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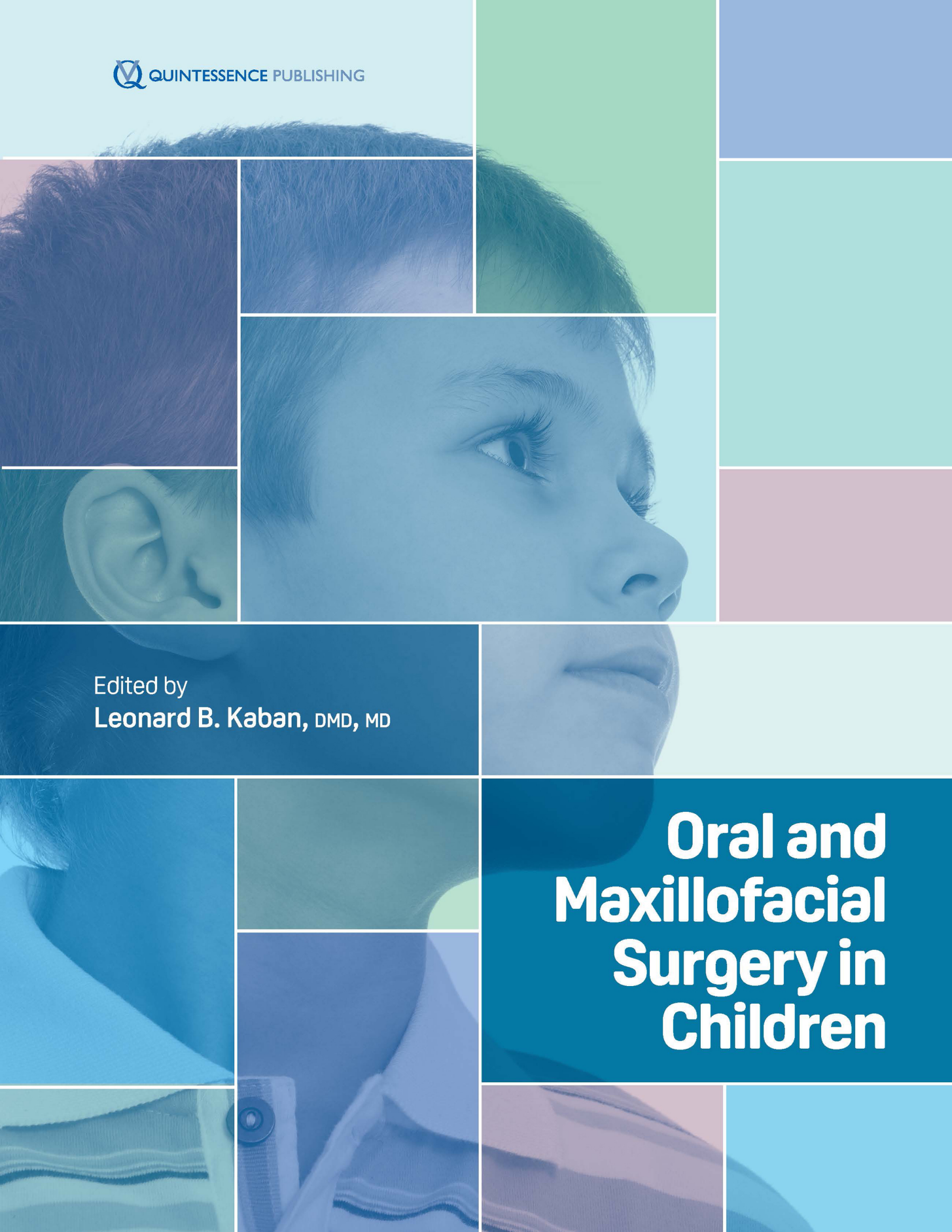

Edited by
Leonard B. Kaban, DMD, MD

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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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

I would like to thank my colleagues and friends who contributed chapters for this book. I appreciate that they are busy with their own projects, and I am grateful that they gave generously of their time to participate in this one. I also want to acknowledge Bernard Friedman, Director of Oral & Maxillofacial Radiology at Harvard School of Dental Medicine, for his contribution of 3D CBCT images; Paul Caruso, Director of Pediatric Neuroradiology, for prenatal cleft ultrasounds and MRIs; Cheryl Hersh, speech pathologist at MGH, for video fluoroscopy images; and Angela Lin, my long-time friend and genetics colleague, for photographs of her Turner syndrome patient. At Quintessence, I was fortunate to be able to work with my initial editor Marieke Zaffron and then Bryn Grisham, Director of Publishing, who helped so much with the nuts and bolts of bringing this book to fruition. Zachary Turner prepared the illustrations for the text. Aileen McElroy, my administrative assistant, was instrumental in the success of this project. Her computer and editing skills as well as overall organizational talents helped me immeasurably. Being computer challenged, I could not have gotten through the research, writing, and editing phases without her. Debra Sybertz, my long-time friend and clinical manager, provided encouragement and help with contacting patients and securing archived material for me. Renee Swank, my current patient care coordinator, also helped to get patients back for follow-up and documentation. Nicole Eichole-Belair, lead surgical assistant in the OMS clinic, and Amy Colp helped me navigate the electronic health record to obtain images I needed.

Much of the work for this book was done during my sabbatical at New York University College of Dentistry. I want to thank Dean Charles Bertolami, a resident of mine many years ago and now a close friend, and Robert Glickman, Chair of the Department of OMS, for their hospitality and support during my time at NYU.

Finally, I would like to thank my wife Barbara, my daughter Jody, and my son Jeff for their support and understanding over the years, when I have been unavailable to them because of my commitment to patient care, teaching, scholarly activity, and sequentially running two OMS departments.

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1

Molecular Genetics and Syndrome Recognition for the Clinician

Joan M. Stoler

Why 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.

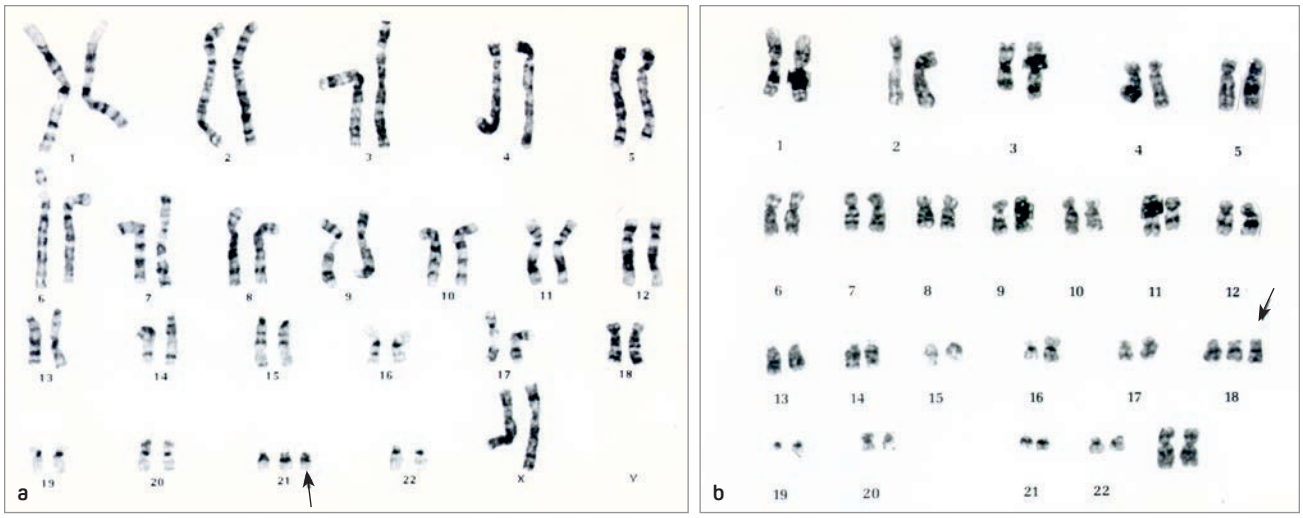
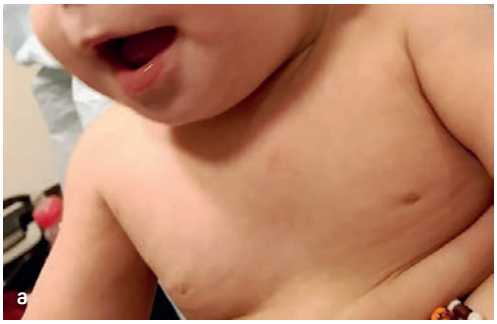


