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Edited by
Leonard B. Kaban, DMD, MD

Oral and Maxillofacial Surgery in Children

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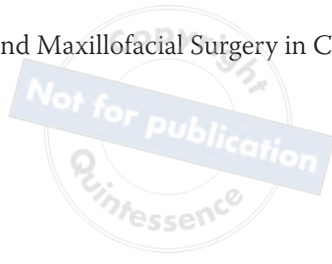
Dedication

To my patients over the years who have enriched my life and inspired me with their courage during hard times.

To my residents and colleagues.

And finally, to my grandchildren Taylor, Keira, and Aaron who have brought me great joy and happiness as I watch them growing up.
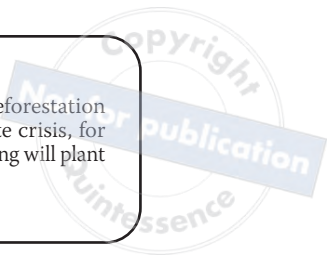
Oral and Maxillofacial Surgery in Children

Edited by

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Contents

Preface

When I began this journey in the early 1970s, there were only four oral surgeons in the United States who considered themselves specialists dedicated to pediatric oral and maxillofacial surgery (OMS): William Grau at University of Cincinnati and Cincinnati Children's Hospital, Robert Myall at University of Seattle and Seattle Children's Hospital, Bruce Sanders at University of California Los Angeles, and myself at Boston Children's Hospital (BCH). There was no formal recognition of this area of subspecialty in OMS.

At BCH, I was invited to be part of a multidisciplinary craniofacial center and to start a pediatric OMS service in a newly named Division of Plastic and Oral Surgery. This was made possible by a collaboration with Dr Walter Guralnick, chief of the Department of OMS at Massachusetts General Hospital (MGH), and Dr Joseph Murray, chief of the Division of Plastic Surgery at BCH.

Physicians, dentists, and other hospital staff did not know what an oral and maxillofacial surgeon would be doing in a children's hospital. The dental department was started in 1933 and had pediatric dentistry and orthodontic residency programs, a busy outpatient clinic, and a long history of doing dental rehabilitations in the operating room, which included extractions and minor oral surgery procedures. However, I did not see my first private patient referral for approximately 3 months. My first operation was excision of a chronically infected submandibular gland resulting from sialolithiasis. When I arrived in the operating room, I was informed by the head nurse that she had cancelled my case because a dentist was not allowed to make skin incisions at BCH.

Despite the shaky start, it became evident after 6 months that there was a real need for OMS at BCH. Similarly, the pediatric practices of Drs Grau, Myall, and Sanders grew and became established. The scope of services included dentoalveolar and soft tissue procedures, maxillofacial infections, trauma, jaw tumors, salivary gland disease, temporomandibular disorders, orthognathic and craniofacial deformities, among others. Prior to my arrival, the intraoral soft tissue pathology and salivary gland problems at BCH were handled by the general pediatric surgeons, and facial trauma and jaw tumors were managed by Dr Murray. They were happy to have an oral and maxillofacial surgeon at the hospital to also see these patients. Dr Guralnick started assigning each OMS chief resident to rotate at BCH for 3 months. Eventually this became a 6-month rotation that was fully integrated into the OMS program during the chief resident year. Dr Murray secured a permanent slot for an OMS resident at BCH, and after 2 years, we recruited a second oral surgeon, Dr Robert Chuong. I continued my interest in pediatric OMS and craniofacial surgery during my tenure as Professor and Chairman of OMS at University of California San Francisco from 1984 to 1994. When I returned to MGH and Harvard in 1994 as the WC Guralnick Professor and Chairman of the Harvard Department of OMS, I established a Division of Pediatric OMS at MGH, collaborated with the Division of Plastic Surgery to establish a cleft and craniofacial clinic at the Shriner's Hospital, and started a pediatric OMS clinical and research fellowship. I also enthusiastically supported the growth of OMS at BCH.

I am proud to say that the current Department of Plastic and Oral Surgery at BCH has four full-time oral and maxillofacial surgeons who are members of the Harvard academic department. Bonnie Padwa serves as the Oral and Maxillofacial Surgeon-in-Chief as well as the Leonard B. Kaban Chair in OMS at BCH. The growth of OMS at BCH and at other hospitals around the country has resulted in a recognition of this subspecialty.

More recently, the American Association of Oral and Maxillofacial Surgeons (AAOMS) and the Commission of Dental Accreditation have approved fellowships leading to certificates of advanced training. At the 2022 annual

meeting of the AAOMS there was a full-day preconference symposium on pediatric and craniofacial surgery, highlighting seven of the current pediatric and craniofacial fellowships in the United States. The increased number of pediatric oral and maxillofacial surgeons and the advent of fellowship training have resulted in further advances and expansion of the clinical scope of OMS as well as an increase in scholarly activity and research.

