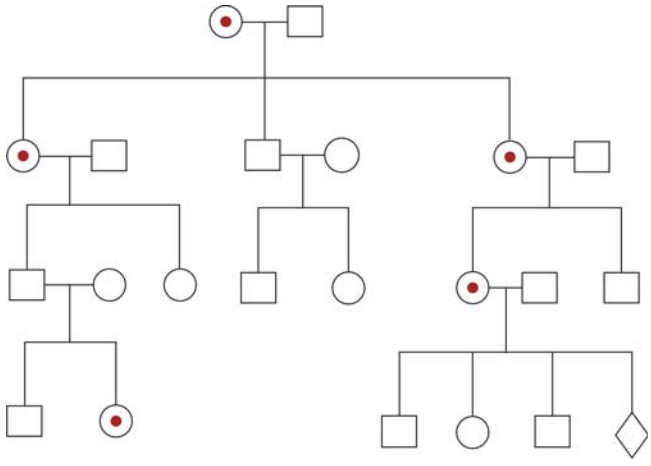


Fig. 5: X-linked recessive pedigree

Postconceptional Causes

These are primarily nongenetic and the birth defect is usually caused by an intrauterine environmental factor. These can be caused by various teratogens interfering with normal growth and development of the embryo or fetus, mechanical forces causing deformation of the fetus, and vascular accidents that disrupt the normal growth of organs. This category accounts for approximately 5 to 10% of all birth defects.[4]

Unknown Causes

In about 50 to 70% of all children born with birth defects, a specific cause cannot be designated. Some of these may be due to new autosomal dominant mutations, submicroscopic chromosome deletions or uniparental disomy.[4]

Based upon the degree of involvement and causes, they can also be divided as:

Single System Defects

A malformation is a primary structural defect occurring during the development of an organ or tissue. Most malformations have occurred by 8 weeks of gestation. Single system defects constitute the largest group of birth defects, affecting a single organ system or local region of the body. The commonest of these include cleft lip and palate, club foot, pyloric stenosis, congenital dislocation of the hip and congenital heart defects. They can occur in an otherwise normal child and can also occur frequently as a component of a more generalized multiple abnormality disorder. Most single malformations are inherited as polygenic traits with a fairly low risk of recurrence, and corrective surgery is often successful.

Multiple Malformation Syndromes

When a combination of congenital abnormalities occurs together repeatedly in a consistent pattern due to a single underlying cause, the term “syndrome” is used. The literal translation of this Greek term is “running together”. Multiple malformation syndromes comprise defects in two or more systems and many

are associated with mental retardation.The risk of recurrence is determined by the etiology, which may be chromosomal, teratogenic, due to a single gene or unknown. Minor anomalies are those that cause no significant physical or functional effect and can be regarded as normal variants if they affect more than 4% of the population. The presence of two or more minor anomalies indicates an increased likelihood of a major anomaly being present. Identification of a birth defect syndrome allows comparison of cases to define the clinical spectrum of the disorder and aids research into etiology and pathogenesis.