Fig 1-1 *(a)* Female karyotype with trisomy 21. The *arrow* indicates the extra chromosome 21. Note the presence of 2 X chromosomes and no Y chromosome, indicating it is a female. *(b)* Female karyotype with trisomy 18. The *arrow* shows the presence of three copies of chromosome 18.

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.)



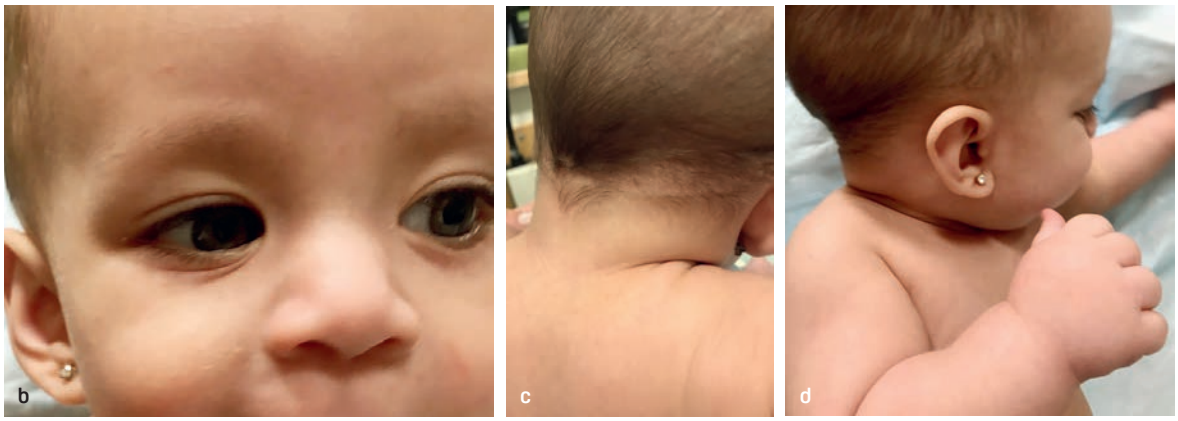


Fig 1-3 A 3-year-old girl with velocardiofacial/DiGeorge syndrome. The characteristic features of this syndrome include rectangular-shaped nose, low-set ears, micrognathia (mild in this child), and long tapered fingers (left hand here). Patients also have cleft palate, velopharyngeal insufficiency, thymic 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.

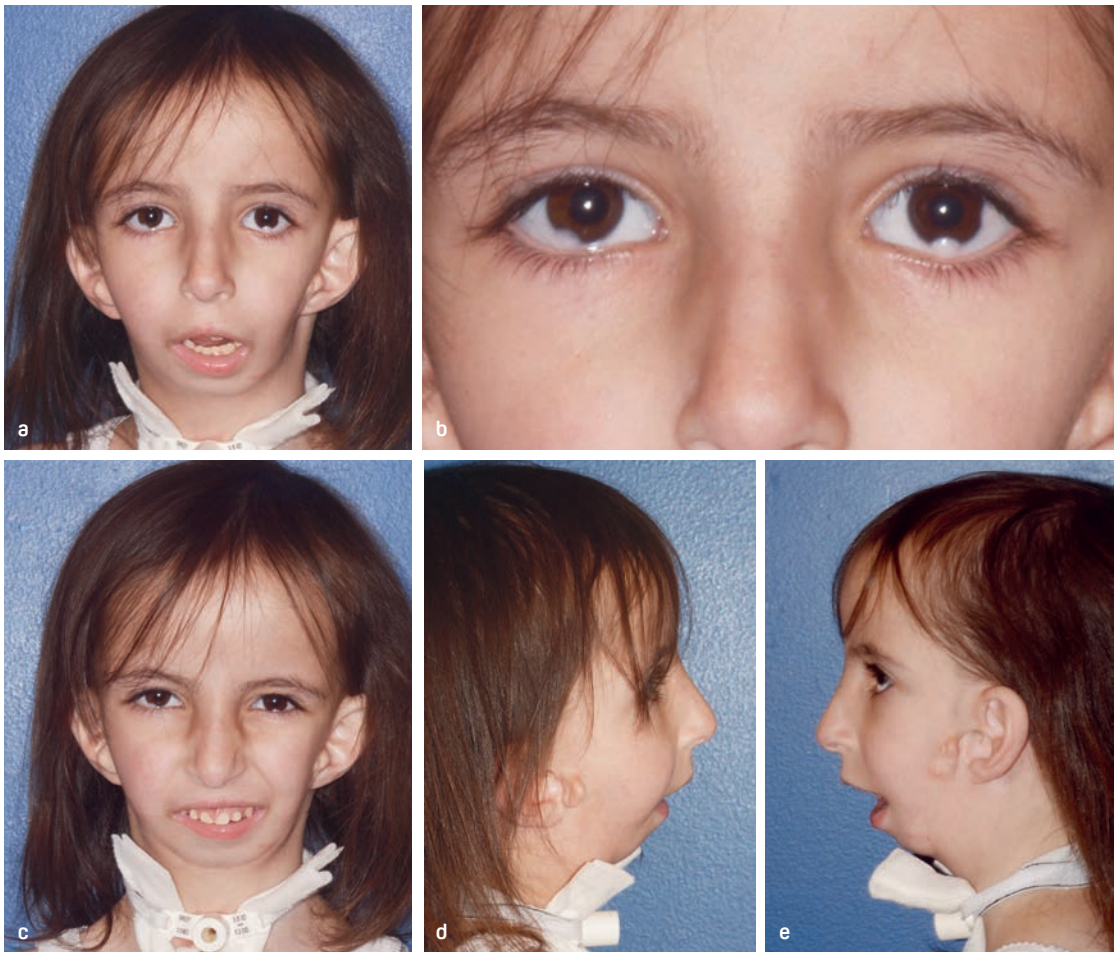


Fig 1-5 *(a to e)* Photographs of a 4-year-old girl with cateye syndrome and bilateral craniofacial microsomia. Her problems include 22q11 tetrasomy, anal atresia and fistula, single kidney, total anomalous pulmonary venous return, submucous cleft palate, low-set ears, multiple ear tags, abnormal external 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).

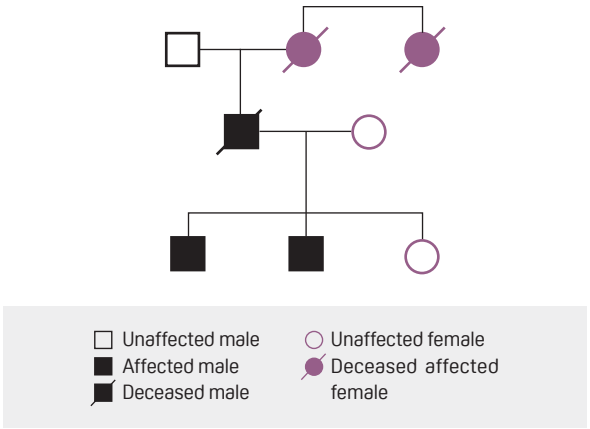


Fig 1-6 Autosomal dominant pedigree. Each child (male or female) of an affected individual has a 50% chance of inheriting the abnormal copy of the gene and of being affected. Note the multigenerational involvement.