Therefore, this new book, *Oral and Maxillofacial Surgery in Children*, is long overdue. Since OMS is a specialty based on anatomical region, most oral surgeons treat children, at least occasionally. This book was written to provide a reference for surgeons, residents, and students in the principles of diagnosis and management of pediatric OMS problems encountered in the setting of office and hospital practice. The differences between children and adults are emphasized as well as the unique nature of pediatric management because of the "fourth dimension," ie, time and growth. OMS in children is primarily problem based and it is not meant to be a detailed technical atlas of specific procedures.

For this book, I have invited many new contributors and addressed topics that have not been covered in my past books, including, contemporary pediatric outpatient sedation and anesthesia in the oral surgery office, vascularized skeletal and soft tissue reconstruction, obstructive sleep apnea in children, acquired TMJ deformities with expanded sections on juvenile idiopathic arthritis and idiopathic condylar resorption, midfacial trauma, craniosynostosis, microtia and ear reconstruction. advances in imaging, 3D treatment planning, custom surgical guides, and fixation implants. Taken together, this book covers much of the scope and range of current OMS, and I hope it will guide many who are on this journey too.

Acknowledgments

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Molecular Genetics and Syndrome Recognition for the Clinician

Joan M. Stoler

hy is knowledge of genetics important? During the last century, physicians have made great strides in treating infectious diseases and lowering associated morbidity and mortality. Advances have also been made in the management of medical conditions such as hypertension, diabetes mellitus, and heart disease. There have been significant improvements in the surgical management of disease, such as transplantation and repair of congenital and acquired facial deformities. In some ways, the last frontier is the field of genetics. Understanding the role of genes in the pathogenesis of anatomical and physiologic abnormalities will aid in diagnosis and the development of rational treatments. Genetic disorders accounted for 5% of pediatric admissions in a general hospital and 34% of deaths in a children's hospital series. In a neonatal intensive care unit, 28% of deaths were due to malformations or genetic disorders.[1–3] Understanding the etiology of such disorders and devising new methods of prevention and treatment would be of enormous benefit.

The "New Genetics"

There has been an explosion in genetic knowledge with the ability to examine almost all human genetic information by exome or genome analysis. The identification of specific genes responsible for many diseases has become a reality. In some cases, such identification has led to a better understanding of the pathophysiology of a disorder, and hopefully, in the future, genetic diagnosis will result in targeted treatment. The identity and the roles of genes responsible for various disorders inherited in the classical Mendelian patterns (eg, autosomal recessive, autosomal dominant, X-linked) have been documented. Similarly, genes responsible for multifactorial or complex inherited disorders have also been discovered. Congenital diseases that have traditionally been labeled as multifactorial, such as cleft lip and palate, may represent abnormalities in genes which confer susceptibility to exogenous influences, thereby leading to development of the disorder.[4] Acquired conditions such as cancer have been found to have a specific genetic basis with accumulation of somatic

(non-germline) mutations over time. Advances have been made in understanding the underlying pathogenesis of nontraditional types of inheritance, such as *imprinting* (in which the expression of a gene depends upon the parent of origin) and *anticipation* (in which the disorder becomes more severe in subsequent generations due to expansion of a series of nucleotide repeats in a gene).

Next-generation sequencing

Many of the recent advances in genetics have resulted from the development of next-generation sequencing. This is a high-throughput technique, making use of massive parallel sequencing, which has made multigene panels, exome, and whole genome testing possible.[5]

A short primer on molecular genetics

Genes are the basic unit of heredity and are composed of molecules of deoxyribonucleic acid (DNA). They are located on *chromosomes*, which are the physical structures transmitted in the sperm and ovum. Most of the DNA on chromosomes does not code for specific genes. The genes themselves are composed of various compartments and regulatory elements needed for the machinery of transcription. Exons and introns are two examples of such elements. Exons contain the exact sequence needed to make a protein. A gene is transcribed into messenger RNA (mRNA) in the nucleus of the cell. The mRNA then leaves the nucleus and enters the cytoplasm. It contains the exact sequence for making the protein but lacks the intron component of the gene. The introns are removed after transcription of the RNA through a precise process called *splicing*. The mRNA is then translated into the respective protein.[6] Mistakes affecting the production, composition, and activity of the protein may occur at various levels, from a single base pair change to duplication or deletion of whole genes, parts of chromosomes, and whole chromosomes.

Birth Defects

Birth defects are a common cause of morbidity and mortality, with an incidence in the newborn period ranging from 1% to 4% depending on the population analyzed.[7] The method and time period of ascertainment and the definition of a malformation also affect the reported incidence.[8] With age, the rate of diagnosis rises, doubling by 1 year of age, and tripling by school age.[7] It is known that low birth weight, twinning, and consanguinity are all associated with an increased frequency of birth defects.[9–11] In addition, male sex is associated with an increased frequency of many, but not all, malformations.[12] The etiologies of birth defects are classified as chromosomal disorders, single-gene disorders, genetic disorders resulting from teratogens, and multifactorial conditions (combinations of genes and environmental factors).