Disruption

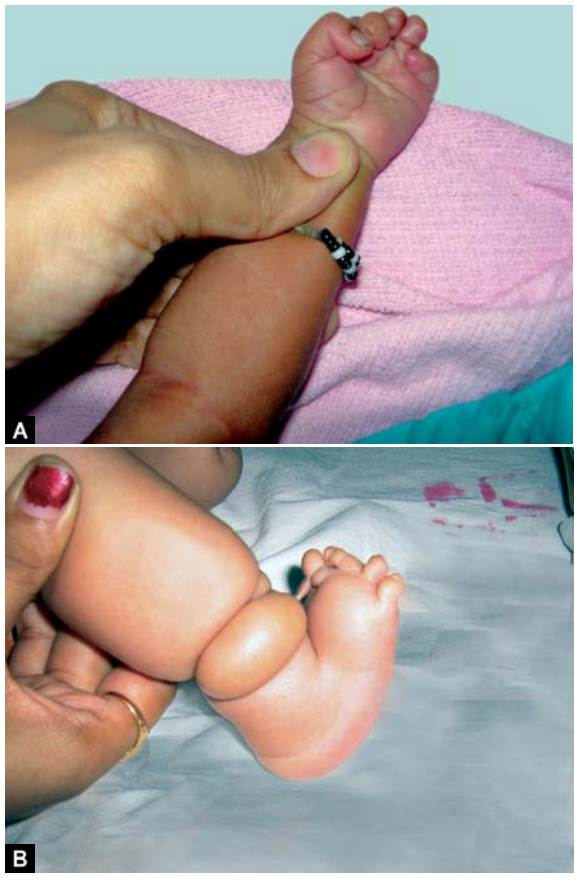
A disruption defect implies that there is destruction of a part of fetus that had initially developed normally. Disruptions usually affect several different tissues within a defined anatomical region. Amniotic band disruption after early rupture of the amnion is a well-recognized entity causing constriction bands that can lead to amputations of digits and limbs. Sometimes more extensive disruptions occur, such as facial clefts and central nervous system defects. Interruption of the blood supply to a developing part, due to other causes, will also cause disruption due to infarction with consequent atresia. The prognosis is determined by the severity of the physical defect. As the fetus is genetically normal and the defects are caused by an extrinsic abnormality, the risk of recurrence is small (Figs 6A and B).

Deformation

Deformations are due to abnormal intrauterine molding and give rise to deformity of structurally normal parts. Deformations usually involve the musculoskeletal system and may occur in fetuses with underlying congenital neuromuscular problems, such as spinal muscular atrophy and congenital myotonic dystrophy. Paralysis in spina bifida also gives rise to positional deformities of the legs and feet. In these disorders, the prognosis is often poor and the risk of recurrence for the underlying disorder may be high. Oligohydramnios causes fetal deformation and is well recognized in fetal renal agenesis (Potter sequence). The absence of urine production by the fetus results in severe oligohydramnios, which in turn causes fetal deformation and pulmonary hypoplasia. Oligohydramnios caused by chronic leakage of liquor has a similar effect. A normal fetus may be constrained by uterine abnormalities, breech presentation or multiple pregnancy. The prognosis is generally excellent, and the risk of recurrence is low, except in cases of structural uterine abnormality.

Dysplasia

Dysplasia refers to abnormal cellular organization or function within a specific organ or tissue type. Most dysplasias are caused by single gene defects and include conditions, such as skeletal dysplasias and storage disorders from inborn errors of metabolism (Fig. 7). Unlike the other mechanisms causing birth defects, dysplasias may have a progressive effect and can lead to continued deterioration of function.



Figs 6A and B: Amniotic band disruption

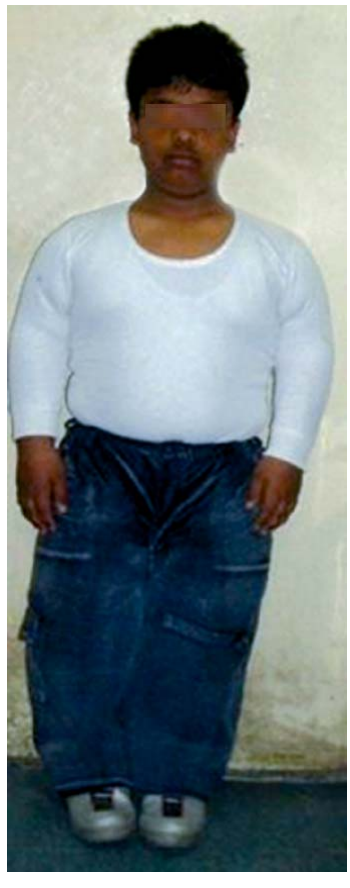


Fig. 7: Achondroplasia

Sequences

The term sequence implies that a series of events occurs after a single initiating abnormality, which may be a malformation, a deformation or a disruption. The features of Potter sequence are classed as a malformation sequence because the initial abnormality is renal agenesis, which gives rise to oligohydramnios, secondary deformation and pulmonary hypoplasia. Other examples are the holoprosencephaly and the sirenomelia sequence. In holoprosencephaly the primary developmental defect is in the forebrain, leading to microcephaly, absent olfactory and optic nerves, and midline defects in facial development, including hypotelorism or cyclopia, midline cleft lip and abnormal development of the nose. In sirenomelia the primary defect affects the caudal axis of the fetus, from which the lower limbs, bladder, genitalia, kidneys, hindgut and sacrum develop. Abnormalities of all these structures occur in the sirenomelia sequence.