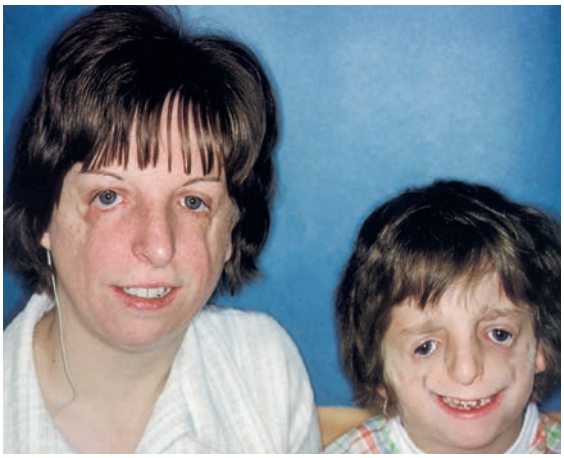
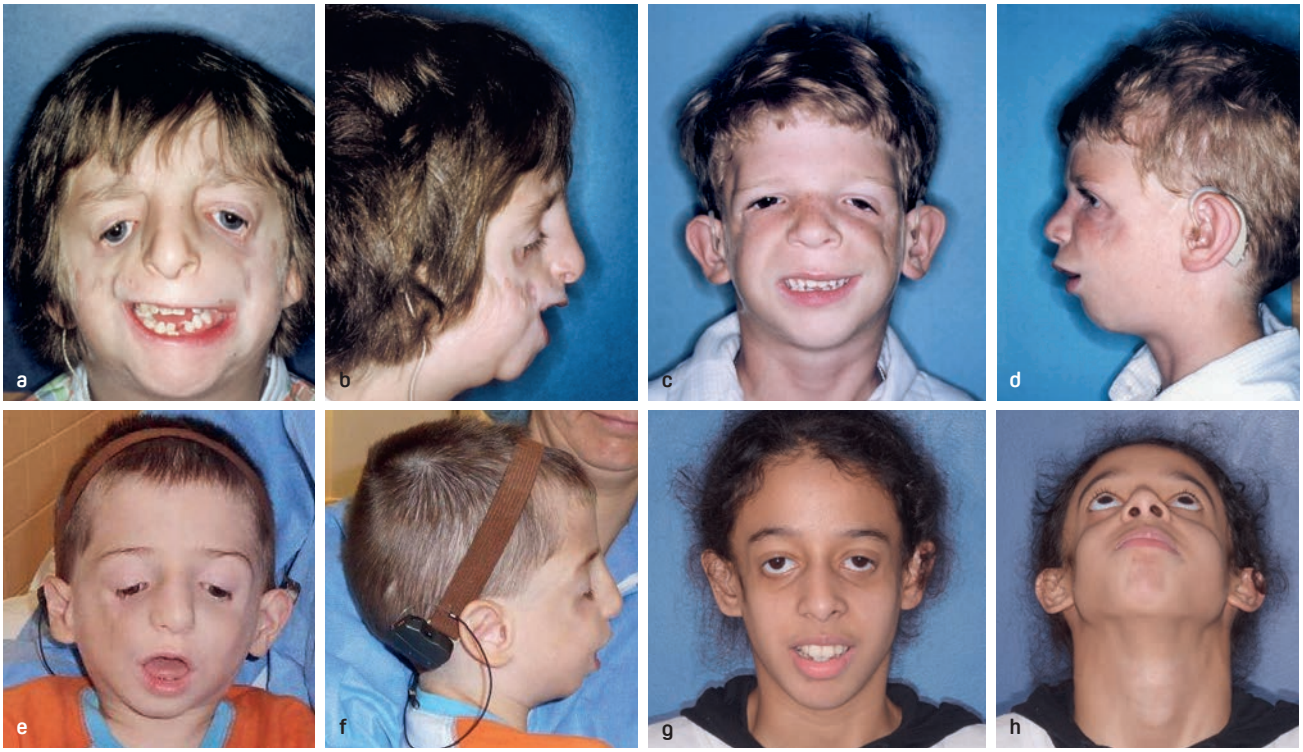


Fig 1-7 Mother and daughter with Treacher Collins syndrome (autosomal dominant *TCOF1* gene). Offspring of a parent with an autosomal dominant disorder have a 50% chance of inheriting the abnormal gene. Frontal photographs demonstrate downturned lateral canthi, zygomatic hypoplasia, soft tissue colobomas,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



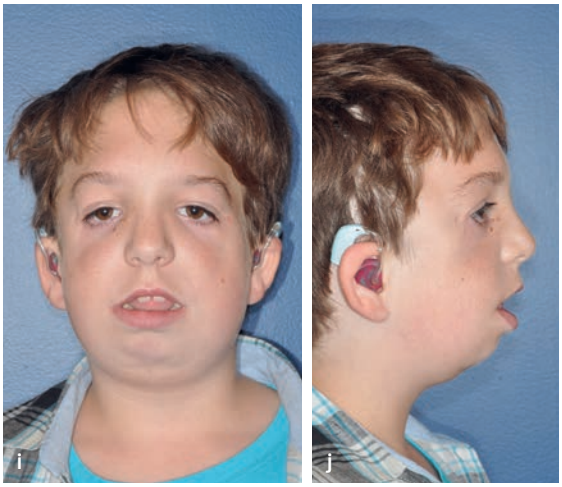


Fig 1-8 Treacher Collins is an autosomal dominant disorder with incomplete penetrance and variable expressivity. This set of photographs demonstrates the variable expressivity of the disorder. *(a and b)* A girl with severe involvement of the orbits, eyelids, midfacial soft tissue, mandible, and ears. *(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.

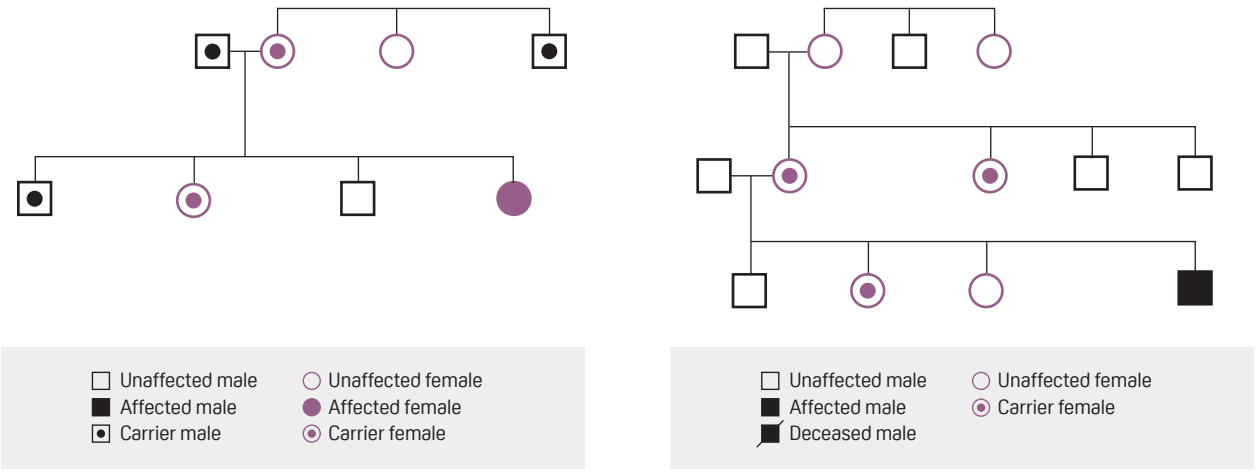


Fig 1-9 Autosomal recessive pedigree. Each parent has one normal and one abnormal copy of the gene and is an unaffected carrier. Each child (male or female) has a 25% risk of inheriting the two abnormal copies of the gene and of being affected.

