3 Congenital Malformation Syndromes

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The birth of a child with single or multiple congenital anomalies is a source of stress for the family and the healthcare team, even in the presence of a known family history of the condition or of prenatal diagnosis. Identifying the correct etiology is relevant to plan for appropriate interventions, to search for possible associated abnormalities, to establish a prognosis, and to predict recurrence risk. This chapter summarizes the clinical evaluation of the child with congenital anomalies in the context of a syndrome, defined as a *recognizable pattern of abnormalities that share a common underlying etiology.* Approaches to common clinical problems with a brief depiction of some relatively frequent syndromes are included. Several thousand syndromes have been recognized and their individual description is beyond the scope of this section. References to specialized textbooks or databases have been incorporated for further reading.

Definitions/Classifications

Dysmorphology is the term used to describe the study of congenital anomalies. It is estimated that 2–3% of newborns have *major congenital abnormalities*, that is, those that are present at birth and require surgical or medical treatment because of functional or cosmetic consequences. Most newborns with major congenital anomalies have isolated ones, but it has been estimated that about a third to a half of those with congenital abnormalities, or 0.7–1% of all newborns, have multiple anomalies.

Recognizable patterns of anomalies are usually categorized as syndromes, sequences, and associations. As mentioned above, a *syndrome* is a recognizable pattern of anomalies with a common underlying etiology. For example, individuals with Down syndrome have identifiable facial features, developmental delay and mental retardation, central hypotonia, risk of congenital heart disease, hearing and visual impairment, among others; these manifestations are due to the presence of additional material from chromosome 21. Marfan syndrome is characterized by tall stature with long extremities, pectus carinatum or excavatum, lens dislocation, aortic root dilatation, and other features (*Fig. 3.1*) that are the result of mutations in the *FBN1* gene encoding for fibrillin, an extracellular matrix protein. A *sequence* is defined as a group of anomalies resulting as a cascade from a single initial defect in morphogenesis. Robin sequence, for example, refers to the association of microretrognathia (small and receding chin), glossoptosis and respiratory distress with or without cleft palate. It is presumed that microretrognathia in early development is the initial defect, causing a displacement of the tongue backwards and upward to a position that interferes with palatal closure. Potter sequence is characterized by flat facial features, abnormal positioning of the extremities, and pulmonary hypoplasia – findings that are secondary to oligohydramnios – and this is due to renal agenesis. An *association* refers to a group of congenital anomalies that occur together with higher frequency than expected by chance, but without a known common etiology. For instance, VACTERL (or VATER) association includes vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal and limb defects. Though there is no agreement on how many of these anomalies are sufficient to establish the diagnosis of VACTERL (authors suggest anomalies in at least three different anatomic regions), it is relevant to be aware of this association, as the presence of one of the defects should prompt the clinician to carefully search for the others. MURCS association includes Mullerian duct (upper vagina and uterus) hypoplasia, renal and cervical vertebra defects, also of so far unknown etiology.

With the increasing knowledge on the pathogenesis and availability of molecular tests, some conditions previously categorized as associations are now classified as syndromes. One example is CHARGE syndrome (coloboma, heart disease, choanal atresia, renal anomalies, growth and mental retardation, genital hypoplasia, and ear anomalies): microdeletions and mutations in the *CHD7* gene have recently been identified as the cause of the multiple and apparently unrelated anomalies. *CHD7* is a member of the chromodomain helicase DNA-binding (*CHD*) genes that encode for a class of proteins that are thought to have pivotal roles in regulating chromatin structure and gene expression in early embryonic development.

Clinical series and large epidemiologic studies have shown that syndromes may be recognized in the neonatal

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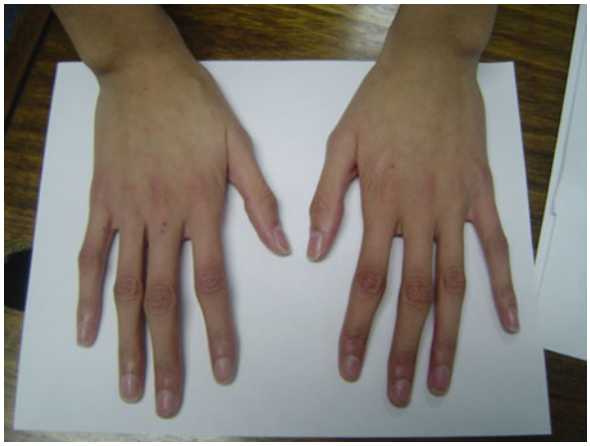


Figure 3.1
Arachnodactyly in a girl with Marfan syndrome

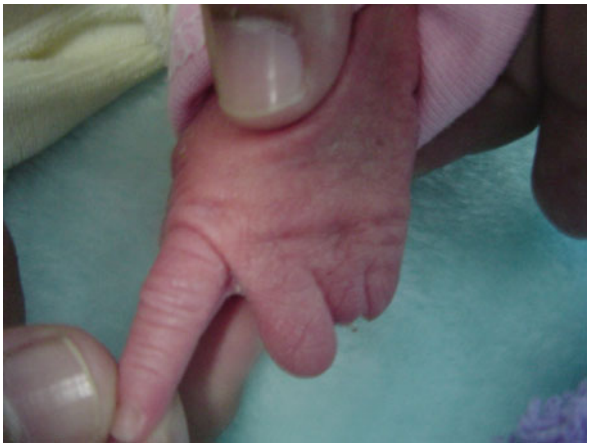


Figure 3.2
Third to fifth digit amputations due to amniotic bands

period in about 25% of newborns evaluated for congenital anomalies. A substantial portion of syndromes are recognized later in life, especially since several cardinal manifestations, such as developmental or growth delays can present in an age-dependant manner. This has practical implications for the clinician and the family, since arriving to a correct diagnosis may require long-term follow up and re-evaluation.

Several thousand syndromes have been delineated and many are described and catalogued in textbooks, such as Smith's Recognizable Patterns of Malformations and Syndromes of the Head and Neck, or computer or web-based clinical databases, such as the Baraitser-Winter Dysmorphology database (formerly London Dysmorphology database) and Pictures of Standardized Syndromes and Undiagnosed Malformations (POSSUM).

