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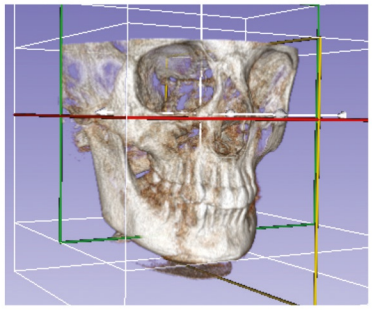

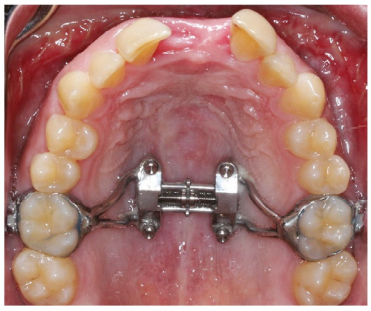

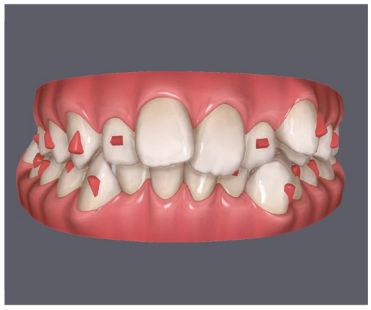

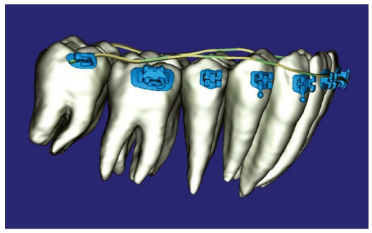

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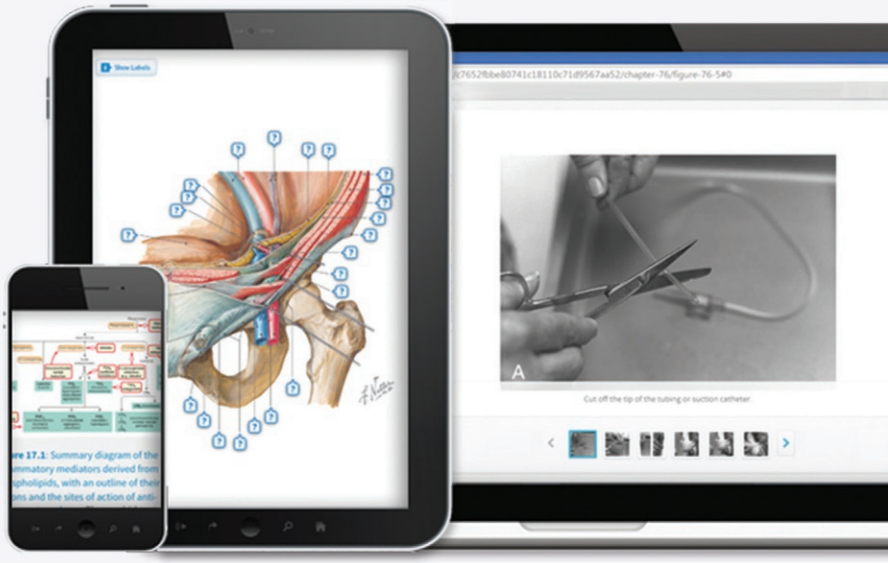

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DEDICATION

Robert L. Vanarsdall, Jr., DDS

It Is Never Too Late to Remember and Give Thanks

This 7th edition of *Orthodontics: Current Principles and Techniques* is dedicated to its long-time co-editor, Robert L. Vanarsdall, better known by his colleagues as "Slick." Slick passed away shortly after the publication of the 6th edition of this textbook, but his influence on the scope of this edition and indeed the specialty of orthodontics remains current today. For those who did not know Dr. Vanarsdall and even those who were privileged to know or even work with him, we want to share a picture of who Slick was and his manifold contributions.

Robert Lee Vanarsdall was born in 1930 in Crewe, a small town in south-central Virginia. Named after his father and carrying the historic name of a southerner, as a child and teen he demonstrated an outgoing nature and an affinity for being well dressed and polite. "Slick" was the name he reportedly was given by a local clothing store where he bought his clothes, always looking to be neat and stylish and becoming a trend setter with his peers. The name stuck, as did an expanded scope of leadership.

Slick graduated from the College of William and Mary and in 1962 married his college sweetheart, Sandra Hoffman. Slick's love for international travel developed after joining the United States Navy (1962), in which he served as a lieutenant, returning for his dental education and graduating from the Medical College of Virginia in 1970 with a DDS, but knowing he wanted to specialize. Dr. Vanarsdall often spoke of how "lucky" he was to be the first student at the University of Pennsylvania School of Dental Medicine to graduate with a combined orthodontic and periodontal specialty education in a then unique program developed by innovative dental educator and school dean, Dr. Walter Cohen. Slick subsequently was board certified in both Periodontics and Orthodontics, becoming an examiner for the American Board of Orthodontics.

On completion of his dual dental specialty education, Slick joined the Penn faculty initially as a teaching fellow and rose through the professorial ranks while further developing the postgraduate individual and combined orthodontic and periodontic specialty programs. He became chair of the Department of Periodontics and, later, the Department of Pediatric Dentistry. Slick directed the Department of Orthodontics for almost 30 years, serving as department chair until 2011. He continued to actively teach, practice, and lecture internationally until his passing.

During an academic career that spanned 44 years, Dr. Vanarsdall was a prolific writer with more than 100 papers and 12 book chapters. He served on multiple editorial boards and was editor-in-chief for the *International Journal of Adult Orthodontics and Orthognathic Surgery* for 17 years. In 1994, Slick joined Tom Graber as co-editor and a chapter author in the 2nd edition of this textbook published by Mosby-Elsevier. He continued in that role until the 6th edition published in 2017 (the initial text was published in 1969 by W.B. Saunders). Dr. Vanarsdall also was a co-editor and author in a comprehensive textbook on the use of implants for orthodontic anchorage, titled *Applications of Orthodontic Mini Implants,* with co-authors J. S. Lee, J. K. Kim, and Y. C. Park, all of whom remain recognized chapter authors in this 7th edition as well.

Dr. Vanarsdall was active in professional associations as a participant speaker and organizer. He lectured all over the world and was awarded every major honorary lecture. He chaired multiple local, national, and international professional meetings, including the 1994 and 2002 American Association of Orthodontists (AAO) Annual Sessions. He was a member of numerous committees and boards, including the AAO's Council on Scientific Affairs, for which he served as chair. An active contributor and member of the Eastern Component of the Edward H. Angle Society of Orthodontists, he served as its president from 2004 to 2005. Slick was the recipient of numerous national and international awards for his academic work, topped by the American Association of Orthodontists Foundation highest academic award, the Jarabak Memorial International Teachers and Research Award (2017).

Although Dr. Vanarsdall was an outstanding mentor to his students, he was even a better friend to them and his colleagues. Dr. David Musich, a longtime chapter author in this book, tells the story of receiving a patient transfer of a 16-year-old with an ankylosed/impacted canine and getting an offer of help from Slick. "This was her 4th surgery on that tooth. She was anxious—so was her mom. After 10 minutes of explanation and 35 minutes of gentle luxation, the tooth moved, and it was free to be moved into the arch. It was Slick's genuine compassion and caring spirit that allowed this young lady to finally have her canine positioned. As a clinician, he was a true artist and unique as a colleague." Important to note is that Dr. Vanarsdall flew halfway across the country just to help with this one patient and colleague. It was not unusual for Dr. Vanarsdall to share his expertise with colleagues and students, distant from the site and approbation of others.

What is extraordinary about the contributions of this dedicated teacher and clinical research scientist? Dr. Vanarsdall had the ability to come to clinical issues with an open mind. At a time when specialty orthodontics was directed at adolescents, he looked to how adult dental care could be enhanced, even in the face of periodontal concerns. In a specialty then focused on anteroposterior discrepancies, with diagnosis and treatment often driven by lateral cephalometric measures, he looked to enhanced diagnosis and therapeutics by way of the transverse dimension. He was one of the first to present patients treated with surgical arch expansion and many other clinical approaches we now use routinely. Lest we forget, he changed the way that the specialty of orthodontics is practiced today.

Author, clinician, teacher, scientist, innovator, researcher, lecturer, administrator, world traveler, practitioner, humanitarian, mentor, husband, father, friend. We all were bettered by Slick! It is never too late to remember and give thanks.

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PREFACE

Nothing is known in our profession by guess; and I do not believe, that from the first dawn of medical science to the present moment, a single correct idea has emanated from conjecture. . . .

Sir Astley Paston Cooper

Since the publication of the previous (6th) edition of *Orthodontics: Current Principles and Techniques* our specialty and the wider world have witnessed dramatic change, disruption, adaptation, and renewal. The 7th edition reflects this period of rich ingenuity and continues to be a valuable, comprehensive resource for the contemporary orthodontic specialty student and practitioner.

As in our previous editions, the goal is to target a readership of Orthodontic Residents and Specialist Orthodontic Practitioners. Excellent textbooks already exist to educate dental students in the fundamental knowledge and basic concepts and principles of orthodontics, which every dentist should have assimilated in dental school. Orthodontics, after all, is an integral part of dentistry that should be considered by generalists and other specialists in a team approach to oral health care.

We are delighted that the 7th edition continues to be used in Graduate Orthodontic programs throughout the world. This has been further facilitated by translation into multiple languages, permitting global distribution in educational settings and beyond. For graduate orthodontic programs and orthodontic specialist education, the 7th edition is available in an "eBook" format. Availability through a website and as a searchable reference text allows rapid access to clinical topics and access to fresh information in a fast-paced and rapidly changing technological world.

In this edition, we acknowledge the increasing focus on the expanding armamentarium at our disposal, including fixed sagittal correctors, bone-borne expanders, in-house aligners, autotransplantation, and computer-assisted diagnosis and treatment. Our aim has been to update the content to reflect contemporary orthodontic specialty practice, while retaining a strong theoretical and evidence-based underpinning. The opportunity to move some sections to an online format has allowed us to address more topics without substantially increasing the physical size of the book.

Given our expressed aim of providing a holistic review of our specialty from both clinical and theoretical perspectives, an overview of the history of orthodontics has been introduced. Classic chapters and case reports have been moved online, which allows us to more fully provide a historical perspective while focusing on current principles and techniques.

The pandemic-related shutdown in dental practices early in 2020 spawned creative new technology, including programs that allow us to virtually meet with patients and monitor their progress. The reintroduction of chairside practice in the summer of 2020 was accompanied with a keen focus on the generation, behavior, and mitigation of aerosols. A new chapter provides valuable insights into the topic of aerosols in orthodontic practice.

The accelerated development of new techniques and materials places ever-greater onus on the conduct and appreciation of high-quality, independent clinical trials. Moreover, the wider availability of information and ever-increasing pool of journal articles places a premium on the ability of both residents and seasoned practitioners to digest research findings and ascertain whether and when to implement new or revised treatment approaches. A new chapter dedicated to evidence-based orthodontics is a valuable resource for all. Likewise, Machine Learning and Artificial Intelligence are rapidly being integrated into orthodontics, enhancing our ability to predict, plan, and analyze tooth movement and soft tissue response. Increased use of computers for diagnosis, treatment planning, and robotics are certainly part of our future, and this is embraced in a new chapter on Artificial Intelligence and Big Data as applied to Orthodontics, as well as an updated chapter on Computer-Assisted Orthodontics.

We think that this 7th edition continues to recognize the global nature of the orthodontics specialty, which is reflected in a larger pool of international authors. Some of the topics covered by our international colleagues include autotransplantation, orthodontic-periodontic relationships, orthognathic surgery, interdisciplinary adult treatment, fixed functional appliances, biomaterials, and temporary anchorage devices.

The chapter on craniofacial dysmorphology and cleft lip and palate has been completely revised and updated with the inclusion of advanced methods of neonatal maxillary orthopedics for hospital-based orthodontists and residents enrolled in craniofacial fellowship programs. An aspect of interest for the orthodontist is the inclusion of a speech and language pathologist, describing the effects of adolescent growth and surgical maxillary advancement on velopharyngeal mechanisms. Likewise, the chapter on airway considerations in orthodontics has been revised to reflect advances in knowledge over the past 5 years.