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

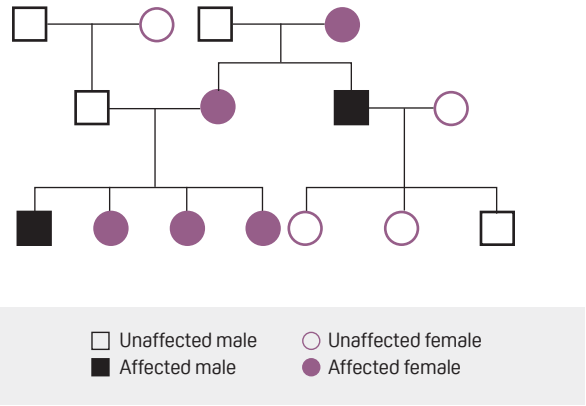


Fig 1-11 Mitochondrial inheritance pedigree. Abnormalities in the mitochondrial DNA follow a maternal pattern of inheritance.

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

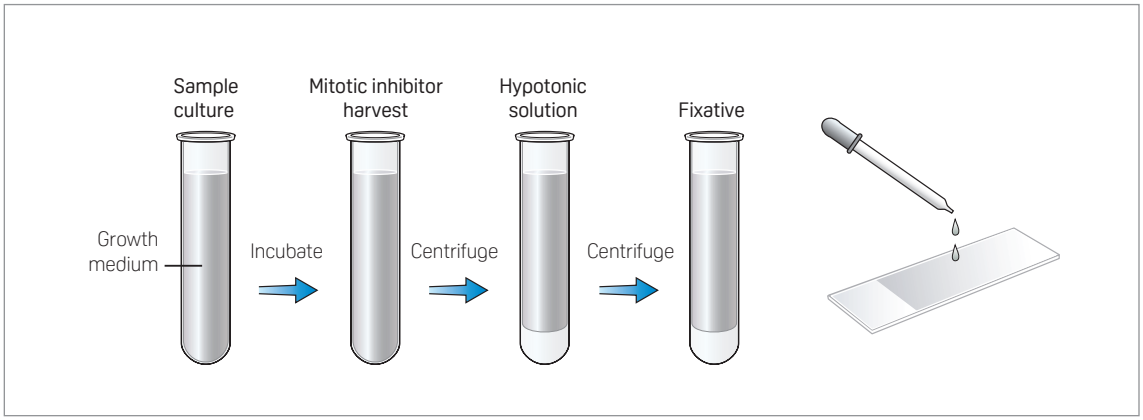


Fig 1-12 Karyotype technique. Cells are cultured, harvested, fixed, and stained. The mitoses are then examined microscopically.

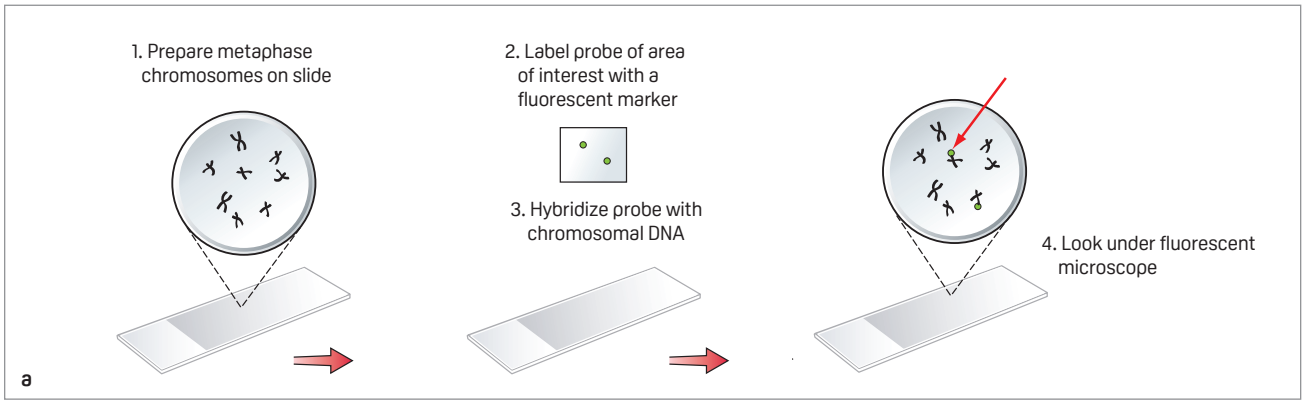


Fig 1-13 *(a)* FISH technique. Fluorescent-labeled DNA probes are hybridized to specific chromosomal segments only. *(b)* FISH image of 22q11.2 deletion. One probe labels chromosome 22 and both chromosomes 22 fluoresce. The other probe is specific to the 22q11.2 segment, and only one of the chromosomes 22 fluoresces in that area *(arrow)*. The normal chromosome 22 shows two areas of fluorescence.

there is concern for trisomies or aneuploidies (eg, Down syndrome, trisomy 18, trisomy 13, Turner syndrome), mosaic aneuploidies, or a chromosomal rearrangement when there is a history of multiple miscarriages.

A karyotype involves cell culture. Cells are harvested, fixed, and stained for mitoses. The specimen is then examined under a microscope (Fig 1-12). A karyotype can be performed on white blood cells from a peripheral blood sample and fibroblasts from skin. It is useful for detection of small missing or extra pieces of chromosomes.

Deletions and duplications are better defined using a chromosomal microarray. This hybridization technique uses a single nucleotide as a probe and evaluates all of the chromosomes.[20] It can detect copy number variants, including deletions and duplications of variable sizes, and can also detect areas of homozygosity (where portions of both members of the chromosome pair are identical). This can reflect consanguinity or uniparental disomy (where both members or parts of both members of the chromosome pair come from one parent).[21] A chromosomal microarray may also indicate a potential recessive disorder within the area of homozygosity.[22] A chromosomal microarray cannot detect chromosomal rearrangements or changes in single genes (other than if a gene is deleted). A copy number variant can be pathogenic (known to be associated with a condition), benign, or of uncertain significance (in which there are not enough data available to assign it being either benign or pathogenic).[23] A chromosomal microarray is considered the first-line test for individuals with multiple congenital anomalies, autism, or intellectual disability.[24] While a chromosomal microarray looks at all of the chromosomes, FISH (fluorescent in situ hybridization) or MLPA (multiplex ligation-dependent probe amplification) can be used for targeted microdeletions or microduplications. The FISH technique requires additional steps to hybridize fluorescent-labeled DNA probes to specific areas on the gene[25] (Fig 1-13). MLPA is a PCR-based (polymerase chain reaction) technique that amplifies a specific DNA segment. For example, specific testing for 22q11 deletion syndrome can be done using either the appropriate FISH probe or MLPA.