Etiology

On a pathogenic basis, congenital anomalies are classified as *malformations* (abnormal organ or tissue formation, as seen in congenital heart defects or spina bifida), *dysplasias* (abnormal organization of cells, such as skeletal dysplasias and lysosomal storage diseases), *deformations* (effect of extrinsic forces acting on an otherwise normal fetus or embryo, for example, intrauterine constraints leading to club foot), and *disruptions* (destruction of normal tissue, for example, by amniotic bands (*Fig. 3.2*), infections or hypoxia). Though there may be overlap within these categories, the classification has practical implications in terms of prognosis and recurrence risks. Patients with deformations tend to have relatively good therapeutic prognosis and low recurrence risks unless the underlying cause persists (such as uterine myomata or bicornuate uterus). Dysplasias are usually of genetic origin with recurrence risks that depend on the pattern of inheritance, and there is, in general, a paucity of curative therapies.

The term "congenital" (present at birth) does not in itself imply a specific etiology and is not synonymous with genetic cause. It has been estimated that chromosome abnormalities or rearrangements account for 5–10% of cases of major congenital anomalies, single gene defects for 10–15%, environmental (non genetic) causes such as infections or teratogens in 10%, polygenic/multifactorial (i.e., the result of an interaction between genetic and nongenetic factors) in 30–40%, and unknown cause in 30–50%.

Epidemiology

Birth defects surveillance systems have been implemented in different countries or regions to monitor the occurrence of congenital anomalies and conduct research geared towards understanding the causes, decreasing their consequences, and elaborating preventive strategies. The International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) (http://www.icbdsr.org) collects information from over 40 programs around the world, a strategy that has been useful in understanding the causes that underlie several defects.

Based on data provided by these monitoring systems, it has been estimated, as described above, that about 2–3% of newborns have major congenital abnormalities.

In addition, other relevant anomalies, such as growth failure, developmental delays, mental retardation, hearing or vision loss, may be evident later, so that, by age 5 years, approximately 7% of children may have major anomalies that warrant the search for an underlying etiology.

Major congenital anomalies were estimated to account for half a million deaths worldwide in 1997 and constitute a substantial cause of neonatal and infant mortality in both developed and developing countries. As infant mortality rates have decreased worldwide in the past 50 years, the relative contribution of congenital anomalies to infant mortality has increased. Major congenital anomalies are also one of the most frequent causes of pediatric hospitalization, accounting for a third to one half of admissions to tertiary care hospitals.

Common types of major anomalies include, among many others, congenital heart disease, cleft lip and/or palate, and neural tube defects (including anencephaly and spina bifida) that have average incidences of 8/1,000, 1.6/1,000, and 1.1/1,000 live births, respectively. There is evidence of geographic or ethnic differences in frequencies of several birth defects. For example, the incidence of neural tube defects was highest, almost 19/1,000, in the Netherlands and 5/1,000 in France in the early 1990s, before folic acid supplementation was widely implemented in these countries. Regional differences have also been observed in the incidence of cleft lip.

Clinical Manifestations and Diagnosis: The Clinical Evaluation of the Child with Congenital Anomalies

Finding the correct diagnosis for a patient with single or multiple congenital anomalies has several implications: existing knowledge of the natural history of the condition will allow planning for additional evaluations and necessary care, available information on the particular syndrome will serve as a prognostic guideline, and knowledge of the cause of the syndrome will be necessary to estimate risk of recurrence and to consider and implement available preventative measures. Nevertheless, it is estimated that a definitive diagnosis is reached in only approximately 20–50% of children with multiple anomalies.

A genetic evaluation of an infant or child with congenital anomalies should be considered in the presence of two or more major anomalies (including mental retardation and short stature), one major and multiple minor anomalies, or a major anomaly and/or multiple minor ones and a family history of congenital anomalies, recurrent miscarriages (>2), neonatal death, parental consanguinity and infants with congenital anomalies and a history of potential teratogen exposure (◉ *Table 3.1*).

Table 3.1
Common reasons for referral to pediatric genetics evaluation

Two or more major anomalies
One major and multiple minor anomalies
One or more major and/or multiple minor anomalies and family history of congenital anomalies, parental consanguinity, recurrent miscarriages or teratogen exposure
Known genetic syndrome
Neonatal death

As in every area of medicine, achieving a correct syndrome diagnosis starts with a detailed clinical history and physical examination. The clinical evaluation of a child with congenital anomalies requires thoroughness. Relevant elements of the clinical history include the pregnancy history (pregnancy planning, parental age, occupation and health status, exposure to drugs, medications, alcohol, evidence of maternal infectious diseases and chronic illness, fetal movements, oligo- or polyhydramnios, ultrasound or other antenatal screening results), delivery (gestational age, presentation and mode of delivery, birth weight, length and head circumference and their relationship to gestational age), as well as neonatal adaptation and behavior, including evidence of asphyxia, neurological and biochemical abnormalities, such as hypoglycemia or hypocalcemia. If the child is older, information on growth and development as well as the interval medical history may also provide important diagnostic clues.

The family history is also relevant to diagnosis, since there may be other relatives with similar or related findings, including more subtle ones, or it may reveal other individuals at risk of developing the disease or of transmitting it to their offspring. Information is gathered as a minimum of three-generation pedigree and should include affected individuals, miscarriages, and consanguinity. A useful way of summarizing the family history is the drawing of a pedigree using standardized symbols (◉ *Fig. 3.1*).

The physical examination of the affected child, and other family members if necessary, constitutes another crucial diagnostic element. Growth and proportions should be documented and compared to age-appropriate percentiles. The basic parts of the general and segmental physical exam are performed, but special attention should be given to findings that may constitute major or minor