Chromosomal disorders

Abnormalities in chromosome number and structure result in significant pathology. A normal karyotype consists of 46 chromosomes, divided into 23 pairs: 22 autosomal and 1 sex chromosome pair (either XX or XY). Normally, an individual receives one copy of each chromosome from each parent. Abnormal division of a chromosome pair (nondisjunction) can occur during meiosis or during mitosis (after fertilization). *Mosaicism*, ie, some cells with a normal chromosome number and others with an extra chromosome, occurs as a result of abnormal division during mitosis. Theoretically, an extra copy of any chromosome pair (trisomies) can occur, but most of these affected embryos abort spontaneously. Only a few trisomies are compatible with a liveborn infant, as follows:

- Trisomy 21 (Down syndrome; Fig 1-1a)
- Trisomy 13
- Trisomy 18 (Fig 1-1b)
- 47, XXY (Klinefelter syndrome)
- 47, XXX
- 47, XYY

These are usually associated with advanced maternal age, and the features differ according to the chromosome involved.

Monosomy (one missing chromosome) has only been reported for the sex chromosomes, as fetuses with other monosomies are nonviable. Turner syndrome (45, X) has a high in-utero mortality rate, but some fetuses do survive (Fig 1-2). In general, 45, X is not associated with advanced maternal age. The X chromosome is of maternal origin in the majority of cases (70%), indicating that the paternal copy was lost.[13]

Structural chromosomal abnormalities, such as deletions, duplications, and rearrangements (eg, translocations, inversions) also occur. Deletions and duplications may be visible microscopically (seen with the usual method of performing a karyotype) or at a submicroscopic level using a chromosomal microarray.
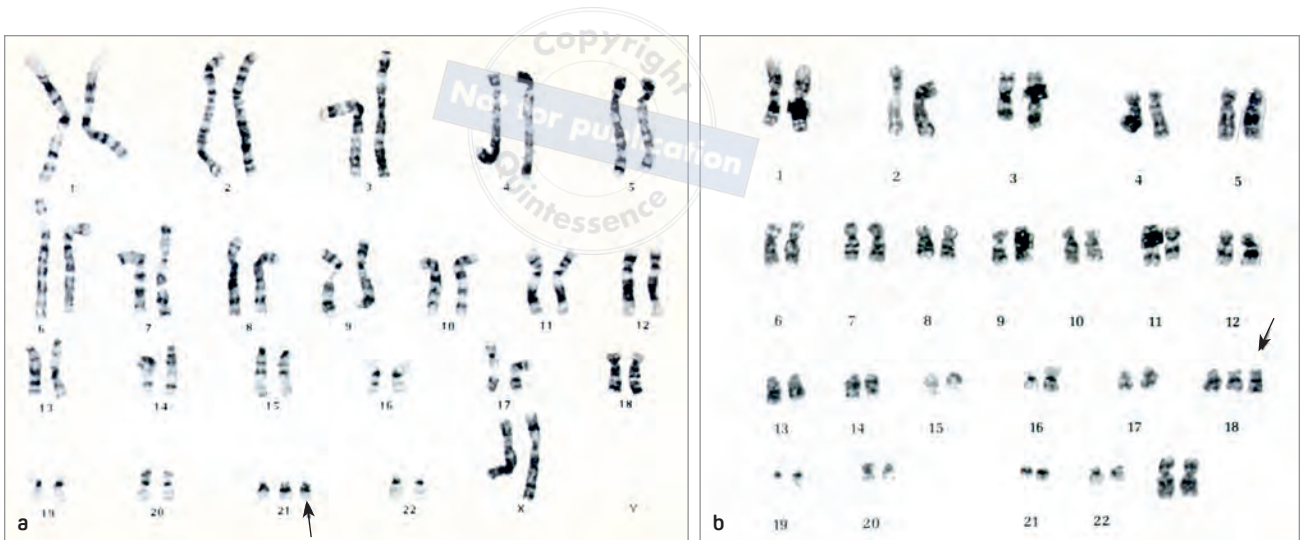
Fig 1-1 *(a)* Female karyotype with trisomy 21. The *arrow* indicates the extra chromosome 21. Note the presence of 2 X chromosomes and no Y chromosome, indicating it is a female. *(b)* Female karyotype with trisomy 18. The *arrow* shows the presence of three copies of chromosome 18.