If the condition is a single-gene disorder, then the clinician must determine if the responsible gene has been identified. For some conditions, only one gene is known to cause the disorder, and specific gene sequencing and deletion/duplication analysis can be done. If there is

genetic heterogeneity, in which different genes can cause the same disorder, a multigene panel may be best.[26] Variants in genes can be detected and are graded (ie, benign, likely benign, uncertain significance, pathogenic, or likely pathogenic) according to specific guidelines.[27]

What would be the next step for diagnosis? When the clinical diagnosis is unknown, whole exome sequencing (WES) may be indicated to analyze those genes that code for proteins (approximately 1% of the total DNA). WES is done using NGS (next-generation sequencing) and generates multiple copies of the genes, which are then analyzed using bioinformatics techniques. It has been reported that 25% of these cases have been diagnosed using WES,[28] with even higher diagnostic yields in select populations.[29] In addition, new genes for known conditions and new conditions have been discovered. Limitations of WES are that not every gene is analyzed equally, deletions and duplications may be missed, and disorders due to methylation abnormalities and expanded repeats will not be detected. Typically, this testing is done using a trio (proband and both parents). Therefore, the possibility of misattributed parentage must be addressed during counseling and consent for this testing.

Whole genome sequencing analyzes more of the genome but is limited in its availability and may detect more variants of uncertain significance. With such wide analysis using these techniques, genes for conditions other than the indication for testing may be found. In fact, the American College of Medical Genetics has recommended a list of genes (secondary findings) that are considered medically actionable and that should be identified when possible. Such genes include those for inherited cancer syndromes, connective tissue disorders, and inherited cardiomyopathies.[30] However, individuals may opt in or opt out for the secondary findings. These tests help confirm a clinical diagnosis and help guide the geneticist in management of the patient and family. Furthermore, location of a specific mutation facilitates prenatal diagnosis and identification of at-risk family members.

There are some concerns about genetic testing. DNA analysis of pre-symptomatic individuals may have adverse effects on their insurability. There is the Genetic Information Nondiscrimination Act, which prohibits genetic discrimination in health insurance and employment. However, there is no protection for life, disability, or long-term insurance.

Testing individuals for a late-onset disease for which there is no treatment is controversial. While testing for some autosomal dominant disorders, other family members with the disease may be identified against their wishes. For example, a man seeks testing for an adult-onset autosomal dominant disorder, which his grandfather had. His own parent has not shown signs of the disorder and has not been tested. If the man's test is positive, then his parent can also be assumed to have the disease. The parent may not wish to know this, which poses an ethical dilemma. Geneticists try to counsel their patients extensively about these issues prior to testing. Such counseling should be part of the decision-making process.

Metabolic studies such as analysis of amino acids, organic acids, and lysosomal enzymes are ordered in certain circumstances. This testing is based on the signs and symptoms, such as episodic illnesses, food avoidance, the cyclical nature of the symptoms (if applicable), regression, and deterioration of mental state.

Common syndromes with facial deformity

Branchiootorenal spectrum disorder

Branchio-oto-renal (BOR) spectrum disorder is also known as BOR dysplasia or BOR syndrome and includes branchio-otic syndrome (which, as a subset, does not include renal abnormalities, and deafness is variable). The clinical features of this disorder include sensorineural, conductive, or mixed hearing loss; "cup" shaped pinnae (lop ear); preauricular pits; Mondini malformation (hypoplasia of cochlear apex); bilateral branchial cleft fistulae or cysts; high arched palate; cleft palate; bifid uvula; and varying renal anomalies. Renal anomalies may include renal dysplasia or aplasia, abnormalities of the collecting system, and polycystic kidneys.[31] Renal evaluation should be carried out, and these diagnoses should be considered whenever deafness, malformed pinnae, preauricular pits, and branchial clefts are present, with or without a cleft palate. If there are affected family members, the diagnosis can be made with the presence of only two findings (hearing loss, preauricular pits or tags, lop-ear deformity, branchial fistula, or renal anomalies). If there are no affected family members, the diagnosis is made when there are three or more major criteria or two major and two minor criteria.[32] The major criteria are branchial arch anomalies, deafness, preauricular anomalies, and renal anomalies, and the minor criteria are external auditory canal anomalies, middle ear anomalies, inner ear abnormalities, preauricular tags, facial asymmetry, or palate abnormalities.[32] Other diagnoses to consider include cat eye syndrome (see Fig 1-4), and BOR-Duane hydrocephalus contiguous gene syndrome. This has the additional features of Duane anomaly and hydrocephalus and is due to a deletion at 8q12.1-q21.2.[33]

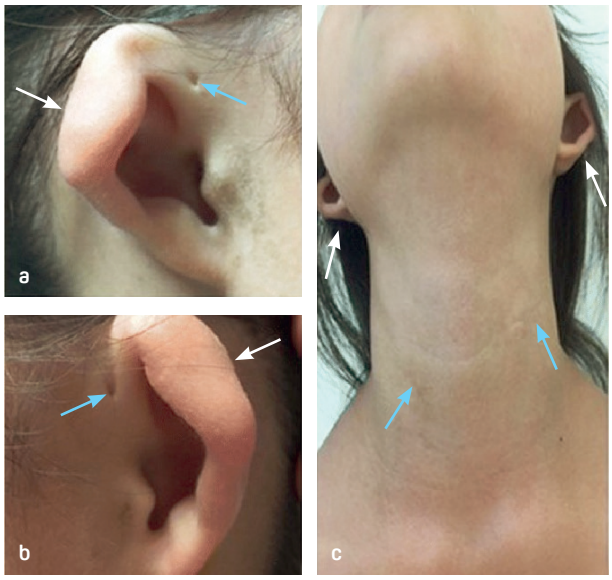


Fig 1-14 BOR syndrome. *(a and b)* Images of both ears with microtia, preauricular pits, and branchial cleft fistulae. *Blue arrows* indicate preauricular pits, and *white arrows* indicate microtia. *(c) Blue arrows* indicate branchial cleft fistulae, and *white arrows* indicate microtia. (Reprinted with permission from Wang et al[34] under the Creative Commons Attribution 4.0 International License [http://creativecommons.org/licenses/by/4.0/]).

BOR syndrome (Fig 1-14)[34] is an autosomal dominant disorder with variable expressivity. Accordingly, each child of an affected individual has a 50% chance of inheriting the abnormal gene and exhibiting the phenotype, although expression may vary. In approximately 40% of families with BOR syndrome, there is a mutation in the *EYA1* (eyes absent1) gene located at the chromosomal locus 8q13.3.[35] An additional 2.5% are found to have mutations in the *SIX5* gene, and 2% are found to have mutations in the *SIX1* gene.[31] Testing using a gene panel for these three genes is available. However, one must interpret the results with caution, as 55% to 60% of other affected families with BOR syndrome do not have a pathogenic variant in one of these genes. Studies show that 90% of patients have an affected parent, and 20% have de novo mutations.[31] Kidney function must be evaluated in affected individuals because of the potential severity of the renal disease. In addition, the family should be counseled about the possibility of significant renal abnormalities in future affected family members.