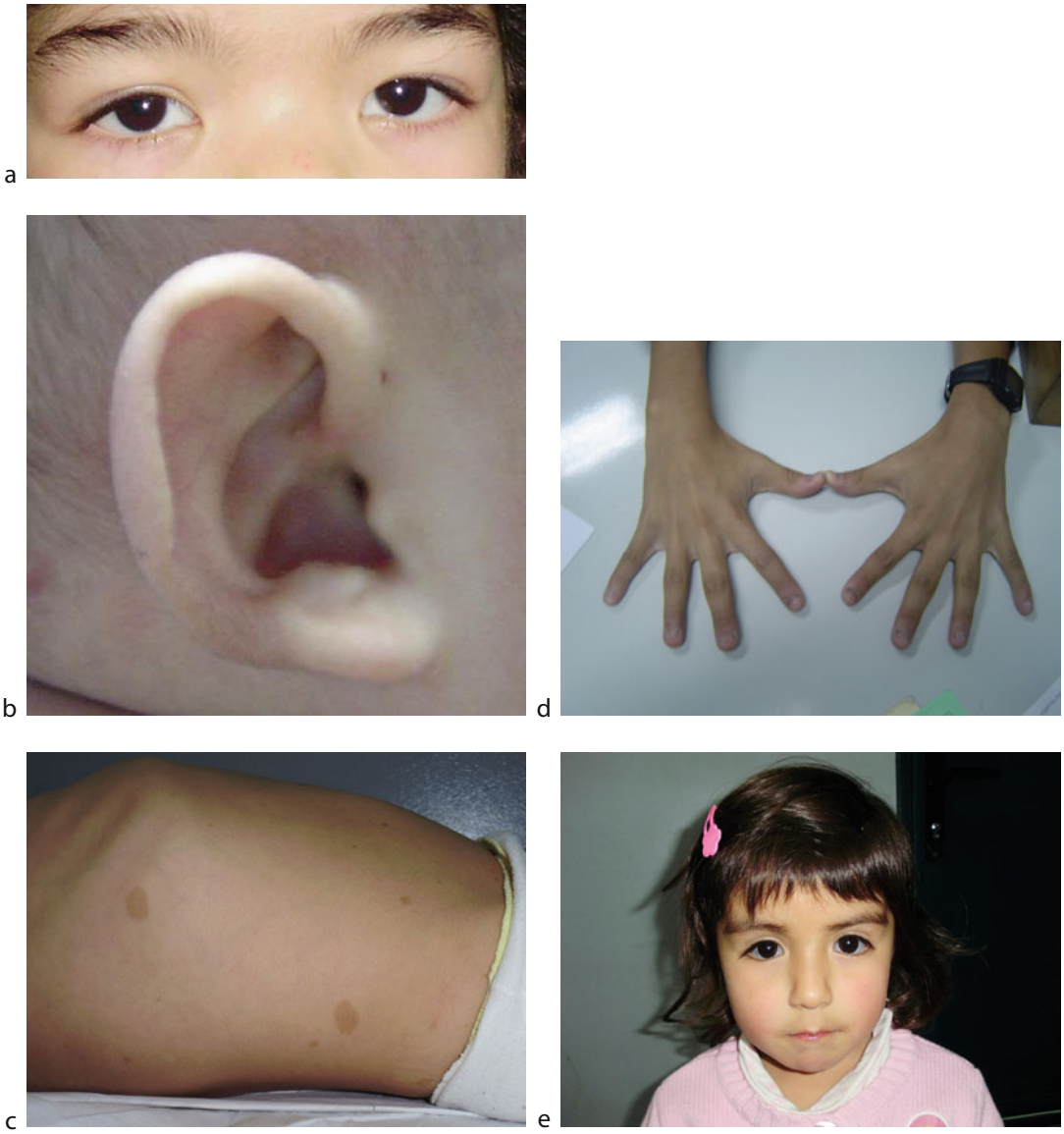


Figure 3.3
Examples of minor anomalies. (a) Inner epicanthal folds and depressed nasal bridge, (b) preauricular pit, (c) multiple café au lait spots, (d) interdigital webbing, (e) blue sclerae

anomalies, as well as the distinction of the latter from normal variants. *Minor anomalies* are those that constitute morphologic abnormalities that are of no serious medical or cosmetic consequence, and are present in 4% or less of the population. They tend to be more frequent in areas of complex formation, such as the face, ears, and hands. Examples include epicanthal folds, preauricular tags or pits, hypo-or hyperpigmented maculae, etc. (*Fig. 3.3*). The identification of these minor anomalies is relevant since they may provide diagnostic clues in the evaluation of a child with major anomalies. Additionally, it has been shown that the presence of three or more minor anomalies may be associated with the presence of major ones in 20–90% of infants. Therefore, it has been recommended to search for major anomalies in newborns with multiple minor anomalies. It can be challenging for the clinician to distinguish these minor anomalies from *normal variants*, defined as structural variations without

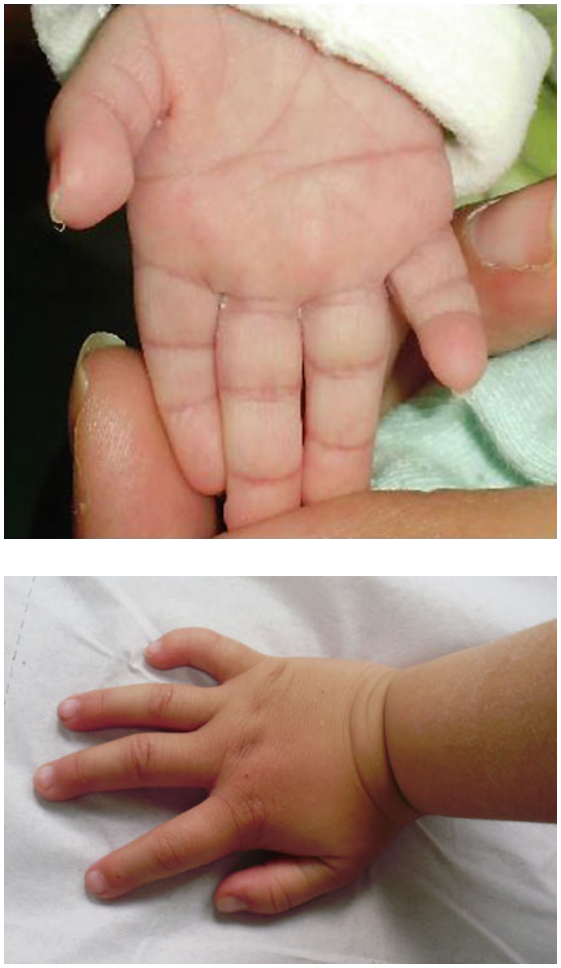


Figure 3.4
Examples of normal variants. (a) (Incomplete) transverse palmar crease, (b) fifth finger clinodactyly

medical consequences that are common in a population, occurring with a frequency of 4% or greater, such as transverse palmar creases, fifth finger clinodactyly, etc. (*Fig. 3.4*). The clinician should be aware of ethnic differences in frequencies of these minor findings; for example, epicanthal folds are common in Asian individuals and would thus be considered a normal variant in these populations, but they are infrequent in Caucasian individuals and therefore, would be catalogued as a minor anomaly in them.