In this new edition of the textbook we are delighted to welcome a new, talented editor and author, Padhraig Fleming. Padhraig is our first Europe-based co-editor. He has been Professor and Postgraduate Training Lead in Orthodontics at the Institute of Dentistry, Queen Mary University of London and in the summer of 2022 was appointed to a new position as Professor and Chair of Orthodontics, Dublin Dental University Hospital, Trinity College Dublin, Dublin, Ireland. He is also an Associate Editor of the *American Journal of Orthodontics and Dentofacial Orthopedics,* the *British Dental Journal,* and the *Journal of Dentistry and Progress in Orthodontics* and is on the editorial board of numerous other journals.

We are greatly indebted to each of our chapter contributors for their invaluable input. We sincerely hope that we have succeeded in doing full justice to the meteoric change that our specialty has witnessed over the past years while helping to perpetuate the fundamental principles and knowledge that we are certain will never lose relevance or import.

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CONTENTS

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The History of Orthodontics… From an Idea to a Profession

David L. Turpin and Norman Wahl

Today, the specialty of orthodontics is looked upon by the public with respect and even admiration. There are at least 30 English-language journals whose primary focus is orthodontics. Most orthodontists, though, know little about the struggles that took place when the profession was in its infancy. In the last half of the 19th century, orthodontics was not viewed as a specialty of dentistry, and Angle even speculated that it was destined to become a specialty of medicine. At that time the mechanisms of tooth movement were a complete mystery. We have certainly come a long way.

Some of the developments in our specialty are particularly impressive. For example, the perfection of fixed appliances was far ahead of the many contributions made in later years to assist with diagnosis and treatment planning. The use of enamel bonding has almost eliminated the need for metal bands, the application of orthognathic surgery has widened the envelope of correction, and a better understanding of the biology of tooth movement and growth have all had a profound impact on our work. One has to believe that the publication of scientific journals for the past 100 years has also played a major role in disseminating ideas and knowledge and in helping to bring many of these ideas to fruition.

In recognition of the rich history and ongoing improvements in our specialty, Norm Wahl and I were asked by the editors of this 7th edition to compile a history of orthodontics, starting from the middle of the 19th century. To tell this story, we highlight many of the careers of prominent educators and clinicians who have contributed to the development of orthodontia, or *orthodontics* as we now know it. We hope that the inclusion of this chapter will not only shed light on our profession's development but also serve as a pleasurable "read."

PRE-1900 DEVELOPMENT OF THE ORTHODONTIC SPECIALTY

At this time in history, many questioned whether teeth could be moved safely to new positions. Would the pulps remain vital? Would the uncompleted roots of growing teeth be bent? Would tooth longevity be affected? It would take pioneering dentists, working without the benefit of graduate training, to build the body of orthodontic knowledge brick by brick. Kingsley pioneered cleft-palate treatment. Case showed us the importance of facial esthetics. Dewey and Ketcham created the American Board of Orthodontics (ABO), the first certifying board in dentistry. But it was Edward H. Angle, the Father of Modern Orthodontics, who gave us our first school, journal, society, and practical classification of malocclusion.

THE PROFESSIONALIZATION OF ORTHODONTICS

Dentistry's first specialty organization, the Society of Orthodontists, was formed in 1900, and the first specialty journals began to appear. In the 1930s, creative thinkers in orthodontics began to more openly question the status quo. Apprenticeships had given way to formal instruction, and proprietary schools bowed to graduate university programs, including some taught or headed by women. Edward Angle was elected president of the society in 1900, and the first annual meeting was to be in St. Louis the following June. During its first year, the fledgling society claimed only 13 members.

THE AMERICAN BOARD OF ORTHODONTICS, ALBERT KETCHAM, AND EARLY 20TH-CENTURY APPLIANCES

Early in the past century, three events put Colorado in the orthodontic spotlight: the discovery—by an orthodontist—of the caries-preventive powers of fluoridated water, the formation of dentistry's first specialty board, and the founding of a supply company by and for orthodontists. Meanwhile, inventive practitioners were giving the profession more options for treatment modalities, and stainless steel was making

its feeble debut. Angle led the way, designing the expansion (E) arch around 1900, which was the precursor to our modern brackets.

MORE EARLY 20TH-CENTURY APPLIANCES AND THE EXTRACTION CONTROVERSY

The trying conditions of the Great Depression and World War II did not deter innovative orthodontists from adding new appliances to our armamentarium. Clinicians became fragmented into various "camps." Silas Kloehn's neck gear became a more patient-friendly version of extraoral anchorage, but it still had drawbacks. Angle's stranglehold on the specialty was finally broken when four of his disciples advocated extractions as a reasonable option to be considered in patients with crowding and/or protrusion.

THE CEPHALOMETER TAKES ITS PLACE IN THE ORTHODONTIC ARMAMENTARIUM

After World War II, cephalometric radiography came into widespread use, enabling orthodontists to measure changes in tooth and jaw positions produced by growth and treatment. Cephalometrics revealed that many malocclusions resulted from faulty jaw relationships, not just malposed teeth, and made orthodontists wonder if it was possible for jaw growth to be altered by orthodontic treatment.

FUNCTIONAL APPLIANCES TO MIDCENTURY

The history of functional appliances can be traced back to 1879, when Norman Kingsley introduced the "bite-jumping" appliance. In the early 1900s, parallel development began in the United States and Europe in fixed and functional techniques, respectively, but the Atlantic Ocean was a geographic barrier that restricted the early sharing of knowledge and experience in these philosophies.

THE GOLDEN AGE OF ORTHODONTICS

For orthodontists, the post–World War II era was characterized by the introduction of fluoridation, sit-down dentistry, and an increase in extractions. Postwar prosperity, the baby boom, and increased enlightenment of parents contributed to what was later called the "golden age of orthodontics." The subsequent clamor for more orthodontists led to a proliferation of graduate departments and inauguration of the American Association of Orthodontists (AAO) Preceptorship Program. There was also an increase in mixed-dentition treatment, requiring improved methods of analyzing arch lengths.

TWO CONTROVERSIES: EARLY TREATMENT AND OCCLUSION

From the beginning, orthodontists have been faced with the decision of when to start treatment. Until the late 20th century, this decision was based on clinical observation, the influence of strong leaders, and (after midcentury) the results obtained by what Europeans called "functional jaw orthopedics." Recent findings questioning the efficacy of early treatment have forced orthodontists to ask themselves whether their decision to "start early" is being influenced too heavily by practice-management considerations.

THE TEMPOROMANDIBULAR JOINT AND ORTHOGNATHIC SURGERY

The temporomandibular joint (TMJ) has always been the practitioner's no-man's land. Who's in charge here? The general dentist, the prosthodontist, the oral surgeon, the otolaryngologist, the psychiatrist, or the orthodontist? Theories about the cause of problems are as varied as the specialties involved.

SURGICAL ADJUNCTS TO ORTHODONTICS

Around 1970, after overcoming obstacles related to anesthesia, infection, and blood supply, orthognathic surgeons came into their own. The history of cleft lip and palate treatment has a much earlier beginning, because a deformed infant evokes a strong desire to intervene. Angle's belief that orthodontists can grow bone finally came to fruition with the advent of distraction osteogenesis, which developed from the limb-lengthening procedures of Gavriil Ilizarov in Russia.

SKELETAL ANCHORAGE

For many years, orthodontists have searched for a form of anchorage that does not rely on patient cooperation, although the answer already lay in the implants that dentists used to replace missing teeth and that oral surgeons used to hold bone segments together. Now these divergent lines have come together with titanium as the most biocompatible material in the form of stationary anchorage. State-of-the-art miniplate and microscrews—temporary anchorage devices (TADs)—now permit movements previously thought difficult or impossible.

LATE 20TH-CENTURY

Orthodontics continues to evolve. It has taken half a century for orthodontic bonding procedures to evolve from chemically cured acrylic to light-cured acrylic, and even having precisely placed adhesive when brackets are shipped from the manufacturer. The device that threatens to replace conventional brackets altogether—the aligner—also relies on bonded buttons, so it appears that some form of bonding will be with us for a while. The digital revolution has been occurring over the past 20 years, with the advent of digital photographs, two-dimensional (2D) and 3D imaging, intraoral scanning, and 3D printing.

As mentioned earlier, these advances have all been aided by our scientific journals. The current era of evidence-based research strives to make the orthodontic literature more accessible, useful, valid, and generalizable. Please visit the complete online chapter titled The History of Orthodontics in this 7th Edition of *Orthodontics: Current Principles and Techniques* to learn more about our profession's interesting journey over the past 150 years.

2

Craniofacial Growth and Development
Developing a Perspective

David S. Carlson and Peter H. Buschang

OUTLINE

This chapter is enhanced with the following electronic assets at www.expertconsult.com: Two tables.

An appreciation of the biological principles associated with growth and development, especially of the structures composing the craniofacial complex, is essential for attaining competency within the field of orthodontics. Particular emphasis for the advanced practice of orthodontics is placed on the hard tissues comprising the craniofacial regions, that is, the skeletal structures and the teeth, because these are the primary components of the craniofacial complex that the orthodontist addresses during treatment. Development, growth, and function of other craniofacial structures and tissues, such as muscles, neural tissues, and pharyngeal structures, as well as spaces such as the airway, are also of major interest to orthodontists. However, those elements are important primarily in terms of their influence—structurally, functionally, and developmentally—on the growth, size, and form of the skeletal elements of the face and jaws.

This chapter emphasizes postnatal growth, principally of the skeletal structures of the craniofacial complex, because of its importance in orthodontic treatment. Considerable attention is also given to prenatal development of craniofacial tissues and structures because it is critical for understanding postnatal growth. The reader is referred to a number of excellent references on developmental biology and human embryology for comprehensive reviews of early craniofacial development.[1,2]

SOMATIC GROWTH

The size and form of the craniofacial complex are major components of an individual's overall body structure. Moreover, the growth and maturation of the body as a whole, referred to generally as *somatic growth,* are highly correlated with those of the craniofacial complex. Therefore clinical evaluation of the status and potential for craniofacial growth, and thus of treatment planning in orthodontic patients, is highly dependent on an understanding of the somatic growth process.[3]

Differential Development and Maturation

In his classic work during the 1930s, Scammon[4] drew attention to the fact that the rate and timing of postnatal maturation, measured as a proportion of total adult size, vary widely among major systems of the human body (Fig. 2.1). In what has become known as "Scammon's curves," for example, maturation of the central nervous system (CNS) is shown to be completed primarily during the last trimester of gestation through age 3 to 6 years. As a result, the cranial vault, which houses the precociously developing and enlarging brain, is disproportionately large in the infant relative to the rest of the craniofacial region (Fig. 2.2). In contrast, the reproductive organs become mature a decade later, during adolescence.

The rate of general somatic growth and development, which includes the skeletal and muscular systems, is characterized by an S-shaped curve. The relative rate of growth is very high prenatally but then decreases during infancy and becomes even slower during childhood. The rate then accelerates greatly with the initiation of adolescence through the point of peak growth velocity, after which it slows once again and effectively stops altogether in adulthood. Development and growth of the craniofacial complex is intergraded between neural and somatic maturity patterns. The gradient moves from the cranium, which is the most mature, through the anterior cranial base, posterior cranial base and maxillary length, upper face height, corpus length, to

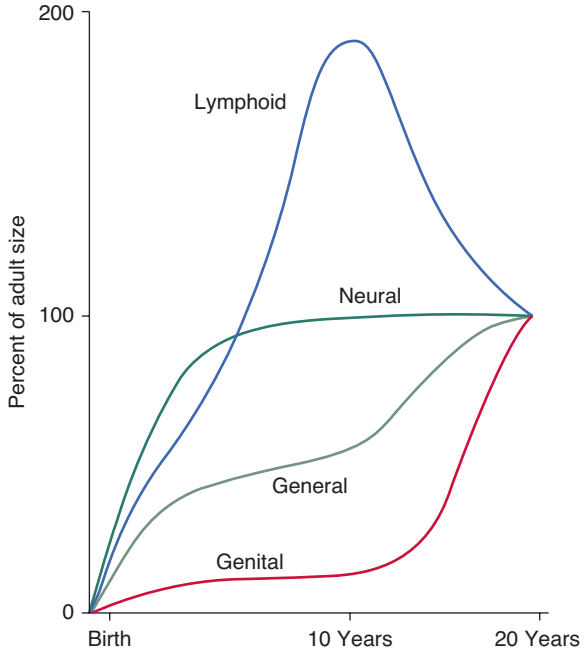


Fig. 2.1 Scammon's curves illustrating the fact that different systems of the body have different rates of development and come to maturity at different ages. (Adapted from Lowry GH. *Growth and Development of Children*. ed 6. Chicago: Year Book Medical Publishers; 1973.)

ramus height, which is the least mature and most closely approximates the general S-shaped pattern of general somatic maturation.[5]

Overall somatic growth, including the onset and end of puberty, is coordinated throughout the body by sex hormones and growth factors that are expressed differentially during the first two decades of postnatal life. However, the timing, rate, and amount of secretion of endocrine factors vary significantly between males and females and within each sex relative to chronologic age.