Cherubism

Patients with cherubism typically present with a history of progressive swelling of the lower face in early childhood, which eventually tilts the eyes upward, giving the "cherubic" appearance[36] (Figs 1-15 and 1-16). The swelling is due to fibro-osseous tissue containing multinucleated giant cells. Radiographs show multilocular radiolucencies in the mandible, maxilla, and ribs. The lesions may occupy a large portion of the ramus and body of the mandible and the zygomatic-maxillary complex. Generally, the swelling recedes after puberty.[37,38] This condition may have a significant impact on facial appearance. It causes concern on the part of the parents, pediatricians, and dentists regarding adverse effects on tooth eruption and the possibility of root resorption and pathologic fracture of the jaw. There may also be secondary complications with swallowing, speech, and vision. The diagnosis is based on the clinical features and should be distinguished from Caffey disease, which has a different radiologic appearance and has more widespread involvement of the skeleton.[39] The differential diagnosis also includes brown tumor of hyperparathyroidism, giant cell lesions, Noonan-like/multiple giant cell lesion syndrome, fibrous dysplasia, aneurysmal bone cyst, and hyperparathyroidism-jaw tumor syndrome.[36]

Cherubism is an autosomal dominant disorder with 80% of affected individuals exhibiting abnormalities in the *SH3BP2* gene located on chromosome 4p16.3.[40] The protein normally produced by this gene affects the bone cell's responses to incoming signals; these mutations may

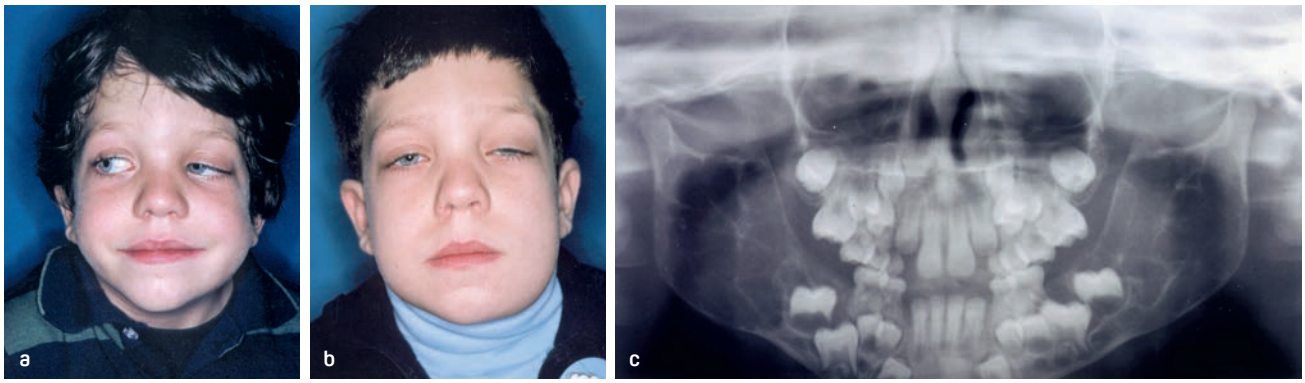


Fig 1-15 *(a)* Frontal photograph of a 5-year-old boy with cherubism. *(b)* Same patient at age 12. Note the progressive swelling of the cheeks and lower face. *(c)* Panoramic radiograph shows the large multilocular radiolucencies that occupy the body and ramus of the mandible.

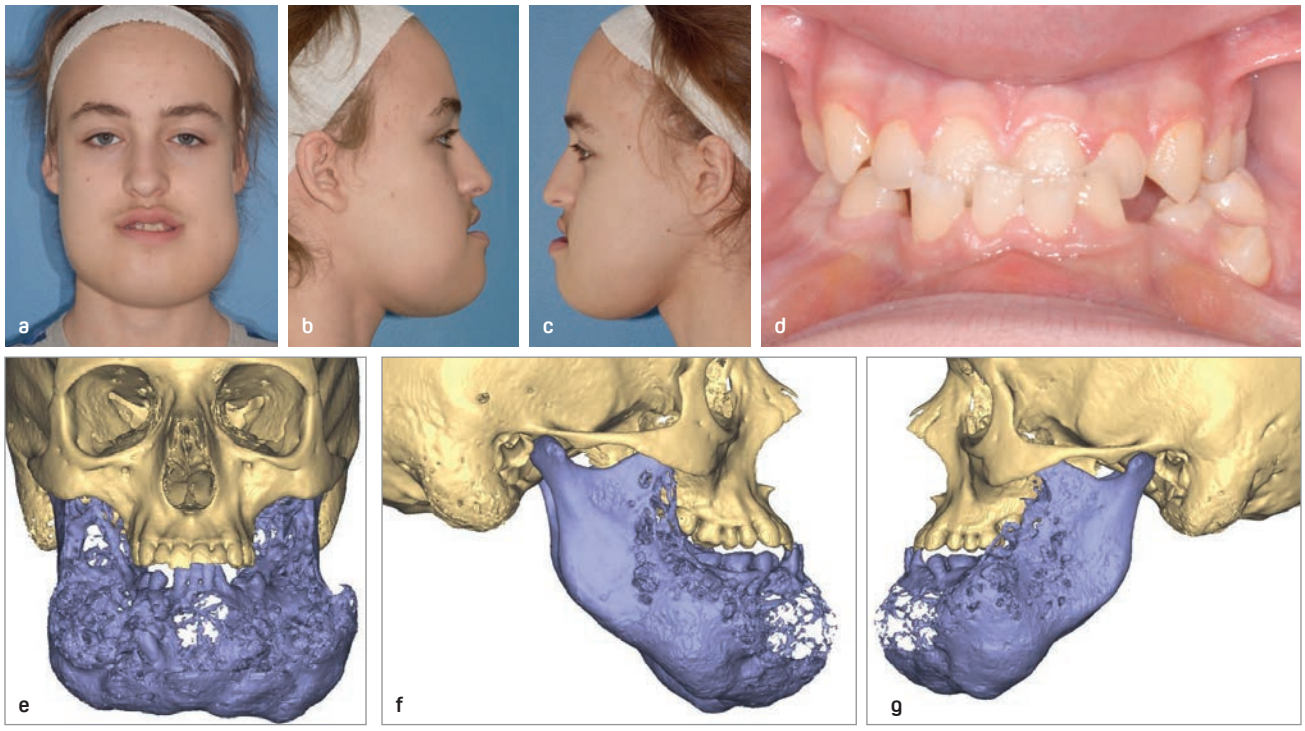


Fig 1-16 *(a to c)* Frontal, right, and left lateral facial views of 14-year-old boy with cherubism. Note that the forehead and orbits are symmetric, the lateral canthi are slightly turned upwards, the zygomas are convex, and the maxilla is "puffy"/enlarged in contour bilaterally. The mandible is grossly enlarged from the angle and mid-ramus on the right to the same region on the left. He has a normal range of jaw motion and no swelling in the preauricular regions. The condyles are spared. The chin is grossly enlarged with a tumorous growth on the alveolar ridge. *(d)* The intraoral view shows the mandible expanded into the sulcus from right retromolar pad to left retromolar pad. There is an anterior crossbite. *(e to g)* 3D reconstructions of mandible and skull showing the massive, expansile, multilocular involvement of mandible with condyles spared. There is minimal involvement of the maxilla.

result in gain of function. Presumably, there are other as yet unidentified genes responsible for cherubism in the 20% of patients who do not have the *SH3BP2* mutation.[36] The absence of a positive family history does not rule out the possibility of cherubism due to a new dominant mutation. Cherubism is also characterized by incomplete penetrance, with some gene carriers not exhibiting any obvious signs of the disorder.[36,40]