It is useful to obtain objective measurements and to compare them with available standards. These standards have been constructed predominantly with data from Caucasian individuals; therefore, comparisons may also need to be interpreted with caution when used for patients of other ethnic origins. Photographs obtained with informed consent are useful to document the condition and age-related changes as well as to facilitate consultation with pertinent specialists. Several sites have implemented telemedicine services to facilitate evaluation of patients in remote locations, and this type of service is likely to continue growing in the future, allowing for access to specialist consultation.

Useful laboratory tests to further assess the phenotypic features include imaging studies to search for malformations not evident on surface exam, hearing and vision evaluations, formal developmental assessments, and biochemical tests, for example mucopolysaccharides when a lysosomal storage disease affecting these metabolites is suspected, or cholesterol levels in the case of Smith-Lemli-Opitz syndrome – a severe defect in cholesterol biosynthesis that causes microcephaly, a distinctive facies, congenital heart disease, genital abnormalities, Y-shaped syndactyly between the second and third toes, high prenatal and neonatal mortality, and mental retardation in the survivors.

Once all this clinical information has been gathered, the next step is to consider possible differential diagnoses. The clinician needs to keep in mind that no single sign is pathognomonic of a syndrome, minor anomalies are seen in otherwise healthy children, and there can be crucial diagnostic signs and symptoms that may appear later in life.

For the experienced clinician, a diagnosis may be achieved through what is known as the "gestalt" or pattern recognition approach. Since most syndromes are individually infrequent, it is unlikely that all of them would have been seen or recognized by a physician. As mentioned above, there are useful textbooks and computer databases that may aid in the identification of a diagnosis. It must be emphasized that the accuracy of such diagnosis relies fundamentally in the adequate recognition, description and prioritization of signs and symptoms by the clinician. As expressed by Hunter, these databases should be considered "systems for experts" rather than "expert systems."

If possible, once a diagnostic hypothesis has been proposed, laboratory confirmatory tests should be performed. Specific genetic tests are not available for all recognizable syndromes. In some cases, the underlying genetic etiology is unknown; in others, cost or accessibility issues may make testing not feasible. These limitations should not preclude the implementation of adequate care measures and education of the patient and his or her family.

The most commonly used genetic test is the karyotype, and it should be considered in the presence of a known recognizable chromosome abnormality syndrome, or in children with multiple major congenital anomalies or minor anomalies, mental retardation, or short stature.

If a specific microdeletion or microduplication is suspected based on the clinical findings, fluorescence in situ hybridization (FISH) testing with specific probes is a necessary additional form of testing. Higher resolution testing for genomic imbalances, such as array comparative genomic hybridization (array-CGH), has been shown to increase the rate of detectable chromosome abnormalities from 5–10% to an average of 17–20%. If a specific monogenic disorder is recognized, molecular testing to identify the causative mutation will be useful for confirmation and, if indicated, to offer testing to other relatives at risk. The detection rate of molecular testing for most monogenic disorders is less than 100% and it is necessary to begin testing with the affected individual if available. Once a mutation has been found, testing can be offered to affected or at-risk relatives. Web-based databases of laboratories that perform genetic clinical and research tests and descriptions of their uses are listed in *Table 3.2*, along with other useful sources of genetics information.

Some inborn errors of metabolism can be a cause of congenital anomalies, and biochemical tests may also be useful as diagnostic tools. Smith-Lemli-Opitz syndrome, described above, is an example. Defects in mitochondrial energy production may cause central nervous system malformations and patients may have abnormalities in lactate and pyruvate levels and in urine organic acids that aid in orienting to a specific diagnosis.

It is estimated that in about 50% or more of the evaluated patients no diagnosis will be made, even after a complete evaluation. The family should be reassured that the lack of a specific diagnosis will not impede access to therapies and that an incorrect diagnosis may be more harmful than no diagnosis. It is relevant, in these cases, to reevaluate the child with certain periodicity, since new and/or more specific signs or symptoms may appear in the patient with age, and new diagnosis or diagnostic tests may have been described or developed. A summary of the approach is presented in *Fig. 3.5*.

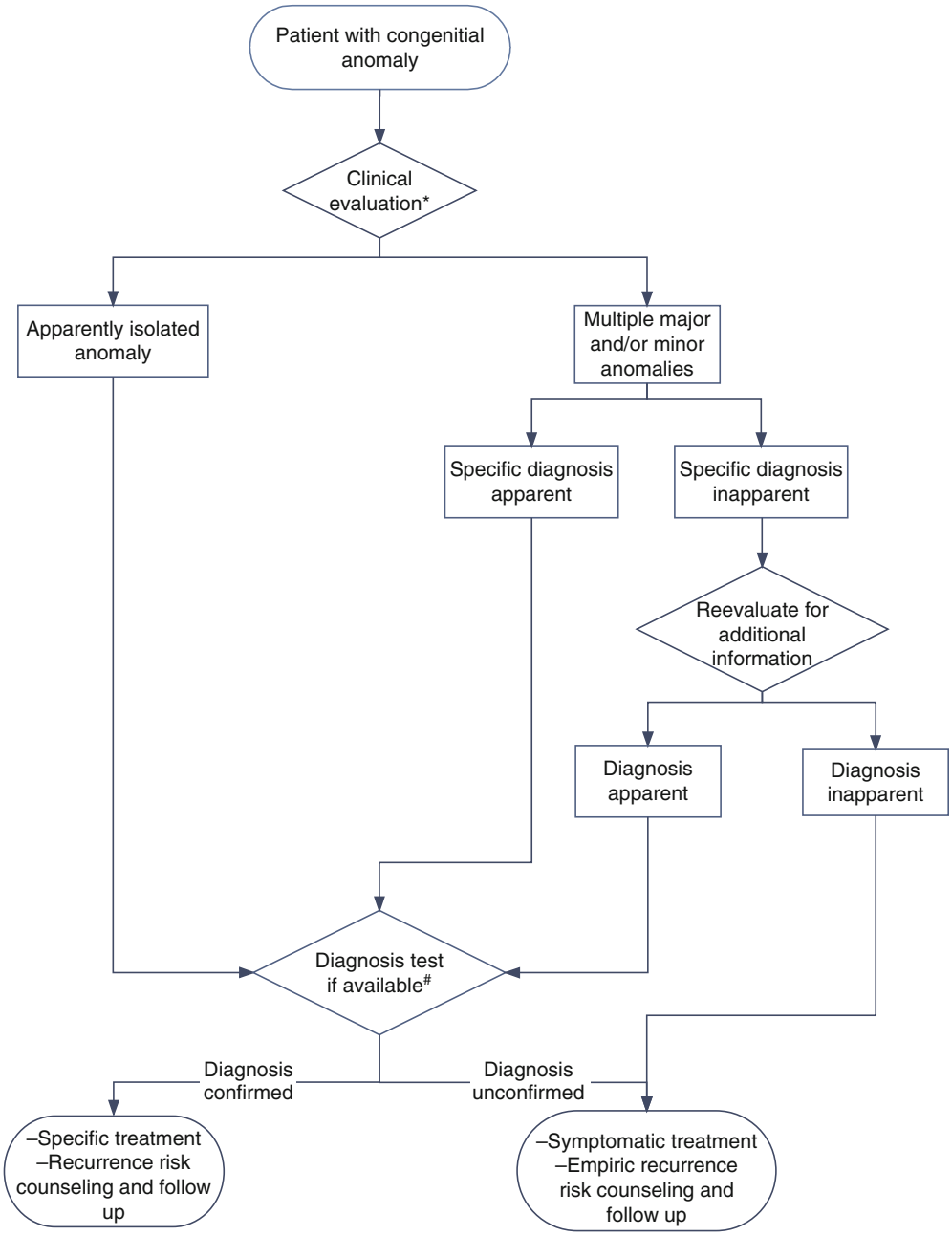
Management of the Child with a Congenital Malformation Syndrome