Variation in Rates of Growth during Maturation

Three episodes of relatively rapid growth have been documented for both general somatic and craniofacial growth. The greatest rates of growth occur prenatally and during infancy. The mid-childhood spurt takes place in approximately 50% of children between 6.5 and 8.5 years of age. The mid-growth spurt tends to occur more frequently and approximately 1 year later for boys than girls.[6] The more prominent adolescent growth spurt begins with the onset of puberty, at approximately 9 to 10 years of age in females and 11 to 12 years in males (Fig. 2.3). Female and male peak height velocities (PHV) are attained on average at 12 and 14 years of age, respectively, for North Americans and Europeans.[7] Females complete adolescence approximately 2 or more years ahead of males. The extra years of childhood growth before adolescence in males, as well as the slightly greater rates of adolescent growth and the slightly lengthier adolescent period, explain most of the sex differences in overall body size and craniofacial dimensions.

Because growth of craniofacial structures is correlated with general somatic growth, the timing of peak height velocity (PHV), which occurs at the pinnacle of the adolescent growth spurt, is especially useful for estimating peak maxillary and mandibular growth velocity. It has been shown that maxillary growth attains its maximum rate slightly before PHV, whereas the maximum rate of mandibular growth occurs just after PHV.[8,9]

The timing, rate, and amount of somatic growth are best determined by changes in overall height. Thus, height provides an important adjunct for cephalometric evaluations, especially during periods of rapid growth. Population-specific height percentiles make it possible to individualize craniofacial assessments. For example, if an individual's rate of somatic growth is particularly high or low, it is likely that his or her rate of craniofacial growth will be similarly high or low. Knowing a patient's height percentile also makes it possible to adjust measures of craniofacial size for the patient's body size. For example, if an individual is at the 90th percentile for body size, you would also expect his or her mandible to be larger than average. Height measurements are recommended because they are noninvasive, highly accurate, and simple to obtain at multiple occasions. Reference data for height are also typically based on larger samples of defined populations than are craniofacial reference data, which makes them more precise at the extreme percentiles.[10]

Assessments of maturation also provide critical information about the likelihood that the growth of craniofacial structures will continue and for how long or that growth has been completed. This is important because patients' maturational and chronologic ages should be expected to differ, often by more than 1 to 2 years, which confounds growth assessments necessary for orthodontic diagnosis and treatment planning. For this reason, it is always better to use the patient's skeletal age based on radiologic assessments of hand/wrist ossification to determine skeletal maturity, especially for determining whether the patient has entered adolescence, attained peak velocity, is past peak

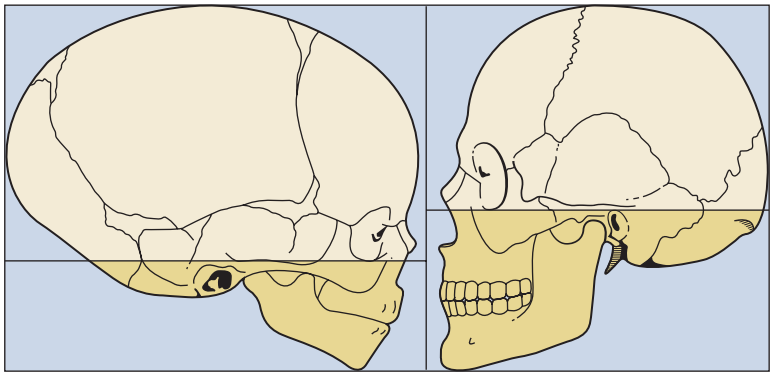


Fig. 2.2 Disproportions of the Head and Face in Infant and Adult. The neurocranium, which houses the brain and eyes is precocious in its development and growth and therefore is proportionately larger than the face during infancy and early childhood. (Adapted from Lowry GH. *Growth and Development of Children*. 6th ed. Chicago: Year Book Medical Publishers; 1973.)

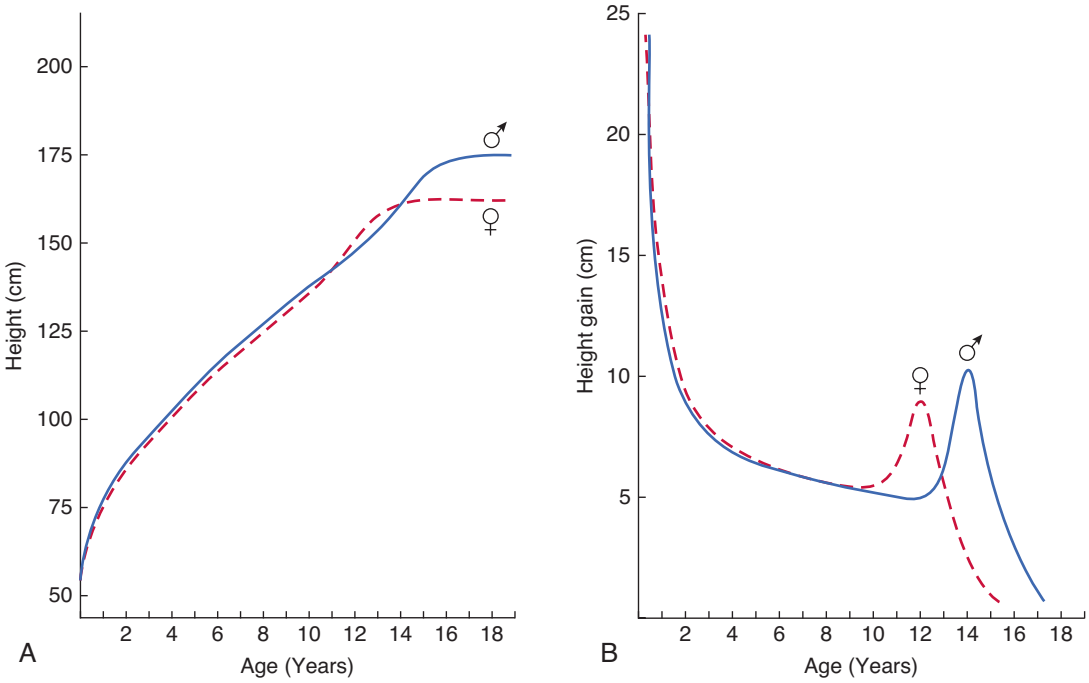


Fig. 2.3 Growth Velocity Curve (Growth per Unit of Time) for Skeletal Growth as General Measure of Human Ontogeny. Velocity of growth is characterized by decrease in growth rate beginning in the last trimester of prenatal development through maturation in the adult. During adolescence, hormonally mediated growth typically occurs to bring about a spurt in skeletal growth (peak height velocity). Pubertal growth spurt is characterized by considerable variability in onset and duration among individuals and according to sex. Onset of the pubertal growth spurt typically begins about age 10 in girls and lasts approximately 2 years. Boys have later onset (12 years); the entire pubertal period can last 4 to 6 years. (Adapted from Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children, 1965. *Arch Dis Childh.* 41:454-471, 1966.)

growth, or is near the end of clinically meaningful growth.[11,12] Cervical vertebrae maturation provides another, albeit less precise, method to determine skeletal maturity.[13] Molecular assays are now being developed to provide more sensitive assessments to determine maturational status of skeletal growth.[14]

CRANIOFACIAL COMPLEX

The craniofacial complex comprises 22 separate bones that can be organized for heuristic purposes into relatively discrete anatomic and functional regions. Each of these regions has distinct mechanisms of development and growth, as well as different capacities for adaptation during growth (Fig. 2.4).

Structural Units

Desmocranium

The term *desmocranium* refers to the portion of the craniofacial skeleton that arises from a membrane of ectodermal, mesodermal, and neural crest origin that surrounds the proximal end of the notochord very early in development. As the brain develops and expands in utero, the desmocranium develops initially as a fibrous membrane covering of the brain that eventually will give rise to the bones of the cranial vault and fibrous joints, or sutures, as well as the dura mater over the brain and the periosteum overlying the bones of the cranial vault. In fact, in the absence of a brain, as with anencephaly, the desmocranial bones will fail to develop at all. Because the skeletal derivatives of the desmocranium have exclusively a membranous precursor, initial

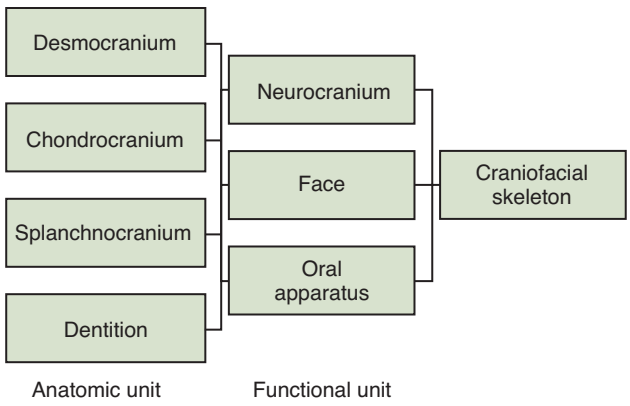


Fig. 2.4 Schematic of Organization of the Craniofacial Skeleton into Anatomic Regions and Overlapping Functional Regions.

morphogenesis and subsequent bone growth take place completely by intramembranous ossification.

Chondrocranium

The *chondrocranium* forms initially as part of the embryonic anlagen of primary cartilage that will become the cranial base, nasal septum, and nasal capsule. Like the desmocranium, the chondrocranium is also a derivative of the embryonic membrane surrounding the developing central nervous structures. However, the chondrocranium is

significantly less dependent on the presence of the brain for its initial formation and subsequent development. Growth associated with the derivative bones of the cranial base occurs by means of endochondral ossification.

Viscerocraniu

The *viscerocranium,* also referred to as the *splanchnocranium,* is composed of all those elements of the craniofacial complex that are derived from the first branchial arch and thus is of neural crest origin. These elements primarily include the bones of the midfacial complex and the mandible. Because the skeletal elements of the viscerocranium have no primary cartilaginous precursors, development and growth of its skeletal derivatives take place by intramembranous ossification that is also characterized by the presence of sutures and a specialized form of membrane-derived (secondary) cartilage at the mandibular condyles.

Dentition

The deciduous and permanent teeth are specialized anatomic components of the craniofacial complex that are composed of unique tissues and undergo a unique mechanism of development characterized by the interaction between ectodermal and mesenchymal tissues.

Functional Units

These four anatomic components can be combined organizationally into three overlapping and very broad functional units composing the craniofacial complex (Fig. 2.5).

Neurocranium

The *neurocranium* houses the brain and other elements of the CNS, such as the olfactory apparatus and auditory apparatus. As the brain rests on the cranial base and is covered by the cranial vault, development and growth of the neurocranium are characterized by a combination of membranous (desmocranium) and cartilaginous (chondrocranium) bone growth.

Face

The upper face may be defined as the region of the orbits of the eye. The midface, comprising primarily of the maxillae and zygomatic bones, is the region between the orbits and the upper dentition. Ectocranially, the bones of the face are composed externally of the intramembranously formed bones of the viscerocranium. However, the face also receives contributions from the chondrocranium as the cartilaginous nasal capsule and nasal septum. The lower face, comprising the mandible, develops entirely from the first branchial arch and thus is derived entirely as part of the viscerocranium. The mandible develops and grows by a specialized form of intramembranous formation of both bone and secondary cartilage.

Oral Apparatus

The oral apparatus is composed of the dentition and supporting structures within the upper and lower jaws. Thus the oral apparatus also is characterized by a unique morphogenesis of the teeth and a specialized form of intramembranous bone growth of the alveolar processes of the maxilla and mandible (viscerocranium). Development and growth of the skeletal structures comprising the oral apparatus are greatly influenced by the muscles of mastication and other soft tissues associated with mastication.