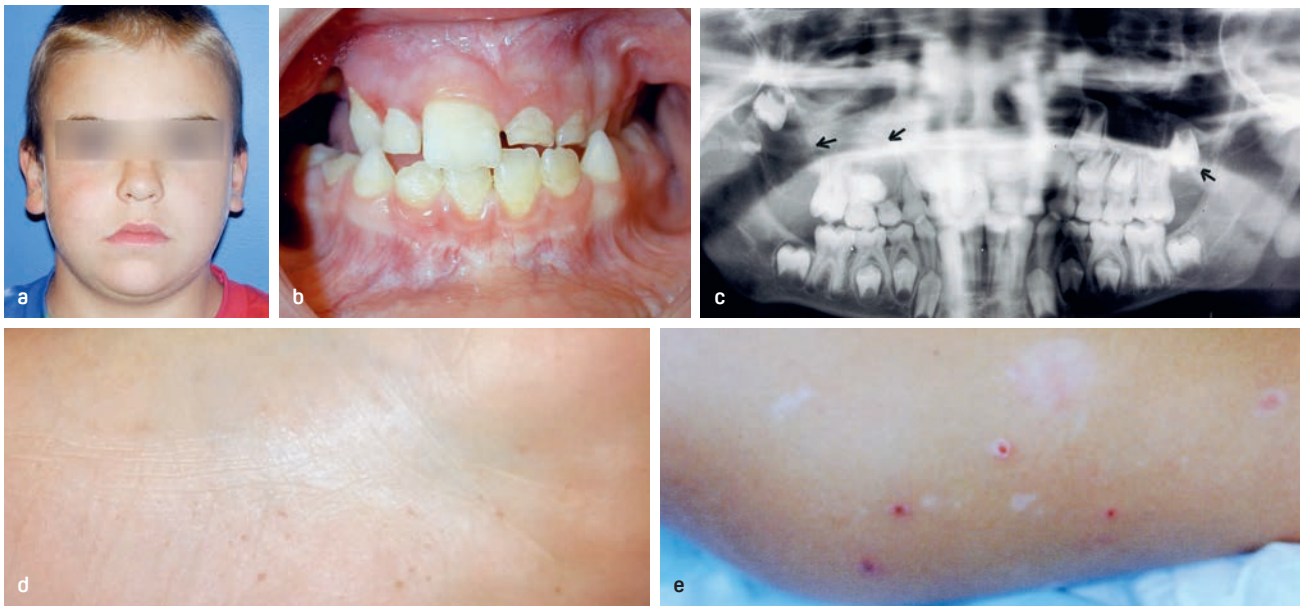


Fig 1-17 *(a)* Frontal photograph of a 10-year-old boy with NBCCS (also called *Gorlin syndrome*). The intraoral view *(b)* and panoramic radiograph *(c)* show the delayed and asymmetric dental eruption. Multiple radiolucent areas are evident *(arrows)*. These were enucleated and confirmed to be odontogenic keratocysts by histology. *(d)* A photograph of the same patient's foot demonstrates plantar pitting, which also may appear on the ventral surface of the hand (palmar pits). *(e)* The photograph of the child's right arm shows multiple nevi. He has had multiple basal cell carcinomas. (Courtesy of Dr Maria Troulis.)

Nevoid basal cell carcinoma syndrome

The clinical features of this syndrome include numerous basal cell carcinomas, epidermal cysts, odontogenic keratocysts, palmar and plantar pits, various tumors or hamartomas, skeletal abnormalities of the ribs and vertebrae, macrocephaly, and cleft lip and/or cleft palate[41,42] (Figs 1-17 to 1-20). The criteria to make the diagnosis of nevoid basal cell carcinoma syndrome (NBCCS) include two major or one major and two minor features.[43] The Basal Cell Nevus Syndrome Colloquium Group[44] also proposed one major criterion plus positive molecular testing. Although they did not reach a specific consensus, the proposed criteria are described in Box 1-1.

NBCCS is an autosomal dominant disorder with complete penetrance but with variable expressivity. The responsible genes are *PTCH1*, *PTCH2*, and *SUFU*, with pathogenic variants being found more often in *PTCH1* and rarely in *PTCH2*.[45] There is some genotype-phenotype correlation; patients with pathogenic variants in *SUFU* can have milder clinical features and no jaw cysts but have an increased risk for medulloblastoma.[46,47] Twenty to thirty percent of cases are due to new mutations.[47]

PTCH1 is a tumor suppressor gene and is a cell cycle regulator.[48] *PTCH1*, *PTCH2*, and *SUFU* are part of the hedgehog signaling pathway. The developmental effects are seen when only one mutation is present, accounting for the autosomal dominant inheritance pattern.[49] With tumor suppressor genes, unregulated cell growth occurs when both copies of the gene are not working. For people who have inherited an abnormal tumor suppressor gene, the likelihood of a "second hit," ie, a change in the remaining gene somewhere in the body, is very high. This leads to unregulated cell growth in that tissue. In the tumors that develop in NBCCS, there does appear to be an abnormality of the other copy of the gene. This is presumed to be responsible for the change in cell growth.[50] In terms of monitoring and treatment for NBCCS, these patients are very sensitive to radiation, and exposure to X-rays and sun should be minimized because of the risk of basal cell carcinomas.[47]

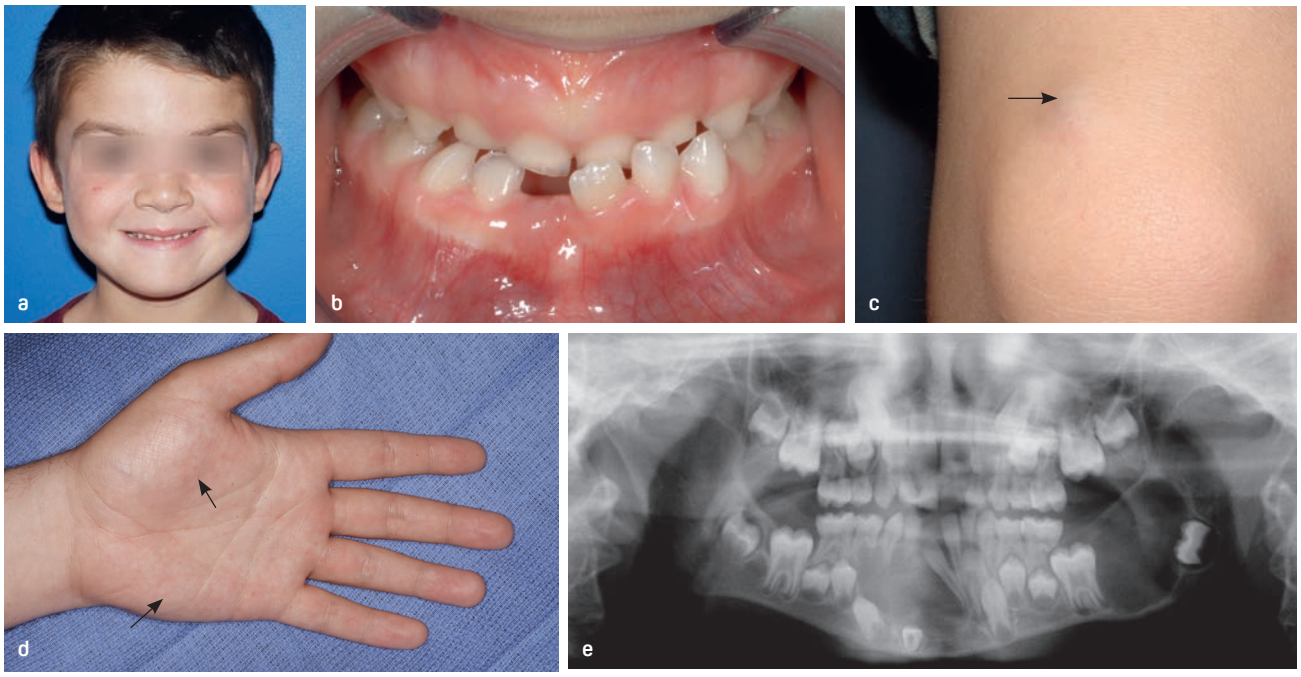


Fig 1-18 *(a)* Frontal photograph of 8-year-old boy at presentation with jaw cysts. There is mild frontal bossing and hypertelorism. *(b)* Intraorally, there is fullness of the sulcus anteriorly and on the left posteriorly with displacement of teeth in the anterior mandible. *(c)* Cystic lesion over right knee *(arrow)*. *(d)* Palmar pitting *(arrow)*. *(e)* Panoramic radiograph shows large radiolucent, expansile lesions at left mandibular posterior and symphysis regions displacing teeth. (See also Fig 5-34.)