Because syndromes can be so different in manifestations and consequences, it is not possible to describe specific recommendations in this chapter. Nevertheless, there are some common relevant points: Medical care, psychological support and education of the family are all integral parts of the care of infants and children with congenital malformation syndromes. Information given to the family regarding prognosis and available therapies should be realistic. Referral to support groups is usually beneficial and appreciated by the parents. Some useful resources for parents are listed in *Table 3.3*.

Anticipatory care guidelines for several common genetic syndromes have been published by the Committee on Genetics of the American Academy of Pediatrics. They include recommendations for the care of children and adults with achondroplasia, Down, fragile X, Marfan, neurofibromatosis type 1, Turner, and Williams syndromes. These are useful sources for the clinician involved in the care of these patients, and place emphasis on the early detection and management of the manifestations of these conditions. Some of these guidelines also include

Table 3.2
Useful resources for information on diagnosis and management of children with congenital malformation syndromes

Website	Description	URL
Eurogentest	Information on genetic testing and clinics available in Europe	www.eurogentest.org
Genetests	Expert-authored reviews on genetic diseases, and listings of laboratories offering research and clinical genetic testing	www.ncbi.nlm.nih.gov/sites/GeneTests/ or www.genetests.org
Kansas University Medical Center Genetics Education Center	Listings of genetics websites and educational resources	www.kumc.edu/gec/
Online Mendelian Inheritance in Man (OMIM)	Updated information on human genes and Mendelian phenotypes	www.ncbi.nlm.nih.gov/omim
Orphanet	European resource for information on rare disorders and orphan drugs	www.orpha.net



* Patient and family history, physical examination, imaging studies, etc.
# Karyotype, molecular, and/or metabolic testing

Figure 3.5
Summary of clinical evaluation of the child with congenital anomalies, based on American College of Medical Genetics Guidelines

diagnosis-specific growth charts and expected development. Other useful sources of clinical information can be found in the sites listed in *Table 3.2*.

Recurrence risks are estimated based on the specific diagnosis and its cause. In the case of monogenic disorders, estimates can be made based on Mendelian proportions if the type of inheritance of the syndrome is known. For autosomal recessive conditions, the risk of having an affected child is 25% for each pregnancy if both parents are carriers. In the case of autosomal dominant disorders, the risk to an affected parent to have an affected child is 50%. In some cases, new mutations give rise to autosomal dominant disorders, implying low recurrence risks, but this information needs to be taken with caution, because of the phenomena of incomplete penetrance (a parent has the mutation but shows no phenotypic consequence, but still has a 50% chance of inheriting it to his/her offspring) and gonadal mosaicism, that is, the presence of other gametes with the mutation, leading to the possibility of recurrence. For X-linked recessive disorders, carrier mothers have a 50% chance of having an affected son and a 50% chance of having a carrier daughter for each pregnancy if the father is unaffected. In the case of fathers affected with X-linked disorders, every daughter will be an obligate carrier and sons will be unaffected, since they will inherit a Y chromosome from their father. In X-linked dominant disorders, both males and females are affected, though phenotypes may be more severe (or even lethal) in males. All daughters and no sons of an affected father are affected; the risk to sons and daughters of an affected woman is 50%.

Most of the isolated anomalies described at the beginning of the chapter have a complex or multifactorial cause, with contributing genetic and nongenetic factors. Their risk of recurrence is usually estimated based on empirical data. Recurrence risks for a selection of common isolated congenital anomalies are summarized in *Table 3.4*.

Empiric figures are also used for recurrence risk estimation of common aneuplodies or other chromosome abnormalities, which take into account the type of abnormality, the mode of ascertainment (e.g., through the birth of a child with anomalies, or through recurrent miscarriages), parental karyotype, and parental age.

The prognosis will depend on the underlying diagnosis, the manifestations in the particular child, and the

Table 3.3
Useful resources for parents (this table lists a limited number of resources, more can be found in the specific disease description in the Genetests or Orphanet websites)

Little People of America	www.lpaonline.org
National Down Syndrome Society	www.ndss.org
National Organization for Rare Disorders	www.raredisorders.org
Support Organization for Trisomy 18 and 13 (SOFT)	www.trisomy.org
Velocardiofacial Syndrome Educational Foundation	www.vcfsef.org

Table 3.4
Empiric average occurrence and recurrence risk for some relatively common, isolated, congenital anomalies (From Harper 2004)

Condition	Baseline population occurrence risk in Caucasians (%)	Recurrence risk for first-degree relatives if one person affected (%)	Recurrence risk for first-degree relatives if two persons affected (%)
Congenital heart disease	0.8	2–3	10
Cleft lip, with or without cleft palate	0.1	4	10
Cleft palate	0.04	1.8	8
Anencephaly/spina bifida[a]	0.16	3	10
Moderate to severe mental retardation	0.3	2.8	25

[a]Without periconceptional folic acid supplementation

availability and access to care. Particular issues arise in the presence of a diagnosis associated with poor survival in the neonatal or early infancy periods. Examples include trisomy 13, trisomy 18, or lethal skeletal dysplasias. In these cases, diagnostic confirmation allows to plan for appropriate and proportionate care and support of the child and family.