MOLECULAR BASIS OF CRANIOFACIAL DEVELOPMENT AND GROWTH

Patterning and subsequent formation of craniofacial tissues and structures have a complex, polygenic basis. For example, it has been shown that there are over 90 specific genes in which mutations will result in major disruptions of development, leading to severe craniofacial malformations.[15] Moreover, variations in craniofacial development and growth, from dysmorphologies to malocclusions, are multifactorial as a result of epigenetic mechanisms.[16,17] No genes are unique to the craniofacial complex. However, certain genes, especially those associated with developmental patterning of the head region and growth of cartilage, bone, and teeth, are of particular relevance for craniofacial development and growth and thus are of special importance for orthodontics. In addition, a number of genes of interest include those responsible for specific craniofacial deformities, such as craniosynostosis and facial clefts. The reader is referred to Hartsfield and Morford (see Chapter 3) for a comprehensive review of genetic mechanisms in the craniofacial region that are most important to orthodontics. A summary of the key genes associated with the patterning, development, and growth of the craniofacial region can be found in E-Table 2.1.

The key genes associated with craniofacial development may be organized informally into two broad yet overlapping groups based on their timing and patterns of expression and also their primary target tissues. First are those highly conserved genes, such as homeobox genes and transcriptions factors, that are responsible primarily for

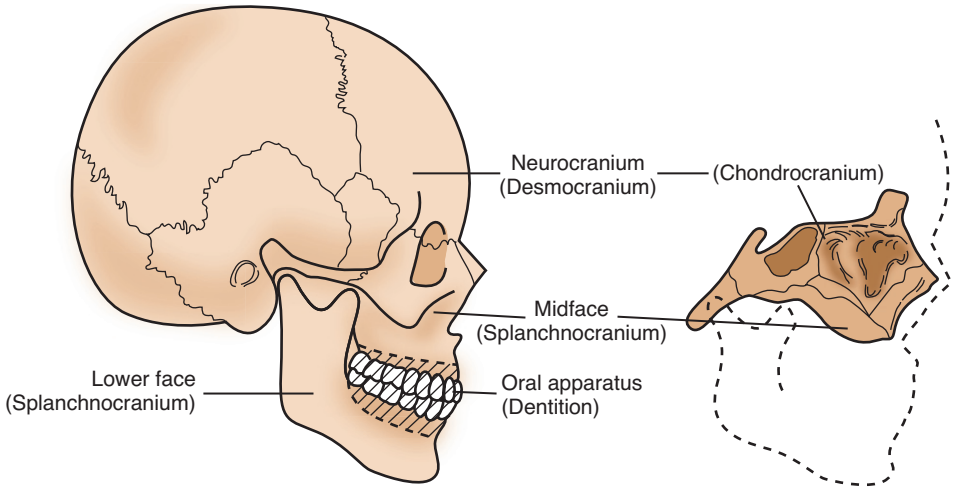


Fig. 2.5 Major Components of the Craniofacial Skeletal Complex.

TABLE 2.1 Comprising the Craniofacial Complex

Gene/Protein		General Role and Function	Significance for Craniofacial Development and Growth	References
Bmp-1 to *Bmp-9*	Bone morphogenetic protein 1-9	*Signaling molecule:* Skeletal differentiation, growth, repair	NCC and CF mesenchyme patterning; suture development; odontogenesis; nsCL/P	1-6
Dlx-1 to *Dlx-6*	Distal-less 1-6	*Homeobox:* Limb development; chondrogenesis; osteogenesis	Orofacial clefting	7-9
Efnb1	Ephrin B1	*Protein coding:* Cell division, adhesion	Craniofrontonasal syndrome; candidate for role in Class III malocclusion	1, 10-12
Fgf-1 to *Fgf-18*	Fibroblast growth factor 1-18	*Growth factors*: Differentiation and growth of multiple tissues and structures	CF ectoderm, NCC patterning; suture development; MCC growth; tooth induction; CL/P	1, 3, 4, 13-15
Fgfr-1 to *Fgfr-3*	Fibroblast growth factor receptor 1-3	*Transmembrane receptors*: Fgf receptor	Anterior cranial base growth; MCC growth; syndromic, nonsyndromic C-SYN; MX hypoplasia; CL/P	1, 3, 4, 15-17
GH	Growth hormone	*Peptide hormone-mitogen*: Cell growth and tissue regeneration	Growth of multiple CF tissues, structures; variations in MD growth, dentofacial treatment	13, 18
GHr	Growth hormone receptor	*Transmembrane receptor*: Receptor for GH	Polymorphisms associated with MD growth and MCC response to dentofacial treatment	19-21
Gli2 to *Gli3*	Zinc finger protein Gli2-3	*Transcription factor*: Regulates Ihh and Shh signaling	C-SYN; Greig cephalopolysyndactyly syndrome	1, 10, 22
Gsc	Goosecoid	*Transcription factor*: Dorsal–ventral patterning of NCC, head formation; rib fusion	Inner ear, cranial base, MX/MD anomalies	1, 8, 13, 23, 24
Hoxa1 to *Hoxa3*	Homeobox A1, A2, A3	*Homeobox*: Patterning of hindbrain rhombomeres and pharyngeal arches	Neural tube closure, 1st-2nd arch deformities	25, 26
Igf-1	Insulin-like growth factor 1	*Growth factor*: Mediator of GH; muscle, cartilage, and bone growth	MX/MD growth; suture development/growth; mediation of MCC to dentofacial treatment	3, 8, 13, 27-30
Ihh	Indian hedgehog	*Signaling molecule*: Endochondral and intramembranous ossification	Cranial base development; mediation of MCC growth during dentofacial treatment	31-33
L-Sox5	Long-form of Sox5	*Transcription factor*: Neurogenesis; chondrogenesis; type II collagen	Mediation of MCC growth during dentofacial treatment	34
Msx1 to *Msx2*	Muscle segment homeobox 1-2	*Homeobox*: Limb development; ectodermal organs	NCC proliferation, migration; odontogenesis; MD development; nsCL/P; Boston-type C-SYN	1, 3, 4, 8, 10, 35
Myo1H and *Myo1C*	Myosin 1H, Myosin 1C	*Protein coding*: Cell motility, phagocytosis, vesicle transport	Polymorphisms associated with MD prognathism	36, 37
Nog	Noggin	*Signaling molecule*: Patterning of the neural tube and somites	Head formation; neural tube fusion	4, 25, 26
Notch		*Transmembrane receptor*: Neuronal development; cardiac development; osteogenesis	MCC development	38
Osx	Osterix	*Transcription factor*: Osteoblast differentiation, mineralization; chondrogenesis	MCC differentiation, endochondral ossification; mediation of MCC growth during dentofacial treatment	39
Pitx1-2	Paired-like homeodomain 1-2	*Homeobox*: Left–right axis; left lateral mesoderm; skeletal development; myogenesis	MD development; role in Treacher-Collins syndrome; CL/P; odontogenesis	8, 13

Continued

TABLE 2.1 Comprising the Craniofacial Complex—cont'd

Gene/Protein		General Role and Function	Significance for Craniofacial Development and Growth	References
Prx-1Prx-2		*Homeobox*: Epithelial development in limbs and face	NCC patterning; malformations of 1st-2nd arch structures	8, 40, 41
PTHrP	Parathyroid-related protein	*Protein coding*: Endochondral bone formation	Development/growth of cranial base, MD, dental arches	42, 43
Runx2	Runt-related transcription factor	*Transcription factor*: Osteoblast differentiation; intramembranous and endochondral bone growth	Closure of fontanelles and sutures; ossification of cranial base, MX, and MCC; cleidocranial dysplasia	32, 43-46
Shh	Sonic hedgehog	*Transcription factor*: Development of limbs, midline brain, neural tube; osteoblastic differentiation; skeletal morphogenesis	Induction of frontonasal ectoderm; cranial base; fusion of facial processes; palatogenesis; odontogenesis; holoprosencephaly	1, 9, 33
Sho2		*Signaling molecule*: Development of digits; organization of brain, CF mesenchyme	Palatogenesis; TMJ development	6, 9, 38
Sox9		*Transcription factors*: Chondrogenesis; type II collagen; male sexual development	Cranial base; MCC growth; CL/P; Pierre-Robin sequence	38, 46-48
Spry 1-2	Sprouty	*Protein coding*: Mediates FGF signaling	MD/TMJ development	38, 48
Tcof1	Treacle	*Protein coding*: Early embryonic nucleolar-cytoplasmic transport	NCC proliferation, migration, survival; Treacher-Collins syndrome	38, 49
Tgf-β1 to *Tgf-β3*	Transforming growth factor-beta 1-3	*Growth factor*: Proliferation, differentiation, growth, function of multiple tissues	Palatogenesis; MD growth; suture development, maintenance, fusion; sCL/P	3, 24
Twist-1	Twist-related protein 1	*Transcription factor*: Skeletal development; syndactyly	MCC development; suture fusion; Saethre-Chotzen syndrome; facial asymmetry	9, 35, 38, 50, 51
Vegf	Vascular endothelial growth factor	*Growth factor*: Ingrowth of blood vessels	Chondrogenesis in cranial base, MCC	38, 45, 52
Wnt-1	Proto-oncogene protein Wnt 1	*Signaling molecule*: Cell fate, patterning during embryogenesis	MCC development/growth; MCC growth during dentofacial treatment	6, 32, 38, 53

CF, Craniofacial; *CPO,* cleft palate only; *CL/P,* cleft lip and palate; *C-SYN,* craniosynostosis; *MCC,* mandibular condylar cartilage; *MD,* mandible; *MX,* maxilla; *NCC,* neural crest cells; *nsCL/P,* nonsyndromal cleft lip and palate; *sCL/P,* syndromal cleft lip and palate; *TMJ,* temporomandibular joint.

References

1. Rice DPC. Craniofacial anomalies: from development to molecular pathogenesis. *Curr Mol Med*. 2005;5:699-722.
2. Zheng L, Yamashiro T, Fukunaga T, et al. Bone morphogenetic protein 3 expression pattern in rat condylar cartilage, femoral cartilage and mandibular fracture callus. *Eur J Oral Sci*. 2005;113:318-325.
3. Opperman LA, Gakunga PT, Carlson DS. Genetic factors influencing morphogenesis and growth of sutures and synchondroses in the craniofacial complex. *Semin Orthod*. 2005;11(4):199-208.
4. Chai Y, Maxson RE Jr. Recent advances in craniofacial morphogenesis. *Dev Dyn*. 2006;235:2353-2375.
5. Nie X, Luukko K, Kettunen P. BMP signaling in craniofacial development. *Int J Dev Biol*. 2006;50:511-521.
6. Greene RM, Pisano MM. Palate morphogenesis: current understanding and future directions. *Birth Defects Res (Part C)*. 2010;90:133-154.
7. Robledo RE, Rajan L, Li X, Lufkin T. The *Dlx5* and *Dlx6* homeobox genes are essential for craniofacial, axial, and appendicular skeletal development. *Genes Develop*. 2002;16:1089-1101.
8. Doshi RR, Patil AS. A role of genes in craniofacial growth. *IIOBA*. 2012;3(2):19-36.
9. Hinton RJ. Genes that regulate morphogenesis and growth of the temporomandibular joint: a review. *Devel Dyn*. 2014;243:864-874.
10. Melville H, Wang Y, Taub PJ, Jabs EW. Genetic basis of potential therapeutic strategies for craniosynostosis. *Am J Med Genet Part A*. 2010;152A:3007-3015.
11. Xue F, Wong RWK, Rabie ABM. Genes, genetics, and Class III malocclusion. *Orthod Craniofac Res*. 2010;13:69-74.
12. Xue F, Wong RWK, Rabie ABM. Identification of SNP markers on 1p36 and association analysis of *EPB41* with mandibular prognathism in a Chinese population. *Arch Oral Biol*. 2010;55:867-872.
13. Hinton RJ, Carlson DS. Regulation of growth in the mandibular condylar cartilage. *Semin Orthod*. 2005;11(4):209-218.
14. Hatch NE. FGF signaling in craniofacial biological control and pathological craniofacial development. *Crit Rev Eukaryot Gene Expr*. 2010;20(4):295-311.
15. Martinez-Abadias N, Heuze Y, Wang Y, et al. FGF/FGFR signaling coordinates skull development by modulating magnitude of morphological integration: evidence from Apert syndrome mouse models. *PLoS One*. 2011;6(10).