Fig 1-2 Turner syndrome. *(a)* Infant with Turner syndrome with widespread nipples and mild pectus excavatum. *(b)* Right eyelid ptosis and epicanthal folds. *(c)* Low posterior hairline and redundant skin of neck. *(d)* Low-set ears and lymphedema in upper extremity and hand. (Photographs courtesy of Dr Angela Lin, Massachusetts General Hospital for Children.)
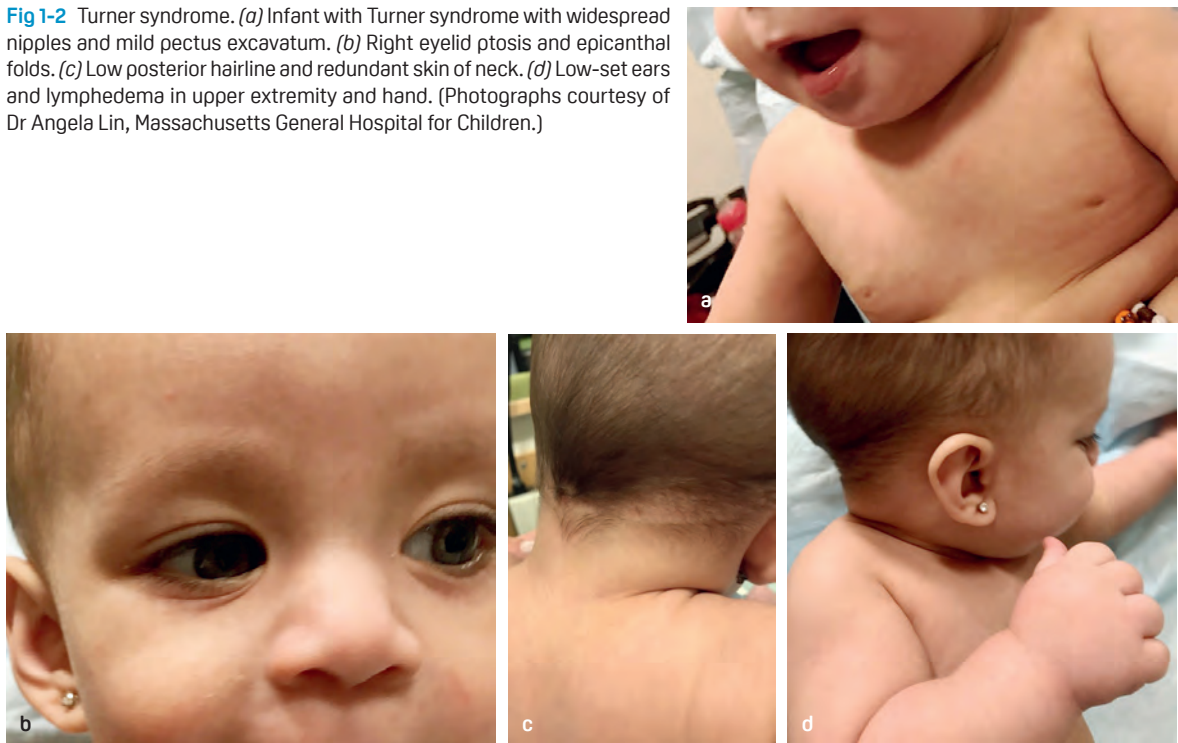
Fig 1-3 A 3-year-old girl with velocardiofacial/DiGeorge syndrome. The characteristic features of this syndrome include rectangular-shaped nose, low-set ears, micrognathia (mild in this child), and long tapered fingers (left hand here). Patients also have cleft palate, velopharyngeal insufficiency, thymic aplasia, and cardiac anomalies.

Fig 1-4 Child with cateye syndrome exhibiting iris colobomas bilaterally.

A very common deletion is located on the long arm of chromosome 22 (22q11). This results in velocardiofacial syndrome (VCFS) and DiGeorge sequence (absent thymus and parathyroids, micrognathia, and heart abnormalities). The features are varied and include cleft palate, Pierre Robin sequence or velopharyngeal insufficiency in the absence of a cleft, conotruncal heart defects, learning disabilities, psychiatric problems, DiGeorge sequence, and a characteristic facial appearance (Fig 1-3).

Duplications of parts or regions of chromosomes result in different phenotypes. Cat eye syndrome is caused by tetrasomy (four copies) of chromosome 22 material with two copies present as an additional small chromosome pair. The clinical features include coloboma of the iris, anal atresia with fistula, down-slanting palpebral fissures, ear abnormalities including tags and pits, heart and kidney malformations, and mild intellectual impairment (Figs 1-4 and 1-5).

Single-gene disorders

Single-gene disorders are caused by one abnormal gene and are inherited in the traditional Mendelian patterns: autosomal dominant, autosomal recessive, X-linked recessive, and X-linked dominant. Mutations in the responsible gene result in abnormal quantity or function of the protein. There may be a single-point mutation (changing one nucleotide for another), insertion of one or more nucleotides, deletion of one or more nucleotides, or expansion of a portion of a gene or other rearrangements within the gene. Depending on the site of the mutation, the coded protein may not be produced at all or may have altered activity or stability. The configuration of the protein may be changed, resulting in alteration of the protein's activity (higher or lower activity).