Approaches to Some Common Clinical Problems and Anomalies

A significant proportion of pediatric patients are referred to genetics evaluation due to a categorical problem or a specific major anomaly. As expressed above, the identification of the underlying cause may aid in the care, prognosis, and recurrence risk estimation. A brief description of key elements in the genetic evaluation of children with suspected syndromic causes of short stature, congenital heart disease, or cleft lip/palate is given below.

Syndromes Associated with Short Stature

Short stature, whether of prenatal or postnatal onset, is a relatively common medical problem, and a frequent reason for genetics evaluation. There are a wide number of causes, including normal variation as well as nutritional, gastrointestinal, renal, endocrine, and social causes that interfere with growth, among others. Nevertheless, short stature is also frequent in syndromes; therefore, genetic causes may need to be evaluated in a substantial portion of infants and children manifesting growth problems. As described above, the clinical evaluation is crucial, and should include a thorough pregnancy history in search for prenatal onset of growth deficiency, maternal illness, exposure to teratogens, etc., medical history in search for other illnesses and evaluation of growth velocity. Family history is important to assess the growth pattern, final height, age at puberty, and presence of hereditary diseases. The physical examination, in addition to the growth parameters, should include a search for major or minor anomalies that might provide clues to the underlying diagnosis. A helpful tool is the measurement of body segments to evaluate body proportions, in addition to height or length. These measurements include arm span (measured from the tip of one middle finger of one hand to the other with the arms fully extended in the horizontal plane) that normally is similar to total height or length. Measurements of lower and upper segments and of limb segments are also useful to assess body proportions. Standards have been published for these more specific dimensions, but should be used with caution since they have been obtained from North American individuals.

The presence of disproportion suggests a skeletal dysplasia. These are abnormalities in growth and development of bone and cartilage and usually affect bones or parts of bones differently, resulting in disproportion. If a skeletal dysplasia is suspected, the laboratory evaluation requires a radiologic skeletal survey, including anteroposterior (AP) and lateral (L) views of the skull, full spine and knees, and AP views of the thorax, pelvis, upper and lower extremities, hands, and feet. On occasion, and due to the age-dependant process of bone ossification, some abnormalities will not be evident in X-rays of infants and small children and therefore clinical and radiologic reevaluation will be required. One of the most common types of skeletal dysplasia is achondroplasia, due to mutations in the *FGRF3* gene that encodes for fibroblast growth factor receptor 3. Patients have short stature with short spine and limbs, macrocephaly, and normal intellectual abilities (*Fig. 3.6*).

Many other conditions show short stature without (or with more subtle) disproportion. Some examples are Williams syndrome, with features that include supravalvular aortic stenosis, hypercalcemia, developmental delays, and recognizable facial features; Russell-Silver syndrome, with relative macrocephaly, limb asymmetry, café-au-lait macules and clinodactyly of the fifth fingers; or Seckel syndrome, with severe pre- and post-natal growth failure, microcephaly that can be more pronounced than the short stature, prominent nose, micrognathia, and varying degree of mental retardation (*Fig. 3.7*).

Karyotype should be included in the evaluation of children with short stature. Several studies have shown that about 20% of girls with pathologic short stature have Turner syndrome. This is characterized by congenital heart disease in 30–40%, puffy hands, and feet at birth due to lymphedema (*Fig. 3.8*) webbed neck, widely spaced nipples, and ovarian dysgenesis, among other features. Molecular diagnosis is available for a constantly increasing number of conditions associated with syndromic and non-syndromic short stature.

Syndromes Associated with Congenital Heart Disease

Congenital heart disease (CHD) is one of the most common major congenital anomalies; with an estimated incidence of 8/1,000 live births. Genetic causes are being

Figure 3.6
A boy with achondroplasia, with a height of 115 cm at age 10 years

Figure 3.7
A girl with Seckel syndrome, with a length of 65 cm at age 2 years

increasingly identified not only for syndromic CHD, but also for nonsyndromic or isolated defects, thereby improving the understanding of the etiology of these anomalies. Several chromosomal syndromes include CHDs: 40–50% of newborns with Down syndrome have CHD and it is recommended that a cardiac evaluation, including an echocardiogram, be performed at the time of diagnosis. Frequent defects include common atrioventricular canal, ventricular septal defects (VSD), and atrial septal defects (ASD). CHD is also frequent in girls with Turner syndrome, with anomalies such as coarctation of the aorta, bicuspid aortic valve, valvular aortic stenosis, and risk of aortic dissection in adulthood. Some chromosome microdeletion syndromes also lead to an increased risk of CHD. About 60–75% of patients with chromosome 22q11 or velocardiofacial syndrome have defects in the cardiac outflow tract, such as tetralogy of Fallot, interrupted aortic arch and VSD, along with developmental delays, cleft palate or velopharyngeal insufficiency, among other features (*Fig. 3.9*). Patients with Williams syndrome, due to a microdeletion at chromosome region 7q11, frequently have supravalvular aortic stenosis, peripheral pulmonary

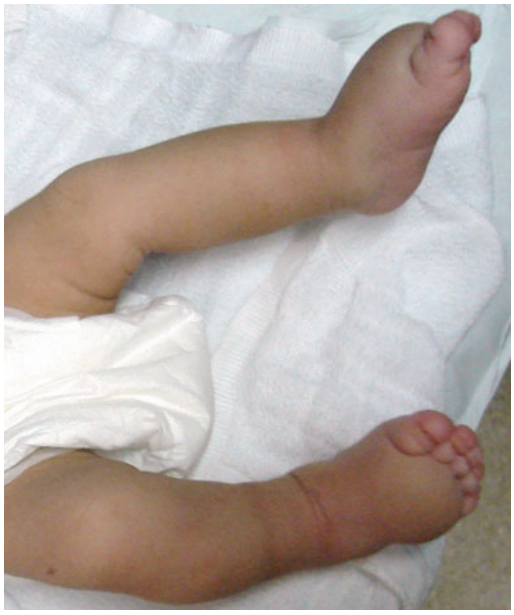


Figure 3.8
Lymphedema in a girl with Turner syndrome (Photograph courtesy of G. Lay-Son, MD)