TABLE 2.1 Comprising the Craniofacial Complex—cont'd

16. Rice DPC, Rice R, Thesleff I. *Fgfr* mRNA isoforms in craniofacial bone development. *Bone*. 2003;33(1):14-27.
17. Heuze Y, Martinez-Abadias N, Stella JM, et al. Quantification of facial skeletal shape variation in fibroblast growth factor receptor-related craniosynostosis syndromes. *Birth Def Res (A)*. 2014;100:250-259.
18. Buschang PH, Hinton RJ. A gradient of potential for modifying craniofacial growth. *Semin Orthod*. 2005;11(4):219-226.
19. Zhou J, Lu Y, Gai XH, et al. The growth hormone receptor gene is associated with mandibular height in a Chinese population. *J Dent Res*. 2005;84:1052-1056.
20. Kang EH, Yamaguchi T, Tajima A, et al. Association of the growth of the growth hormone receptor gene polymorphisms with mandibular height in a Korean population. *Arch Oral Biol*. 2009;45:556-562.
21. Sasaki Y, Satoh K, Hayasaki H, et al. The P561T polymorphism of the growth hormone receptor gene has an inhibitory effect on mandibular growth in young children. *Europ J Orthod*. 2009;31:536-541.
22. Veistinen L, Takatolo M, Tanimoto Y, et al. Loss-of-function of *Gli3* in mice causes abnormal frontal bone morphology and premature synostosis of the interfrontal suture. *Front Physiol*. 2012;3:1-6.
23. Sharpe PT. Homeobox genes and orofacial development. *Conn Tiss Res*. 1995;32:17-25.
24. Spears R, Svoboda K. Growth factors and signaling proteins in craniofacial development. *Semin Orthod*. 2005;11(4):184-199.
25. Carlson B. *Human Embryology and Developmental Biology*. Philadelphia: Elsevier; 2014.
26. Trainor PA, Krumlauf R. Patterning the neural crest: hindbrain segmentation and *hox* gene plasticity. *Nat Rev Neuro*. 2000;1:116-124.
27. Hajjar D, Santos MF, Kimura ET. Mandibular repositioning modulates IGFBP-3, -4, -5, and -6 expression in the mandibular condyle of young rats. *Biorheology*. 2006;43(3-4):311-321.
28. Marques MR, Hajjar D, Franchini KG, et al. Mandibular appliance modulates condylar growth through integrins. *J Dent Res*. 2008;87(2):153-158.
29. Patil AS, Sable RB, Kothari RM. Role of insulin-like growth factors (IGFs), their receptors and genetic regulation in the chondrogenesis and growth of the mandibular condylar cartilage. *J Cell Physiol*. 2011;227:1796-1804.
30. Frazier-Bowers S, Rincon-Rodriguez R, et al. Evidence of linkage in a Hispanic cohort with a class III dentofacial phenotype. *J Dent Res*. 2009;88:56-60.
31. Tang GH, Rabie ABM. Runx2 regulates endochondral ossification in condyle during mandibular advancement. *J Dent Res*. 2005;84(2):166-171.
32. Carreira AC, Lojudice FH, Halcsik E, et al. Bone morphogenetic proteins: facts, challenges, and future perspectives. *J Dent Res*. 2014;93(4):335-345.
33. Balczerski B, Zakaria S, Tucker AS, et al. Distinct spatiotemporal roles of hedgehog signaling during chick and mouse cranial base and axial skeletal development. *Dev Biol*. 2012;371:203-214.
34. Chu FT, Tang GH, Hu Z, et al. Mandibular functional positioning only in vertical dimension contributes to condylar adaptation evidenced by concomitant expressions of L-Sox5 and type II collagen. *Arch Oral Biol*. 2008;53:567-574.
35. Bonaventure J, El-Ghouzzi V. Molecular and cellular basis of syndromic craniosynostosis. *Exp Rev Mol Med*. 2003;5(29):1-17.
36. Tassopoulou-Fishell M, Deeley K, Harvey EM, et al. Genetic variation in *Myosin 1H* contributes to mandibular prognathism. *Am J Orthod Dentofac Orthoped*. 2012;141(1):51-59.
37. Desh H, Gray SL, Horton MJ, et al. Molecular motor *MYO1C*, acetyltransferase *KAT6B* and osteogenetic transcription factor *RUNX2* expression in human masseter muscle contributes to development of malocclusion. *Arch Oral Biol*. 2014;59:601-607.
38. Hinton RJ, Serrano M, So S. Differential gene expression in the perichondrium and cartilage of the neonatal mouse temporomandibular joint. *Orthod Craniofac Res*. 2009;12:168-177.
39. Jing J, Hinton RJ, Jing Y, et al. Osterix couples chondrogenesis and osteogenesis in post-natal condylar growth. *J Dent Res*. 2014;93(10):1014-1021.
40. ten Berge D, Brouwer A, Korving J, et al. Prx1 and Prx2 are upstream regulators of sonic hedgehog and control cell proliferation during mandibular arch morphogenesis. *Development*. 2001;128(15):2929-2938.
41. Martin JF, Bradley A, Olsen EN. The *paired*-like homeobox gene *Mhox* is required for early events of skeletogenesis in multiple lineages. *Genes Develop*. 1995;9:1237-1249.
42. Kyrkanides S, Kambylafkas P, Miller JH, et al. The cranial base in craniofacial development: a gene therapy study. *J Dent Res*. 2007;86(10):956-961.
43. Hinton RJ. Genes that regulate morphogenesis and growth of the temporomandibular joint: a review. *Devel Dyn*. 2014;243:864-874.
44. Rabie ABM, Tang GH, Hägg U. Cbfa1 couples chondrocytes maturation and endochondral ossification in rat mandibular condylar cartilage. *Arch Oral Biol*. 2004;49(2):109-118.
45. Lei WY, Wong RWK, Rabie ABM. Factors regulating endochondral ossification in the spheno-occipital synchondrosis. *Angle Orthod*. 2008;78(2):215-220.
46. Nie X, Luukko K, Kvinnsland IH, Kettunen P. Developmentally regulated expression of Shh and Ihh in the developing mouse cranial base: comparison the Sox9 expression. *Anat Rec A Discov Mol Cell Evol Biol*. 2005;286(2):891-898.
47. Cendekiawan T, Wong RWK, Rabie ABM. Temporal expression of SOX9 and type II collagen in spheno-occipital synchondrosis of mice after mechanical tension stimuli. *Angle Orthod*. 2008;78(1):83-88.
48. Rabie ABM, She TT, Hägg U. Functional appliance therapy accelerates and enhances condylar growth. *Am J Orthod Dentofacial Orthop*. 2003;123(1):40-48.
49. Su P-H, Liu Y-F, Chen J-Y, Lai Y-J, Facial asymmetry and clinical manifestations in patients with novel insertion of the *TCOF1* gene. *Clin Genet*. 2012;82:460-465.
50. Coussens AK, Wilkinson CR, Hughes IP, et al. Unravelling the molecular control of calvarial suture fusion in children with craniosynostosis. *BMC Genomics*. 2007;8:458.
51. Melville H, Wang Y, Taub PJ, Jabs EW. Genetic basis of potential therapeutic strategies for craniosynostosis. *Am J Med Genet Part A*. 2010;152A:3007-3015.
52. Rabie ABM, Hägg U. Factors regulating mandibular condylar growth. *Am J Orthod Dentofacial Orthop*. 2002;122:401-409.
53. Enomoto A, Watahiki J, Nampo T, et al. Mastication markedly affects mandibular condylar growth, gene expression, and morphology. *Am J Orthod Dentfac Orthop*. 2014;146(3):365-363.

early pattern formation and differentiation of primary embryonic tissues and structures, including neural crest cells and head mesoderm. Mutation of those genes typically has a profound role in craniofacial dysmorphogenesis. The second group comprises genes such as growth factors and signaling molecules that are also responsible for mediating development, growth, and maintenance of the tissues and structures associated with the craniofacial complex both during embryogenesis and throughout postnatal development. Although mutations in this latter group of genes also are associated with craniofacial malformation syndromes, minor variants appear to be more common and may play a role in the development of more minor variations in growth. In addition, genes from both groups may be expressed reiteratively during development and growth, producing a highly complex matrix of interactions required for normal craniofacial morphogenesis. Adding to the complexity are the issues of wound healing, tissue regeneration, and repair—all processes important during orthodontic treatment—that can reinitiate the expression of genes required for early morphogenesis and postnatal growth.

Molecular research historically has focused on the role of specific genes critical for craniofacial morphogenesis during embryogenesis. The initial focus in that research typically has been on three areas: (1) naturally occurring genetic mutations associated with craniofacial dysmorphogenesis in humans; (2) development of genetically engineered animal models, typically the mouse, to produce loss of function of selected genes; and (3) mapping of gene expression in experimental animals through in situ hybridization and other biomarker approaches. More recently, significant progress has been made in the identification of gene variants (polymorphisms) that may be important for the origin of minor variations in craniofacial growth of potential relevance to orthodontic diagnosis and treatment. These genes and their variants could be significant for diagnosis and response to treatment of dentofacial deformities and minor malocclusions.[18] Significant advances in the genetic and epigenetic basis of craniofacial development, including the role of key genes in normal growth and orthodontic treatment, are expected to continue at a rapid pace.[19,20]

CRANIAL VAULT

Development of the Cranial Vault

The most prominent feature of the embryonic cephalic region at 6 to 7 weeks' gestation is the frontonasal prominence. The frontonasal prominence is a nonpaired structure that forms a dense desmocranial membrane, which covers the entire forebrain and extends laterally and inferiorly on each side of the developing head to meet the developing maxillary processes. The inner portion of the membrane contains neural crest cells and gives rise to the dura mater covering the brain. The outer portion of the desmocranial membrane, the *ectomeninx,* is composed of surface ectoderm, deep to which is the paraxial mesoderm. Patterning of the frontonasal prominence to form the cranial vault and elements of the nasal region is induced by expression of sonic hedgehog (Shh) and FGF-8.

By 8 weeks' gestation, initial blastemas of bone become apparent within the ectomeninx, first for the frontal bone and the squamous temporal bone and subsequently for the parietal bones and squamous portion of the occipital bone (Fig. 2.6). Over the ensuing 4 weeks, these condensations of bone steadily increase in size by radial expansion of newly differentiated skeletal tissue within the ectomeninx. As the development of new bone exceeds the rate of growth of the brain, the peripheral bone fronts become located closer and closer to each other, until they approximate each other as single-thickness plates of flat bones by about 12 weeks' gestation. At this point, the intervening fibrous tissue becomes highly cellular, and fibrous articulations, or *sutures,* are formed between the individual bone elements (Fig. 2.7).

Growth of the cranial vault bones represents a specialized form of intramembranous ossification that begins prenatally as blastemas of bone tissue that arise de novo within the middle layer of the desmocranial membrane covering of the brain. Once the skeletal elements as plates of bone become located close to each other, their fibrous connections become reorganized with the periosteum and the dura mater derived from the outer and inner layers of the desmocranial membrane, respectively, extending into the sutural articulations. The sutures then continue to support growth of the cranial vault through another specialized form of intramembranous osteogenesis similar to periosteal bone formation.[21-23]

Mechanisms of Suture Growth

Sutural bone growth can best be considered as a specialized form of intramembranous periosteal bone growth. Once formed, the bones of the cranial vault are enveloped, like all bones, in a skeletogenic membrane. On the external surface, this membrane is the periosteum. On the intracranial surface, the membrane is the dura mater, which is also derived from the embryonic ectomeninx and is skeletogenic. Viewed in cross section, the outer fibrous layer of periosteum (uniting layer) spans over the cranial suture and provides structural support to the suture and its two or more skeletal elements. The inner osteogenic

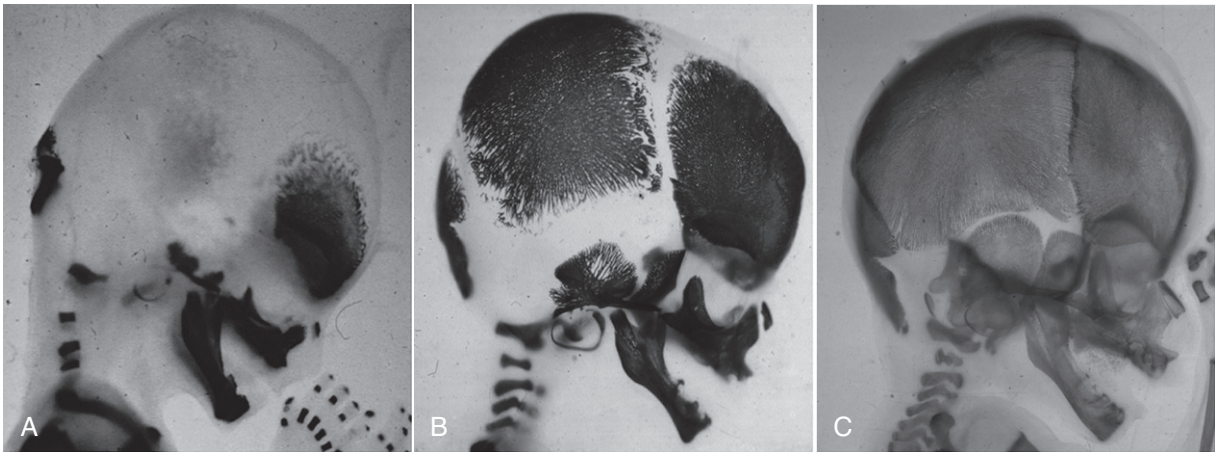


Fig. 2.6 Cleared and stained human fetuses indicating craniofacial skeletal structures at approximately 8 weeks' gestation **(A)**, 15 weeks' gestation **(B)**, and 18 weeks' gestation **(C)**.