Autosomal dominant disorders are the result of one abnormal copy of a gene on any of the 22 non-sex chromosome pairs. Each child of an individual with an autosomal dominant disorder has a 50% chance of inheriting the abnormal gene and exhibiting the phenotype (Fig 1-6). In many cases, there is no family history of the disorder, and it may represent a new mutation in the affected individual. Therefore, the absence of a positive family history does not exclude an autosomal dominant disorder. Typically, autosomal dominant conditions involve structural proteins or receptors. There may be phenotypic variability within families, with different degrees of expression (variable expressivity). For example, a very mildly affected parent may have a child who is more severely affected. Treacher Collins syndrome is a common craniofacial disorder with incomplete penetrance and variable expressivity (Figs 1-7 and 1-8). The mechanism of this phenomenon is not well understood. However, in some disorders (such as myotonic dystrophy), there may be an expansion of the portion of the gene that affects function. Such expansions may increase in subsequent generations, leading to expression of the disorder (such as with Fragile X syndrome) or of increased severity of expression (called *anticipation*), such as that seen with myotonic dystrophy. Penetrance is the proportion of individuals with the abnormal gene who show any features of the condition. For example, a disorder may have complete penetrance in which all the individuals with the abnormal gene show features. Conversely, a disorder has incomplete penetrance when not all individuals with the abnormal gene exhibit characteristics of the condition.

Fig 1-5 *(a to e)* Photographs of a 4-year-old girl with cateye syndrome and bilateral craniofacial microsomia. Her problems include 22q11 tetrasomy, anal atresia and fistula, single kidney, total anomalous pulmonary venous return, submucous cleft palate, low-set ears, multiple ear tags, abnormal external ear morphology, epibulbar dermoids (OD at 7 o'clock at iris and OS at 6 o'clock), hearing loss, micrognathia, syndromic Pierre Robin sequence, severe mandibular asymmetry with bilateral craniofacial microsomia with type III mandible on left and type II mandible on right, VII nerve weakness, and right marginal mandibular and buccal branches (illustrated in smiling photograph).

☐ Unaffected male	○ Unaffected female
■ Affected male	⬤ Deceased affected female
■ Deceased male	
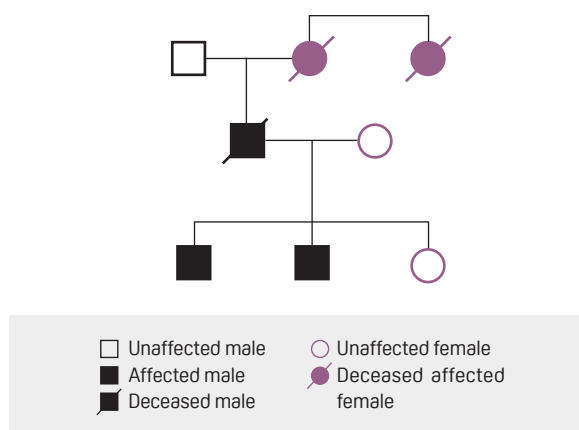
Fig 1-6 Autosomal dominant pedigree. Each child (male or female) of an affected individual has a 50% chance of inheriting the abnormal copy of the gene and of being affected. Note the multigenerational involvement.

Fig 1-7 Mother and daughter with Treacher Collins syndrome (autosomal dominant *TCOF1* gene). Offspring of a parent with an autosomal dominant disorder have a 50% chance of inheriting the abnormal gene. Frontal photographs demonstrate downturned lateral canthi, zygomatic hypoplasia, soft tissue colobomas, lower eyelids, and lateral facial clefts.

Fig 1-8 Treacher Collins is an autosomal dominant disorder with incomplete penetrance and variable expressivity. This set of photographs demonstrates the variable expressivity of the disorder. *(a and b)* A girl with severe involvement of the orbits, eyelids, midfacial soft tissue, mandible, and ears. *(c and d)* A boy with moderate orbital and periorbital soft tissue abnormalities and mild ear and mandibular deformities. *(e and f)* A 4-year-old boy with lack of eyelashes in the medial third of the lower eyelids, soft tissue clefts over the right and left zygomas, zygomatic hypoplasia, low-set ears with abnormal morphology, conductive hearing loss, mandibular retrognathism, and short posterior face height. He has obstructive sleep apnea refractory to tonsillectomy and adenoidectomy. *(g and h)* A 15-year-old girl with missing eyelashes in the medial third of lower eyelids, absent zygomatic arches, maxillary hypoplasia, beaked nose, and minimal mandibular hypoplasia. *(i and j)* An 8-year-old girl with a symmetric forehead. The lateral canthi are downturned. The malar eminences are hypoplastic and flat. She has no coloboma. She has complete eyelashes along the entire lower eyelids. The external ears are small and low set. The nose is prominent. The mandible is retrognathic. The anterior lower face height is very long and the posterior face height short; the chin to throat distance is one fingerbreadth at most.
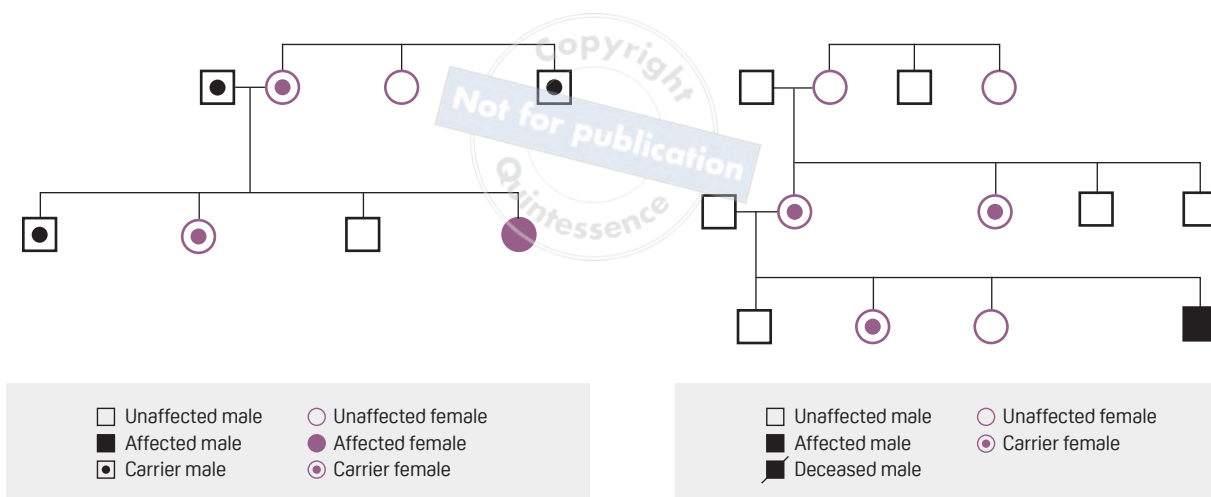
Fig 1-9 Autosomal recessive pedigree. Each parent has one normal and one abnormal copy of the gene and is an unaffected carrier. Each child (male or female) has a 25% risk of inheriting the two abnormal copies of the gene and of being affected.