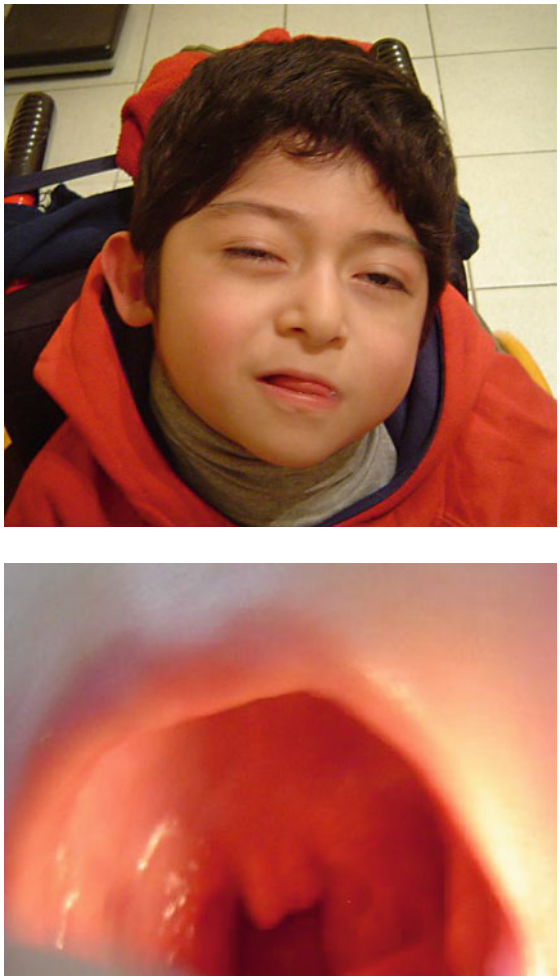


Figure 3.9
A boy with velocardiofacial syndrome (22q11 deletion). (a) facial features, including bulbous or round nasal tip and minor ear anomalies, (b) bifid uvula

artery stenosis or pulmonic valve stenosis associated with short stature, hypercalcemia, and hypertension.

CHD is also a relevant feature of several monogenic syndromes. The majority of patients with Noonan syndrome have CHD; characteristic types include dysplastic pulmonary valve leading to stenosis, and/or hypertrophic cardiomyopathy. Other syndromes, such as Costello and cardio-facial-cutaneous, share similar features (CHD, short stature, developmental delays, and characteristic facial features) and are due to mutations in *PTPN11*, *SOS*, and *KRAS* genes that are part of a common signaling pathway.

CHD can also be a part of syndromes due to teratogenic exposure. Examples include maternal phenylketonuria and maternal diabetes, fetal alcohol syndrome, and retinoic acid embryopathy. In addition, some teratogens can mimic the effect of genetic abnormalities, a phenomenon known as phenocopy. For example, DiGeorge sequence (abnormalities in the embryonic development of the third and fourth branchial arches and pouches leading to cardiac outflow tract defects, thymic and parathyroid aplasia or hypoplasia, resulting in immune deficiency and hypocalcemia respectively) can be caused by prenatal exposure to retinoids or by chromosome 22q11 microdeletion (*Fig. 3.9*).

Cardiovascular disease can also present later in several syndromes, so early awareness of the diagnosis can help in planning for appropriate screening and prevention. As mentioned above, girls with Turner syndrome can develop aortic dissection in adulthood and it is recommended for them to have regular cardiological evaluation in adulthood even if the person did not have CHD. Individuals with Marfan syndrome can have dilatation and dissection of the aorta, a life-threatening complication that can be partly reduced in rate with the use of beta-blockers or angiotensin II-receptor blockers.

Syndromes Associated with Cleft Lip or Cleft Palate

Orofacial clefts are relatively frequent major anomalies, and are second in frequency to congenital heart defects. As has been described for cardiac defects, most cases of orofacial clefts are isolated, that is, without other anomalies (but still may have a genetic etiology) and a proportion of individuals have syndromic clefts. From a pathogenic point of view, cleft lip with or without cleft palate (CL±P) is considered distinct from cleft palate (CP), they occur separately in families, and the former is more frequent than the latter (1–2/1,000 and 1/500 live births, respectively). CL±P is more commonly associated with other anomalies than CP alone.

Several common syndromes are associated with orofacial clefts: CL±P is frequent in trisomy 13 and 18, and CP, whether in overt or submucous forms, is seen in 70–80% of patients with chromosome 22q11 deletion or velocardiofacial syndrome. Monogenic syndromes that may manifest clefts include Stickler (CP with myopia, hearing loss, and arthropathy) (*Fig. 3.10*), Larsen syndrome (CP with flat facial profile and multiple joint dislocations), and van der Woude syndrome (one of the few conditions in which affected family members can have either CL±P or CP, associated with lip pits).

Teratogens can also be a cause of clefting. CL±P is seen in patients with fetal alcohol syndrome (with growth

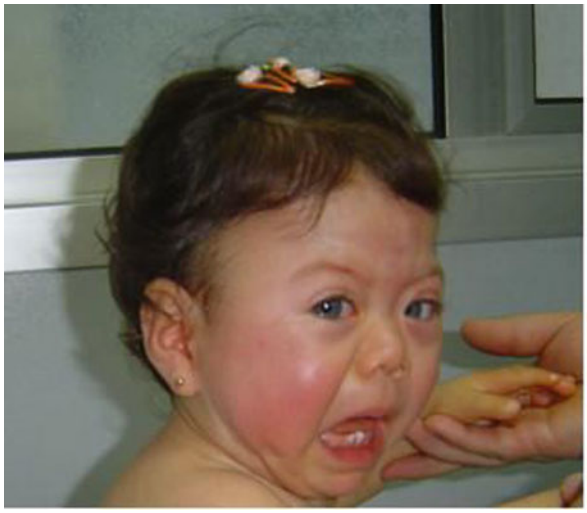


Figure 3.10
A girl with Stickler syndrome, with flat facial profile and relatively prominent eyes

deficiency, variable mental retardation, microcephaly, short palpebral fissures, and flat philtrum), fetal hydantoin syndrome (short stature, mental retardation, hypoplasia of distal phalanges and small nails), and fetal valproate syndrome (with congenital heart disease and spina bifida).