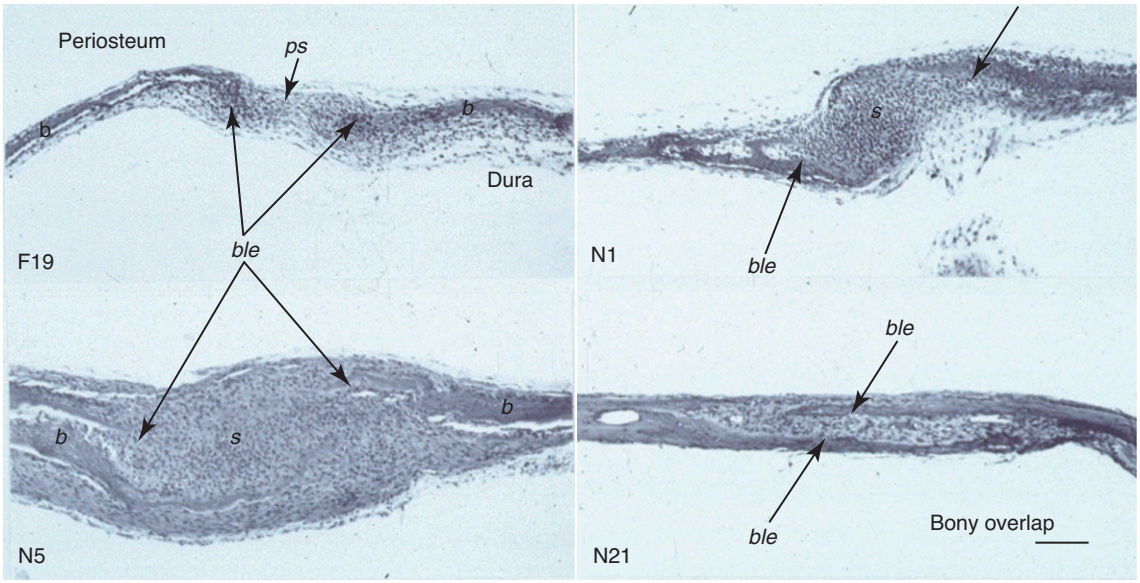


Fig. 2.7 Photomicrographs of hematoxylin and eosin–stained histologic sections through the coronal suture of normal rats at embryonic day 19 and postnatal days 1, 5, and 21. Bone *(b),* bone leading edge *(ble),* presumptive suture mesenchyme *(ps),* and suture *(s).* (From Opperman LA, Gakunga PT, Carlson DS. Genetic factors influencing morphogenesis and growth of sutures and synchondroses in the craniofacial complex. *Semin Orthod.* 2005;11(4):199-208.)

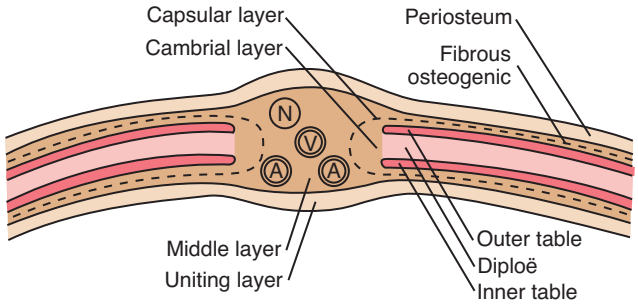


Fig. 2.8 Schematic representation indicating the relationship between the periosteum and dura mater as a mechanism for a specialized of intramembranous growth within the sutures of cranial vault bones. (Adapted from Pritchard JJ, Scott JH, Girgis FG. The structure and development of cranial and facial sutures. *J Anat.* 1956;90:73-86.)

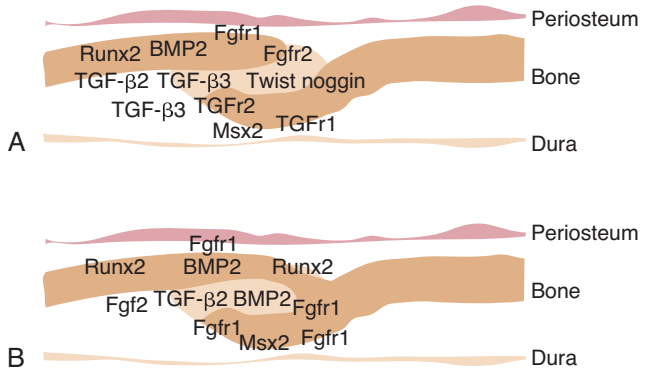


Fig. 2.9 Distribution of growth factors and transcription factors active during suture growth **(A)** and suture synostosis **(B).** (Adapted from Opperman LA, Gakunga PT, Carlson DS. Genetic factors influencing morphogenesis and growth of sutures and synchondroses in the craniofacial complex. *Semin Orthod.* 2005;11(4):199-208.)

layers of the periosteum and the dura reflect into the space between the two cranial vault bones and provide a source of new osteogenic cells (Fig. 2.8). As the bones of the cranial vault become separated because of expansion of the brain and intracranial contents, the osteogenic cells form skeletal tissue and thus provide a mechanism for maintaining relatively close contact through the intervening suture.

The molecular basis of the development and growth of the sutures of the cranial vault has received considerable attention, principally because of the number of naturally occurring and engineered genetic mutations characterized by craniosynostosis (see Wilkie and Morriss-Kay,[15] Rice,[24] and Chai and Maxson[25] for comprehensive reviews). Studies have shown a complex pattern of gene expression within the sutural blastema associated with the periosteal reflection and intracranial dura mater. Secretion of soluble factors by the dura mater in response to growth signals from the expanding underlying brain is essential for normal cranial suture morphogenesis and maintenance of cranial sutures as patent bone-growth sites through complex tissue interactions and feedback between dura mater, bone fronts, and sutures. Both sutures and the dura mater also contain growth factors, such as several members of the family of transforming growth factor-beta 1 (*TGF-β1*, *TGF-β2*, *TGF-β3*), bone morphogenetic protein 2 (*BMP2*), *BMP7*, fibroblast growth factor 4 (*FGF-4*), insulin-like growth factor 1 (*IGF-1*), and sonic hedgehog (*Shh*) (Fig. 2.9).[26,27] Overexpression of transcription factors *Runx2* and *Msx2* and haploinsufficiency of Twist[28] and Noggin[29] are also associated with suture obliteration, and loss of function of *Gli3* results in premature synostosis.[30] Genetic analysis of naturally occurring craniosynostosis in humans has shown that mutations of genes for fibroblast growth factor receptors 1, 2, and 3 (*FGFR-1, FGFR-2,* and *FGFR-3*) and in *MSX2*[31] and *TWIST*[32,33] genes are also associated with premature suture fusion.

Development and growth of the cranial vault as a whole, and development and growth of bone at the sutural articulations, are primarily dependent on the expansion of the brain and other intracranial

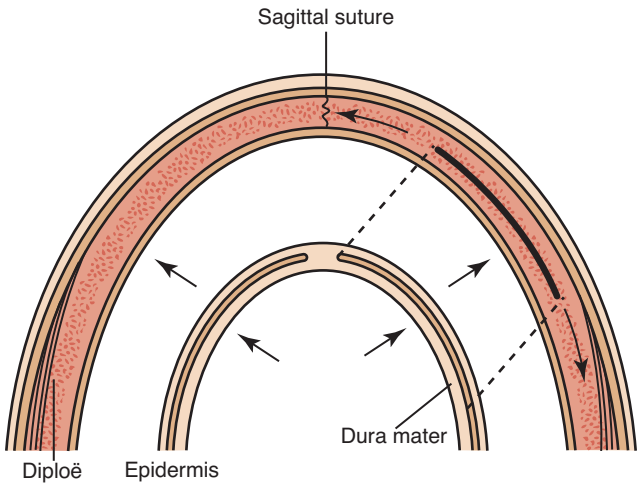


Fig. 2.10 Schematic diagram indicating the relationship between expansile growth of the brain as a stimulus for compensatory growth of sutures of the cranial vault. (Adapted from Moss ML. The functional matrix. In: Kraus B, Reidel R, eds. *Vistas Orthod.* Philadelphia: Lea & Febiger; 1962;85-98.)

contents.[34] Furthermore, it has been clearly demonstrated that sutures are secondary, compensatory, and adaptive sites of bone growth that normally respond to biomechanical forces. As the brain expands during prenatal development and during the first decade of life postnatally, forces are created within the neurocranium that cause the bones of the cranial vault to expand outward, which tends to separate them from each other at the sutural boundaries (Fig. 2.10). Under normal conditions, the cellular and molecular substrate associated with the dura mater, the periosteum, and the suture respond to this biomechanical displacement in the same manner in which periosteum throughout the skeletal system responds—by initiating and maintaining osteogenesis within the sutures to maintain the proximity of the adjoining skeletal structures. When the biological substrate of the suture is abnormal, however, as in the case of many genetic syndromes such as Crouzon syndrome, Apert syndrome, and Jackson-Weiss syndrome, for example, each of which is associated with mutations of *FGFR-2,* premature craniosynostosis may result.[35,36] The opposite condition, reduced suture growth, and prolonged patency, as seen in cleidocranial dysostosis, may occur with abnormalities associated with growth factors, including in particular Runx2, which are necessary for normal suture fusion.

Postnatal Growth of the Cranial Vault

Because of the very precocious nature of prenatal and early postnatal human brain development, the cranial vault is disproportionately large relative to the rest of the face and body. At birth, the cranial vault is initially characterized by the presence of all of the cranial vault bones. At that time, all the major sutural fibrous articulations between the bones of the cranial vault are present, including the metopic suture between the right and left frontal bone. In addition, there typically are four larger remnants, known as *fontanels,* of the desmocranial membrane in areas where the pace of bone growth has not been sufficient to approximate the bones of the cranial vault to form a suture (Fig. 2.11).

During the first 24 months after birth, growth of the cranial vault bones proceeds rapidly enough to close the fontanels as each complex of cranial vault bones becomes organized through interlocking sutures. The metopic suture normally fuses to form a single frontal bone within the first year of life, although the suture may appear to persist for up to 8 years of age or even throughout life in a small percentage of individuals. The cranial vault will continue to enlarge primarily as a result of compensatory growth of the sutural bone fronts stimulated by expansion of the brain. By 4 years of age, the brain and the associated cranial vault will have achieved approximately 80% of adult size; by age 10, the brain and cranial vault have attained 95% of their adult size. Throughout this time of very rapid expansion, the remaining sutures of the cranial vault normally remain patent and actively growing to keep pace with the brain as it expands in size.

Osteogenesis at cranial sutural bone fronts may continue for the first two decades of life. However, by the end of the second decade of life, bone growth at cranial sutures has slowed and the potential for growth of cranial sutures has greatly diminished. Also at that time, the sutures will begin the normal process of bony closure, or *synostosis,* when the potential for sutural growth ceases altogether.