Fig 1-10 X-linked pedigree. There is no male-to-male transmission. Females are carriers.

An *autosomal recessive condition* is the result of two copies of the abnormal gene, one inherited from each parent. The parents each have one normal and one abnormal copy and are therefore asymptomatic carriers. A carrier couple has a 25% risk of having an affected male or female child in each pregnancy (Fig 1-9). Typically, autosomal recessive conditions involve synthesis of enzymatic proteins. These enzyme deficiencies result in inborn errors of metabolism as well as malformation syndromes. For example, Smith-Lemli-Opitz syndrome, which consists of microcephaly, cleft palate, a characteristic facial appearance, cardiac defects, ambiguous genitalia in the male, postaxial polydactyly and syndactyly of toes, growth retardation, and intellectual disability, is due to an abnormality in cholesterol metabolism.[14]

X-linked disorders, as the name implies, are due to abnormal genes located on the X chromosome. In general, males with X-linked disorders are more symptomatic than females. A female who has one copy of an X-linked recessive gene may have only mild or no signs, while the male expresses the full condition. This differential expression is due to X-inactivation. One of the X chromosomes in the female becomes inactivated early in development. In contrast, a female with an X-linked dominant disorder is symptomatic, although usually less than males. Some X-linked dominant disorders, such as Rett syndrome and incontinentia pigmenti, are typically lethal in males. With X-linked inheritance, male-to-male transmission is not possible, as a male receives the X chromosome from the mother. Each son of a carrier mother has a 50% chance of inheriting the abnormal gene and a 50% chance of inheriting the normal gene. Each daughter has a 50% chance of inheriting the abnormal gene (carrier) and a 50% chance of inheriting the normal gene (Fig 1-10). The Y chromosome is passed from father to son only. Therefore, a male with an X-linked disorder who can reproduce will pass on the abnormal X chromosome to each of his daughters, and they will be carriers. None of his sons will inherit the abnormal gene. The affected male can have affected grandsons (via the daughter), but his sons cannot. Hemophilia is a classic example of X-linked inheritance.

Nontraditionally inherited disorders

Mitochondrial inheritance

Mitochondria are the energy organelles of human cells and contain their own DNA. Mitochondrial DNA can be inherited in two ways: *(1)* from genes which are encoded in the nucleus (as part of the nuclear genome), or *(2)* from genes which are located in the mitochondria themselves (the mitochondrial genome). Abnormalities inherited from the nuclear genome follow the usual Mendelian modes of inheritance. Abnormalities of genes located in the mitochondrial genome typically follow a maternal pattern of inheritance. This is because the mitochondrial genome is located in the mitochondria present in

☐ Unaffected male   ○ Unaffected female
■ Affected male   ● Affected female
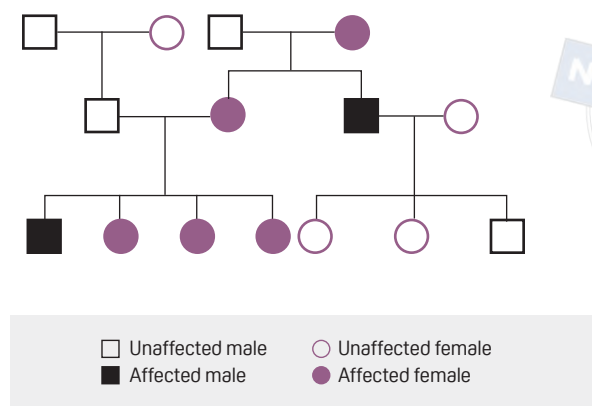
Fig 1-11 Mitochondrial inheritance pedigree. Abnormalities in the mitochondrial DNA follow a maternal pattern of inheritance.

the cytoplasm of the oocyte. Very few mitochondria are derived from DNA in the sperm[6] (Fig 1-11). A woman may have mutations in a small number of mitochondria, producing a variable proportion of mitochondria with mutated DNA in her oocytes. The degree of phenotypic expression from these mutated mitochondria depends on the proportion of mutated and normal mitochondria present in the fertilized egg.