Prevention

As neonatal and infant mortality from infections and complications of prematurity have decreased worldwide, there has been a relative increase in morbidity and mortality from congenital anomalies, both in an isolated manner and in the context of syndromes. Most cases of congenital malformation syndromes will arise in families without a previous history, making the identification of couples at risk difficult. Most common chromosome abnormalities are sporadic, as is the case of the majority of instances of Down and Turner syndromes. With respect to monogenic disorders, de novo or new mutations occur for a large proportion of autosomal dominant (as in achondroplasia and neurofibromatosis type 1, among others) or X chromosome-linked conditions (e.g., Rett syndrome and Goltz syndrome), and most individuals with autosomal recessive conditions have healthy heterozygous carrier parents (as in Smith-Lemli-Opitz syndrome or Seckel syndromes).

Nevertheless, a proportion of these seemingly unexpected conditions have known, identifiable risk factors, such as advanced maternal age for chromosome aneuploidies, advanced paternal age for de novo dominant mutations, parental consanguinity for autosomal recessive syndromes, teratogen exposures, such as fetal alcohol syndrome and chronic uncontrolled maternal illnesses, such as diabetes mellitus or phenylketonuria. Hence, the Latin American Collaborative Study of Congenital Malformations (ECLAMC, for Estudio Colaborativo Latinomericano de Malformaciones Congénitas) has proposed a "Decalogue for Prevention of Congenital Anomalies" focused on the avoidance of known risk factors such as unintended pregnancy, advanced maternal age, deficient prenatal controls, rubella, self-medication, alcohol, smoking, malnutrition, occupational risks, and poor health care.

In addition to these preconceptional preventative measures, options are available for antenatal screening or diagnosis of several syndromes. First and second trimester screening for common aneuploidies such as trisomies 21 and 18 is usually performed by a combination of maternal age, ultrasound markers (most commonly nuchal translucency), and/or biochemical markers. Screening has incidentally been found to be useful to identify fetuses at risk for other conditions such as Smith-Lemli-Opitz syndrome as well as adverse perinatal outcomes. Fetal ultrasound is also useful to identify structural anomalies that may suggest the existence of a syndrome. These screening procedures are useful to select pregnancies that warrant further studies, such as invasive karyotype or molecular testing (by chorionic villous sampling, amniocentesis or chordocentesis) or additional studies such as fetal magnetic resonance imaging.

Education is also a crucial part of prevention. This can be accomplished through genetic counseling, defined as "the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease" (National Society of Genetic Counselors, www.nsgc.org). This process includes, in the case of congenital malformation syndromes, providing information to the patient and/or family about the specific diagnosis, mode of inheritance, occurrence or recurrence risks, and the available therapeutic and preventative alternatives.

Case Histories

Case 1

You are called to evaluate a term adequate-for-gestational-age (AGA) newborn with feeding difficulties and respiratory distress. On physical examination you note that the

newborn shows mild tachypnea with mild intercostal retractions but normal pulse oxymetry in the supine position. You find that she has microretrognatia and a cleft of the soft palate, without other evident anomalies. You position her on her side and the respiratory rate and pattern normalize. The pregnancy history is unremarkable. The mother has high myopia and a history of chronic joint pain, and has been given the diagnosis of arthritis of unknown etiology; the rest of the family history is noncontributory. Given the association of microretrognathia, cleft palate, and respiratory difficulties, you consider that she has Robin sequence. This malformation could be "non-syndromic," of unknown cause, or perhaps due to fetal crowding or decreased intrauterine mobility. You also learn that about 40–50% of cases can be caused by syndromes, the most common ones being 22q11 microdeletion (or velo-cardio-facial) syndrome (◉ *Fig. 3.9*) and Stickler syndrome (◉ *Fig. 3.10*), a connective tissue disorder due to mutations in *COL2A1*, *COL1A1*, *COL9A1*, or *COL11A1*, genes encoding for collagen chains. Karyotype and FISH 22 studies are normal in your patient, and you request an ophthalmologic evaluation that shows that the newborn has high myopia, like her mother. Stickler syndrome is characterized by arthropathy, flat vertebrae, myopia with risk of retinal detachment, Robin sequence, and deafness. You review the maternal X-rays, and they are consistent with this diagnosis. You conclude that the newborn and her mother have Stickler syndrome, and in addition to managing her airway and feeding problems, you make a plan to continue to follow the baby's and mother's vision and hearing, as well as future musculo-skeletal manifestations. The family is counseled that Stickler syndrome is inherited as an autosomal dominant condition and that the probabilities of recurrence are 50% for each subsequent pregnancy. Molecular analysis of the *COL2A1* gene identifies the causative mutation, information that may be used for prenatal diagnosis or other at-risk relatives.

Case 2

A term AGA, 5-day old newborn boy has hypotonia and feeding difficulties, with loss of 12% of his birth weight. On physical examination, he is noted to have a narrow forehead, small hands and feet, small male genitalia, and cryptorchidism. He has moderate hypotonia, poor Moro and suck reflexes, and normal deep tendon reflexes. He is also noted to have hypopigmentation of his skin, hair, and irides compared with his family. He is diagnosed with central hypotonia. Brain imaging studies are normal. Given his findings, the diagnosis of Prader-Willi syndrome (PWS) is considered. Confirmatory genetic studies show a normal karyotype, absent paternal contribution on chromosome 15 methylation analysis, and a microdeletion in the proximal part of chromosome 15 (15q11q13), consistent with the suspected diagnosis. PWS is a genetic disorder due to the absence of the paternal genes in chromosome region 15q11q13. In this case, it was due to a small deletion in the region. PWS is characterized by neonatal central hypotonia with transient feeding difficulties and failure to thrive in the first year or two of life. Children subsequently develop hyperphagia and obesity, short stature, hypogonadism, developmental delays, and mild to moderate mental retardation. Given the transient nature of the infantile feeding difficulties, nasogastric tube feedings were started on the patient, and referral was made to an Early Intervention Program, as well as follow up by an endocrinologist. PWS due to 15q11q13 microdeletion is usually a sporadic condition, and the parents were informed that the risk of recurrence in future pregnancies is probably low (≈1% or less).

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