The cranial sutures normally lose the capacity for growth by the end of the second decade of life, and virtually all become synostosed during the lifespan. Normal suture closure is initiated along the endocranial surface. Initially, this is characterized by bridging of bone across the suture and eventually through modeling of bone, leading to complete obliteration of the suture. Cessation of growth at cranial sutures typically begins around age 25 for the sagittal suture and may be extended for 2 to 3 additional years for the coronal suture.

Despite the fact that the major cranial sutures stop growing by the third decade of life, some enlargement of the cranial vault overall typically occurs throughout the lifespan as a result of periosteal deposition

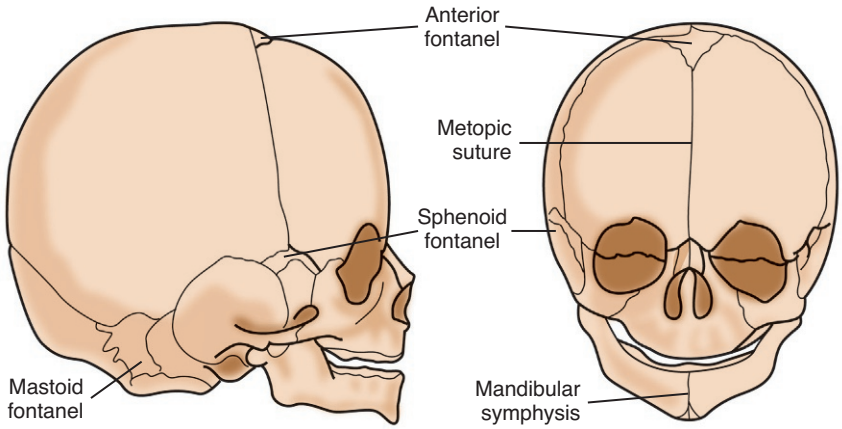


Fig. 2.11 Lateral and Frontal Views of the Neonate Skull Indicating the Location of Sutures and Fontanels. (Adapted from Sicher H, DuBrul EL. *Oral Anatomy.* 5th ed. St. Louis: Mosby; 1970.)

along the ectocranial surface. Certain specific areas of the cranial vault, such as the glabellar and nuchal regions, may exhibit slightly greater periosteal growth as a secondary sex characteristic in males.

CRANIAL BASE

Development of the Cranial Base

The ectomeningeal membrane that surrounds the developing brain in the cranial base region gives rise to a number of paired cartilaginous elements that form the embryonic chondrocranium. The first of the cartilage anlagen to form arises from neural crest cells at about 6 weeks' gestation as the parachordal cartilages, which surround the proximal end of the notochord and give rise to the anterior cranial base. The posterior component of the cranial base is derived primarily from mesoderm to form the basioccipital bone.[37] Development of the chondrocranium then progresses rostrally to the otic capsule, which will form the petrous portion of the temporal bone; the postsphenoid, presphenoid, alisphenoid, and orbitosphenoid cartilages of the sphenoid bone; and the nasal capsule and mesethmoid, which will form the ethmoid bone, inferior turbinate, and nasal septum. By 8 weeks' gestation, the separate cartilage elements have merged to form a single plate of primary hyaline cartilage, the *basal plate,* extending from the foramen magnum rostrally to the tip of the nasal cavity (Fig. 2.12).

More than 110 separate centers of ossification form in the basal plate, beginning with the parachordal cartilages and continuing rostrally through the sphenoid complex around 9 to 16 weeks, to the ethmoid region as late as 36 weeks. As these centers of ossification arise within the chondrocranium, segments of intervening cartilage form synchondroses (Fig. 2.13). The principal cranial base synchondroses that are most relevant for understanding craniofacial growth are the spheno-occipital synchondrosis, between the body of the sphenoid and the basioccipital bone, and the sphenoethmoidal synchondrosis, between the sphenoid and ethmoid bones. The greater wing of the sphenoid bone and the squamous portion of the occipital bone develop and grow by intramembranous ossification.

Mechanism of Synchondrosal Growth

Cranial base synchondroses are temporary cartilaginous joints located between bones of endochondral origin and growth. Synchondroses can best be considered as homologous to the epiphyseal growth plates of long bones. Functionally, both provide a mechanism for rapid endochondral growth of bone in a manner that is capable of overcoming biomechanical loads, thus exhibiting tissue-separating capabilities. Developmentally, cranial base synchondroses and epiphyseal plates of long bones synostose and become obliterated when the skeletal element achieves its mature size and shape. This typically occurs at the end of puberty for epiphyseal growth plates but varies from the end of the juvenile period through the end of puberty for the major cranial base synchondroses.

Cranial base synchondroses and epiphyseal growth plates are both derived from the primary hyaline cartilage that arises as part of

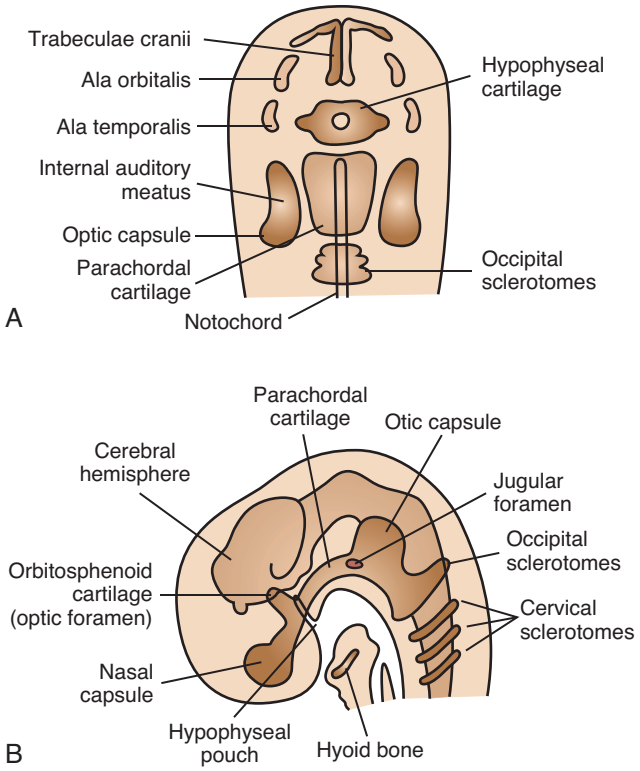


Fig. 2.12 Schematic Representation of the Cartilaginous Basal Plate Comprising the Embryonic Chondrocranium. A, Dorsoventral view. B, Lateral view.

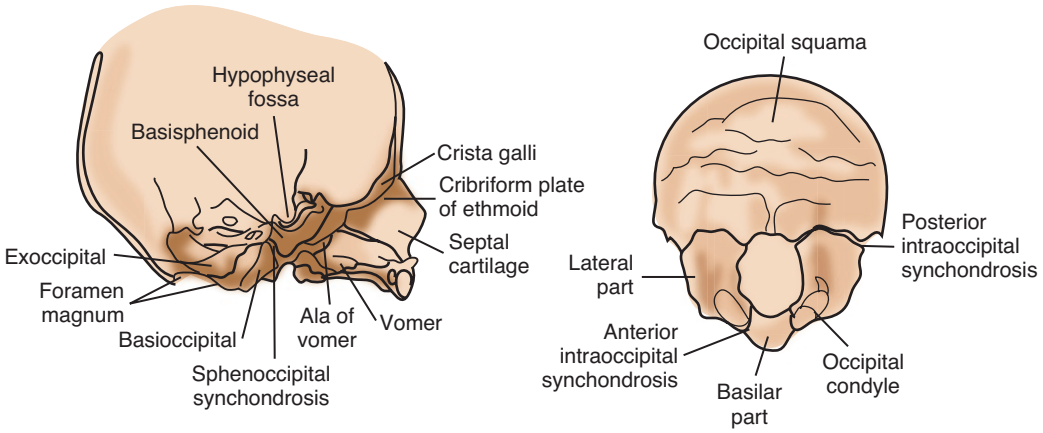


Fig. 2.13 Drawing of sagittal and basal views of the neonatal skull indicating spheno-occipital synchondrosis and intraoccipital synchondroses. The sphenoethmoidal synchondrosis will arise between the sphenoid and ethmoid bones. (Adapted from Bosma JF. Introduction to the symposium. In: Bosma JF, ed. *Development of the Basicranium*. Bethesda, MD: US Department of Health, Education, and Welfare; 1976:3-28.)

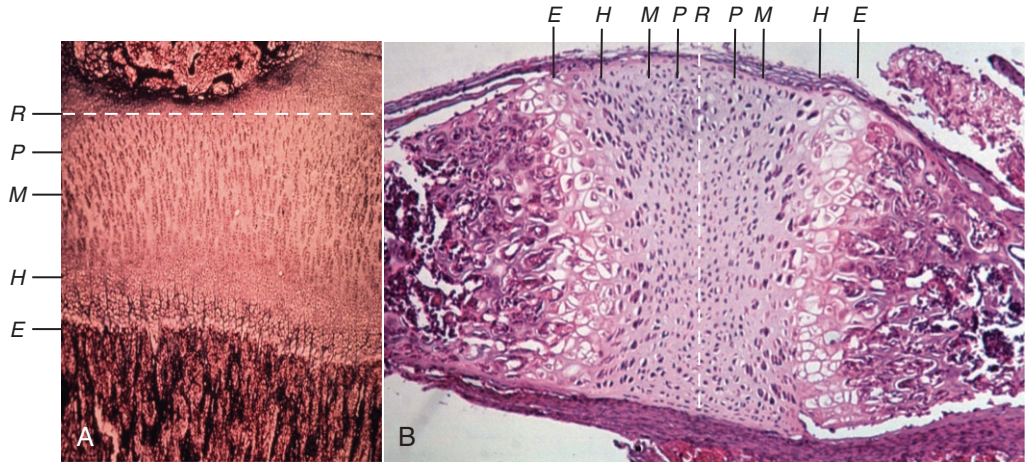


Fig. 2.14 Histologic comparison between the cartilages within a growing epiphyseal plate (A) and cranial base synchondrosis (B) (hematoxylin and eosin–stained). *R,* Resting zone *(dashed line); P,* proliferating zone; *M,* maturational zone; *H,* hypertrophic zone; *E,* zone of endochondral ossification.

the embryonic cartilaginous anlagen. Like endochondral bones and growth plates throughout the body, growth of synchondroses is controlled principally by expression of Indian hedgehog gene (Ihh) and sonic hedgehog (Shh).[38,39] The significance of *FGFR-3* for growth of the anterior cranial base is also indicated by mutations associated with achondroplasia.

Histomorphologically, both cranial base synchondroses and epiphyseal growth plates, are characterized by primary chondrocytes that are distributed into zones that are highly typical for growth plate cartilage (Fig. 2.14). However, a major difference between epiphyseal growth plates in long bones and cranial base synchondroses is that synchondroses are "bidirectional." Thus each cranial base synchondrosis effectively has two back-to-back growth plates with a shared region of newly forming cartilage in the center and bone at each end. Growth plates are unidirectional.

The primary hyaline cartilage of the cranial base is the same as that found throughout the embryonic cartilaginous anlage that characterizes all the other cartilaginous bones throughout the body. It is well known that growth of tissues derived from the primary embryonic cartilaginous anlagen tends to be relatively resistant to all but very extreme external influences. Growth of cartilage-derived skeletal elements throughout the body tends to be relatively resistant to environmental and other factors and instead is regulated to a large extent by intrinsic, genetically regulated growth factors and cell-signaling molecules.[40] The same is true for the cranial base synchondroses. However, it is important to note that the growth of both epiphyses and synchondroses can be significantly affected by such epigenetic factors as disease, malnutrition, and undernutrition, as well as other conditions that affect production and expression of endocrine factors responsible for bone growth.

The cartilage cells within both epiphyseal growth plates and cranial base synchondroses are characterized by extensive amounts of extracellular matrix that are secreted by and separate the cartilage cells. This matrix makes the cartilage very dense and strong but also flexible relative to bone and thus better able to absorb mechanical forces without directly affecting the cells and potentially altering growth. Because there are no vessels within cartilage extracellular matrix, all nutrients, growth factors, and cell-signaling molecules must diffuse through the matrix to reach the chondrocytes. The matrix thus "buffers" the chondrocytes from extrinsic mechanical forces and many soluble molecules that might provide information about the external environment.[41] As a result, cartilage growth in general, and endochondral ossification from primary hyaline cartilage in particular, tend to be more rigidly programmed genetically than intramembranous bone growth associated with periosteum, such as occurs in the desmocranium and viscerocranium.