Multifactorial inheritance

Some conditions do not exhibit the traditional Mendelian inheritance patterns. In these disorders, it is thought that multiple genes and/or significant environmental interactions are responsible.

Imprinting

Some gene functions are dependent on whether the gene is inherited paternally or maternally. Such genes may only be **active** if inherited from the mother or the father. The inactivation of such imprinted genes is through an epigenetic process called *methylation*. Disorders which are due to imprinting include Prader-Willi syndrome, Angelman syndrome, and Beckwith-Wiedemann syndrome.

Epigenetics

This refers to modification of the DNA that may affect the expression of the gene but does not alter the actual DNA sequence and may occur over time. Imprinting is one form of epigenetic modification. Such modifications are typically reset during formation of gametes. Other types of epigenetic processes include histone modification by acetylation or deacetylation and noncoding RNA (through binding to mRNA and affecting translation).[15]

Syndrome Recognition for the Clinician

As genes are identified and assigned to specific disorders, DNA-based diagnostic testing is becoming a realistic possibility for a variety of conditions. However, there is often a lag time between identification of a gene and clinical correlation. The explosion of genetic information and the rapid rate of identification of new genes have made it near impossible for the non-geneticist to remain current and completely informed. Consultation with a clinical geneticist is therefore imperative.

A *syndrome* is defined as "a pattern of malformations that occur together from a single cause."[16] A major role of the clinical geneticist is to determine whether a child with a particular anomaly has a syndrome or whether the anomaly is an isolated finding. This helps to determine testing options, prognosis, medical problems to anticipate, possible treatments, and recurrence risks for other family members. The geneticist obtains a careful and detailed medical and family history. The patient and, in some cases, other family members undergo a physical examination, laboratory evaluation, and follow-up counseling and management.

Review of medical history

Details regarding the pregnancy, delivery, newborn period, and childhood should be obtained from the parents. A particularly important issue is the maternal drug history during pregnancy, since certain medications are known to be teratogenic. For example, warfarin taken during the first trimester is associated with significant nasal hypoplasia. It should be determined whether any prenatal testing, such as chorionic villus sampling, amniocentesis, or ultrasound was done. This is important to determine what information was available prenatally and whether any untoward complications occurred from any procedures. For example, chorionic villus sampling has been implicated in the etiology of transverse limb and several other vascular disruption defects (gastroschisis, intestinal atresia, and clubfoot).[17] Obstetrical issues such as bleeding, trauma, intrauterine growth retardation, oligohydramnios or polyhydramnios, or decreased fetal movements are also important. A child with a malformation and intrauterine growth retardation may be more likely to have an underlying syndromic etiology for the defect. Decreased fetal movements may indicate an underlying neurologic or neuromuscular problem. The type of delivery, complications during delivery, birth parameters, and the baby's feeding history should

be recorded. For example, an infant with a cleft palate and a small head should be evaluated for an underlying disorder of multiple systems.

Any developmental or cognitive difficulties should be noted. Growth history, with examination of growth curves (appropriate to gender and ethnic background, if available), is essential. Hospitalizations, operations, or frequent illnesses must be documented. Episodic illnesses may lead the clinician to pursue a metabolic etiology. Previous laboratory data should be reviewed.

Family history

This should include details about other siblings, parents, grandparents, and cousins. Specific questions are asked about recurrent miscarriages; stillbirths; neonatal deaths; and family members with birth defects, intellectual disability, and learning difficulties. The family's ethnic background should be noted because certain conditions are more common in specific ethnic groups. Consanguinity must be determined since this increases the risk of birth defects and the chance of rare autosomal recessive disorders.

A number of key points are important when analyzing a family history[18]:

- A negative family history does not eliminate the possibility of a genetic disorder. The disorder may be autosomal recessive and multigenerational involvement would not be expected, or it could be secondary to a new autosomal dominant mutation.
- An attempt should be made to identify other high-risk family members and to determine if they have any resemblance to the affected child. Previously unrecognized affected relatives may be discovered because of variable expressivity.
- For male children, the presence of similarly affected males on the maternal side suggests X-linked inheritance. However, the absence of any other affected males does not eliminate the possibility of X-linked inheritance with the mother as the carrier.

Physical examination

The physical examination is detail-oriented and comprehensive, and specific features may also be assessed in the parents. Careful measurements of height/length, weight, and head circumference are done and are plotted on appropriate growth curves. If a disorder of growth and/or the skeleton is suspected, arm span and upper and lower segments are measured. Major and minor anomalies

and normal variants are noted. Minor anomalies may not be of significance, but they may provide clues to the diagnosis.[18,19] Specific details about the examination are described in Table 1-1.