ASSOCIATIONS

Certain malformations occur together more often than expected by chance alone and are referred to as associations. There is great variation in clinical presentation, with different children having different combinations of the related abnormalities. The names given to recognized malformation associations are often acronyms of the component abnormalities.

Hence, the *VATER* association consists of ***v***ertebral anomalies, ***a***nal atresia, ***t***racheo***e***sophageal fistula and ***r***adial defects. The acronym *VACTERL* has been suggested to encompass the additional ***c***ardiac, ***r***enal and ***l***imb defects of this association. *MURCSs* association is the name given to the nonrandom occurrence of ***Mu***llerian duct aplasia, ***r***enal aplasia and ***c***ervicothoracic ***s***omite dysplasia.

COMPLEXES

The term developmental field complex has been used to describe abnormalities that occur in adjacent or related structures from defects that affect a particular geographical part of the developing embryo. The underlying etiology may represent a vascular event, resulting in the defects such as those seen in hemifacial microsomia (Goldenhar syndrome), Poland anomaly and some cases of Möbius syndrome.

GENETIC ASSESSMENT AND COUNSELING

The assessment of infants and children with malformations requires a detailed history and a physical examination. One should carefully draw a detailed three generation pedigree and document parental age and relevant family history. Any antenatal abnormalities, including possible exposure to teratogens, maternal diabetes, mode of delivery and the occurrence of any perinatal problems should be noted. The subsequent general health, growth and development, and behaviour of the child must also be assessed. Examination of the child should include a search for both major and minor anomalies with documentation of the abnormalities present and accurate clinical measurements and photographic records whenever possible. Increasingly, numerous malformation syndromes are being identified, and many are extremely rare. One needs to review the published case reports and specialized texts before a diagnosis can be reached. Various computer programs like London dysmorphology database are available to assist in differential diagnosis. Despite this, a considerable proportion of malformation syndromes remain undiagnosed.

Recognition of multiple malformation syndromes is very important to advice parents about management, prognosis and risk of recurrence in the future pregnancies. Very often, parents experience feelings of guilt after the birth of an abnormal child. Effective genetic counselling regarding etiology, various treatment options and related prognosis becomes very important. Multiple sessions of genetic counseling may be required depending upon the psychology of the parents. Time spent in discussing what is known about the etiology of the abnormalities may help to alleviate some of their fears. They also need a detailed explanation of what to expect in terms of treatment, anticipated complications and long-term prognosis. Accurate assessment of the risk of recurrence cannot be made without a diagnosis. Hence, depending upon the etiology, necessary investigations like chromosomal analysis and molecular, biochemical or radiological studies should be performed simultaneously.

Appropriate recurrence risks can be provided for chromosomal or mendelian for many multiple congenital malformation syndromes. If the etiology of a recognized multiple malformation syndrome is not known, empirical figures for the risk of recurrence (usually fairly low) derived from family studies can be used.

In consanguineous marriages, the recurrence risk for an undiagnosed multiple malformation syndrome is likely to be high. In any family with more than one child affected, it is appropriate to explain the 1 in 4 risk of recurrence associated with autosomal recessive inheritance, although some cases may be due to a cryptic familial chromosomal rearrangement.

Availability of prenatal diagnosis in subsequent pregnancies will depend on whether there is an associated chromosomal abnormality, a structural defect amenable to detection by ultrasonography, or an identifiable biochemical or molecular abnormality. In the case of a molecular defect or chromosomal defect, an early prenatal diagnosis at 11 to 12 weeks of gestation can be provided.

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