Genetic testing is available for correlation with clinical findings. Such testing detects the genetic abnormality in approximately 73% to 85% of clinical cases.[47] Indications for genetic testing include confirmation of the clinical diagnosis in patients with the classic features and confirmation of basal cell nevus syndrome in a child with medulloblastoma and in individuals younger than 20 years with a basal cell carcinoma and insufficient associated clinical findings.[47] Genetic testing can also be used for prenatal diagnosis and identification of at-risk family members who may appear to be asymptomatic. Sequencing and deletion/duplication can be explored in a stepwise manner by identifying the *PTCH1* gene initially, then followed by *SUFU* and *PTCH2*, or it can be done as a panel including all of these genes.

The risk to other family members depends on whether the mutation in the affected person is inherited or has arisen de novo. Each child of an affected individual has a 50% chance of inheriting the abnormal gene and of expressing the disorder to some extent. For those situations in which the parents test negative, there still is the possibility of recurrence due to a germline mosaicism (when one of the parents carries the mutation only in the gonads).[47]

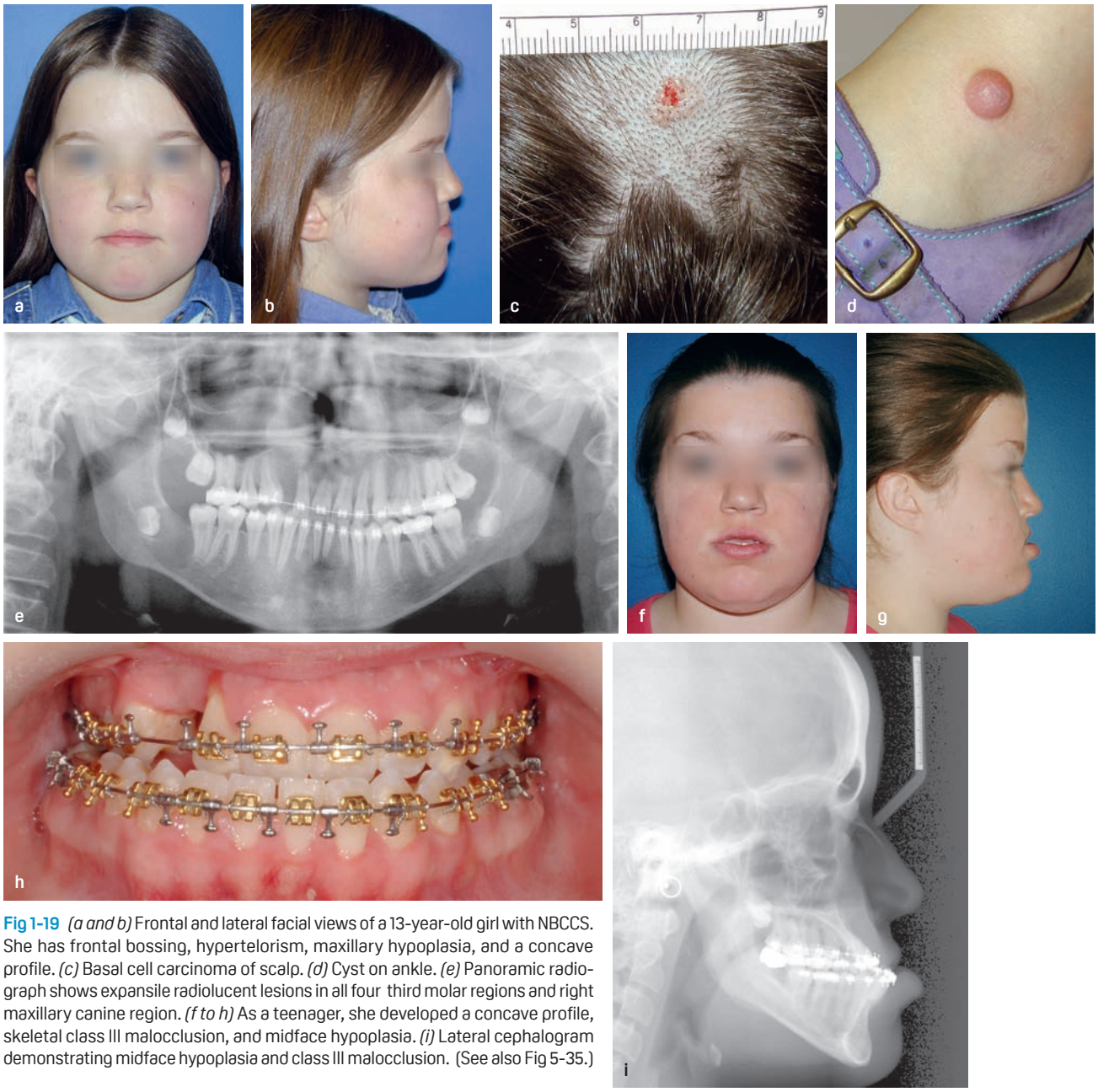


Fig 1-19 *(a and b)* Frontal and lateral facial views of a 13-year-old girl with NBCCS. She has frontal bossing, hypertelorism, maxillary hypoplasia, and a concave profile. *(c)* Basal cell carcinoma of scalp. *(d)* Cyst on ankle. *(e)* Panoramic radiograph shows expansile radiolucent lesions in all four third molar regions and right maxillary canine region. *(f to h)* As a teenager, she developed a concave profile, skeletal class III malocclusion, and midface hypoplasia. *(i)* Lateral cephalogram demonstrating midface hypoplasia and class III malocclusion. (See also Fig 5-35.)

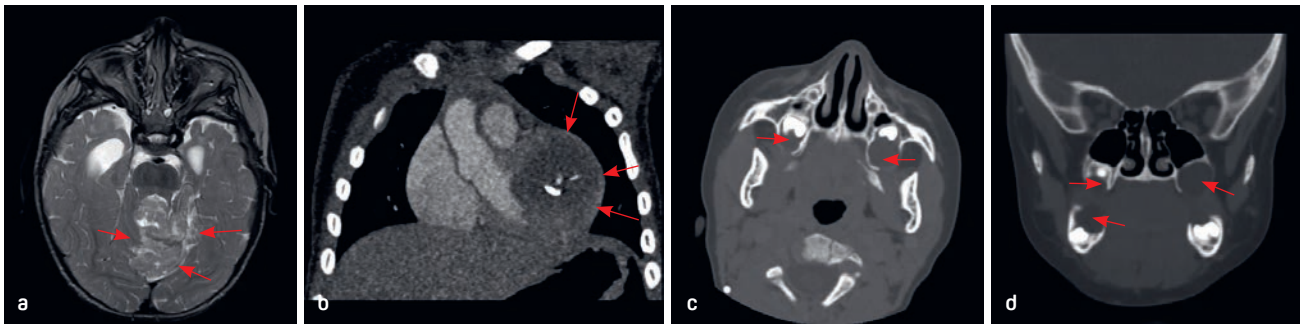


Fig 1-20 *(a)* At 1 year of age, this patient underwent resection and postoperative chemotherapy for a desmoplastic medulloblastoma. An axial MRI cut demonstrates the tumor *(arrows)*. *(b)* Chest CT demonstrates a cardiac fibroma *(arrows)*. *(c and d)* Axial and coronal CT cuts demonstrate expansile jaw cysts in the right and left maxilla and right mandible *(arrows)*.