In cases of facial dysmorphism, the individual is compared to other family members at the same age to assess for familial resemblance. The presence of certain anomalies may serve as clues to the diagnosis. These anomalies may be minor themselves, but they are highly correlated with a specific diagnosis.[18] For example, pits (depressions in the skin) in various locations are often clues to the diagnosis. Lower lip pits are associated with van der Woude syndrome, (an autosomal dominant disorder consisting of cleft palate and lip pits) or Kabuki syndrome (a disorder with a particular facial appearance including long palpebral fissures with lower eyelid eversion, other birth defects, short stature, and intellectual disability). Pits and creases on the back of the external ear should make one think of Beckwith Wiedemann, an overgrowth syndrome. Palmar pits are associated with basal cell nevus syndrome. The presence of more than one malformation or a malformation in association with a minor anomaly may give clues to a specific diagnosis.[19]

A clinical geneticist should recognize and document the pattern of anomalies in various disorders based on clinical experience, review of the literature, or use of various databases such as POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations https://www.possum.net.au), the London Medical Databases, and OMIM (Online Mendelian Inheritance in Man, https://www.ncbi.nlm.nih.gov/omim). Another strategy geneticists employ is to concentrate on the most unusual feature and to determine what conditions are associated with it. In addition, the geneticist must consider the variable expressivity of certain disorders and be open to exploring a range of possibilities.

Laboratory and testing methods

After the geneticist has formulated a differential diagnosis or suspects a specific diagnosis, laboratory testing is performed.

In the case of a specific genetic disorder, it must be determined if the problem is at the chromosomal level or if it is a single-gene disorder. In chromosomal disorders, there is a deletion or duplication of a particular chromosome or chromosomal segment. These disorders are evaluated by a karyotype (see Fig 1-1) or by chromosomal microarray. A karyotype looks at the microscopic structure of the chromosomes. It is indicated if

Table 1-1 Components of a genetic physical examination

SYSTEM	FEATURE ASSESSED
General	Size, body proportions, general appearance
Skin/hair	Pigmentation, hair distribution and texture, and the presence of any lesions or birthmarks Comparison made to the pigmentation of family members
Head size and shape	Asymmetry, possible sutural synostosis, microcephaly, macrocephaly
Eyes	Slant, size, placement, morphology of irises Measure palpebral fissures, innercanthal, outercanthal, interpupillary distances
Ears	Shape, size, location, ear lobe creases, ear pits, tags, morphology
Nose	Shape, configuration of nasal bridge, root, columella, nares
Mouth	Vermilion, shape, dentition, palate, uvula
Philtrum	Length, groove
Chin	Size, position
Neck	Webbing, masses, sinuses, pits, thyroid
Chest	Heart auscultation, symmetry, pectus excavatum, pectus carinatum, placement of nipples
Abdomen	Hepatosplenomegaly, masses, scars
Extremities	Size, symmetry, configuration of hands, feet, nails, creases Range of motion of distal and proximal joints, pes planus, pes cavus, syndactyly
Back	Curvature, lesions
Neurologic	Developmental status, cranial nerves, motor tone, motor strength, gait, cerebellar function, reflexes
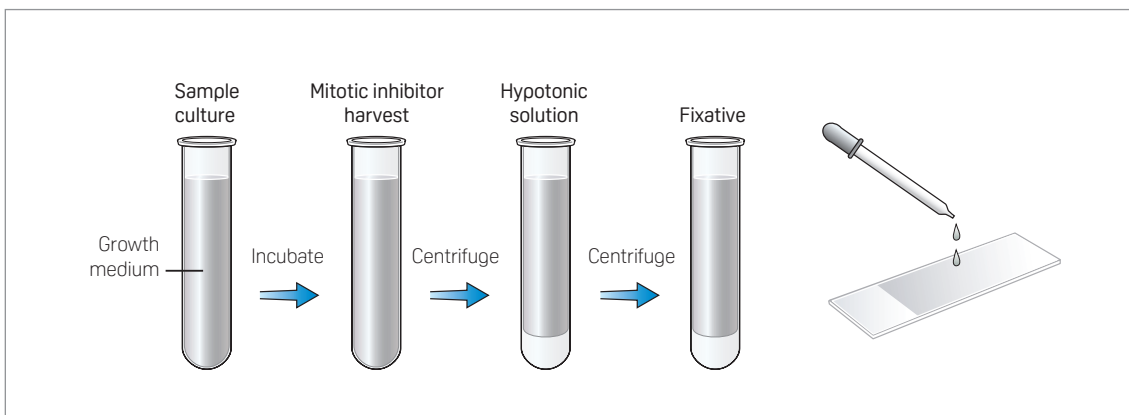
Fig 1-12 Karyotype technique. Cells are cultured, harvested, fixed, and stained. The mitoses are then examined microscopically.