This difference in the mechanisms of growth between bone formed by means of intramembranous ossification and bone derived from endochondral ossification can be summarized through the concepts of skeletal *growth centers* versus skeletal *growth sites*.[42] Development and growth of the skeletal tissues derived from primary cartilage are significantly more intrinsically regulated and less dependent for their expression on epigenetic factors. In particular, *growth centers* have what has been described as "tissue-separating capabilities," emphasizing the capacity to grow and expand despite the presence of mechanical forces that would seem capable of inhibiting or restricting skeletal growth. Thus epiphyseal and synchondrosal cartilage are referred to as *growth centers*. In contrast, a *growth site* is an area of skeletal growth that occurs secondarily and grows in compensatory fashion to growth and function in a separate but proximate location. Growth sites have no tissue-separating capabilities but rather respond more readily to factors extrinsic to their specific area. Periosteal bone growth associated with muscle function is one obvious example of a growth site. Sutural bone growth is another example of a class of growth sites because of its association with bones of intramembranous origin and its clear connection to periosteal bone growth.

Postnatal Growth of the Cranial Base

Late prenatal and overall postnatal growth of the cranial base is related directly to growth of the synchondroses. There are four principal growth-related cranial base synchondroses that separate the bones of the cranial base at birth. The intersphenoid synchondrosis, between the presphenoid and basisphenoid, fuses around the time of birth in humans and thus does not contribute to postnatal growth. The anterior and posterior intraoccipital synchondroses stop growing around 3 to 5 years of age (Fig. 2.15). The sphenoethmoidal synchondrosis, which lies between the sphenoid and the ethmoid bones, is most active with respect to growth of the cranial base through approximately 7 to 8 years of age in humans. At that time, the sphenoethmoidal synchondrosis loses its cartilage phenotype and becomes a suture. Once that transition occurs, growth of the anterior cranial base is essentially complete. As a result, the anterior wall of the sella turcica, which is

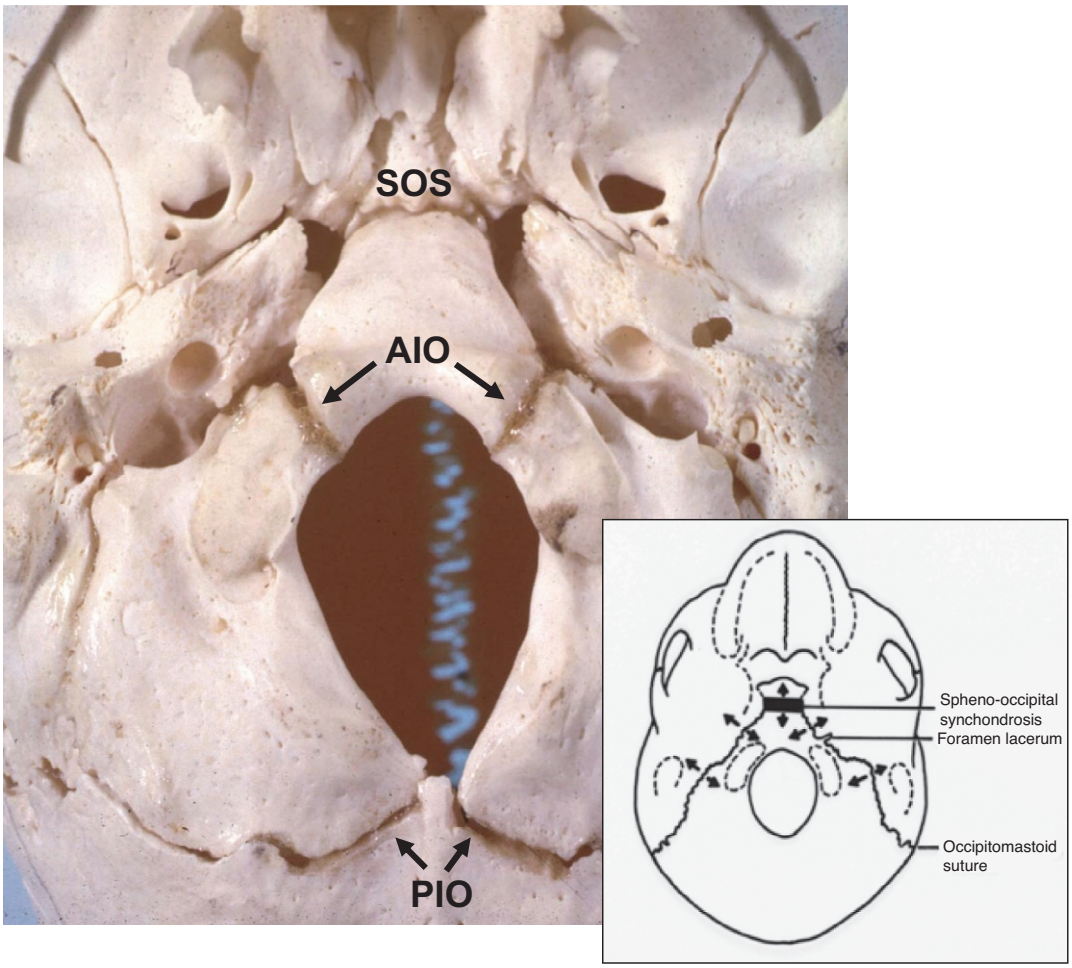


Fig. 2.15 Basal view of a young child showing the anterior (AIO) and posterior (PIO) intraoccipital synchondroses, as well as the spheno-occipital synchondrosis *(SOS)*.

located on the body of the sphenoid; the greater wing of the sphenoid; the cribriform plate; and the foramen cecum are commonly used after age 7 as stable reference structures for analyses of serial lateral radiographic cephalograms.

The spheno-occipital synchondrosis, between the body of the sphenoid and occipital bones, is most prominent throughout the period of active craniofacial growth and fuses shortly after puberty (see Fig. 2.15). Once synostosis occurs, growth of the cranial base, especially in the anteroposterior direction, is essentially over. Subsequent changes in the form of the cranial base, such as in the angulation of the basioccipital bone relative to the anterior cranial base, for example, must come about as a result of bone modeling.

During the early postnatal years, the cranial base undergoes a dramatic shift in its growth pattern (Fig. 2.16). Anterior (nasion-sella) and posterior (sella-basion) cranial base lengths, as well as cranial base angulation (nasion-sella-basion), exhibit greater growth changes during the first 2 to 3 postnatal years than any time thereafter. For example, cranial base angulation decreases more than twice as much during the first 2 postnatal years than between 2 and 17 years of age, primarily as a result of differential growth of the spheno-occipital synchondrosis. Growth continues after 2 years of age, but the changes are smaller and steadier.

Between birth and 17 years of age, the anterior cranial base grows approximately 36% (males) to 53% (females) more than the posterior cranial base, with most of the differences occurring during the first few years.[43] It is important to understand that the anterior cranial

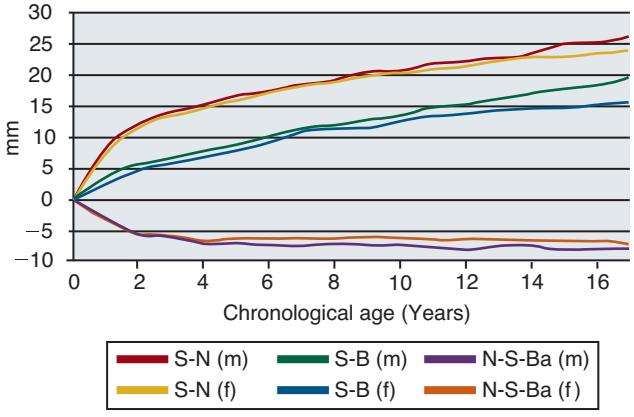


Fig. 2.16 Male *(m)* and Female *(f)* Cranial Base Growth Changes From Birth Through 17 Years of Age. (Data from Ohtsuki F, Mukherjee D, Lewis AB, et al. A factor analysis of cranial base and vault dimensions in children, *Am J Phys Anthropol.* 1982;58(3):271-279.)

base grows more and is also more mature (i.e., closer to its adult size) than the posterior cranial base throughout the postnatal growth. Longitudinal analyses have shown that the anterior cranial base has already attained 86%–88% of its adult size by 4.5 years of age, whereas the posterior cranial base has attained only about 80%–84% of its adult size (Fig. 2.17). The relative maturity differences between the anterior

and posterior cranial base lengths are maintained throughout postnatal growth.

Anterior and posterior cranial base lengths increase because of bony deposition, as well as growth at the spheno-occipital and sphenoethmoidal synchondroses. Postnatally, the posterior cranial base becomes longer primarily due to growth at the spheno-occipital synchondrosis. Histologic studies have shown that the spheno-occipital synchondrosis fuses at approximately 16 to 17 years in females and 18 to 19 years in males.[44] Radiographically, the spheno-occipital synchondrosis shows active growth until approximately 10 to 13 years of age, at which time closure starts superiorly and continues inferiorly around 11 to 14 years in females and 13 to 16 years in males.[45,46]

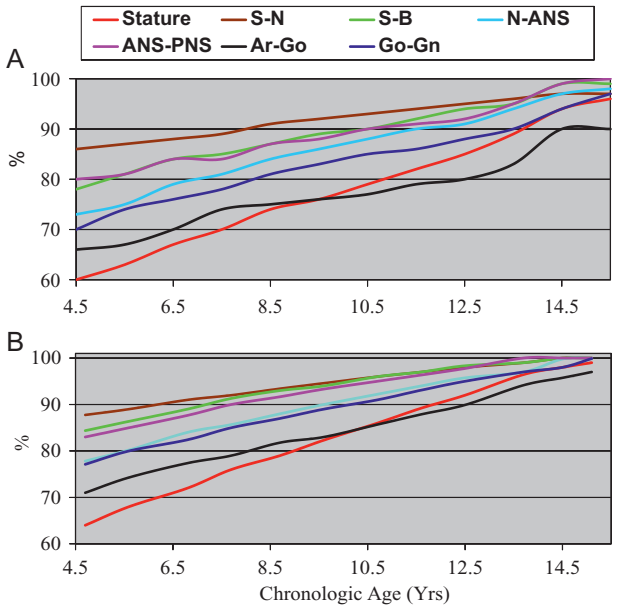


Fig. 2.17 Craniofacial Growth Maturity Gradient of (A) Males and (B) Females. (Adapted from Buschang PH, Baume RM, Nass GG. A craniofacial growth maturity gradient for males and females between 4 and 16 years of age. *Am J Phys Anthrop.* 1983;61:373-382.)

Because both landmarks are commonly used to describe the growth of the anterior cranial base, it is important to distinguish the changes that occur at nasion from those that occur at foramen cecum. After fusion of the sphenoethmoidal synchondrosis, which occurs at approximately 7 to 8 years of age, increases in the distance between sella and foramen cecum are due primarily to the posterior and inferior drift of the sella turcica. The distance sella-nasion, on the other hand, continues to increase primarily as a result of bony apposition on the outer surface of the frontal bone associated with the development of the frontal sinus (the earliest pneumatization of the frontal sinus occurs around 2 years of age). The anterior cranial fossa continues to expand slightly, and the frontal sinus becomes more prominent. As a result, the frontal bone and root of the nose become more anteriorly located. Ford[47] estimated that the frontal bone drifts anteriorly approximately 7 mm between the time that the sphenoethmoidal synchondrosis fuses and adulthood.

MIDFACE/NASOMAXILLARY COMPLEX

The midface, or nasomaxillary complex, is composed of the paired maxillae, nasal bones, zygomatic bones, lacrimal bones, palatine bones, and, within the nasal cavity, the turbinates and vomer. Prenatally, human fetuses also have left and right premaxillary bones; however, these normally fuse with the maxillae within 3 to 5 years after birth (Fig. 2.18).

The midface is connected to the neurocranium by a circummaxillary suture system and, toward the midline, by the cartilaginous nasal capsule, nasal septum, and vomer (Fig. 2.19). There is also an intermaxillary suture system composed of the midpalatal, transpalatal, intermaxillary, and internasal sutures. With the exception of the inferior turbinates, all the bones composing the midface are formed intramembranously from a connective tissue mass.

Development of the Midface

The midface has both viscerocranial and chondrocranial components. The chondrocranial component comprises principally of parasagittal extensions of the cartilaginous anterior cranial base as the nasal septum and cartilaginous nasal capsule into the nasal region. The viscerocranial

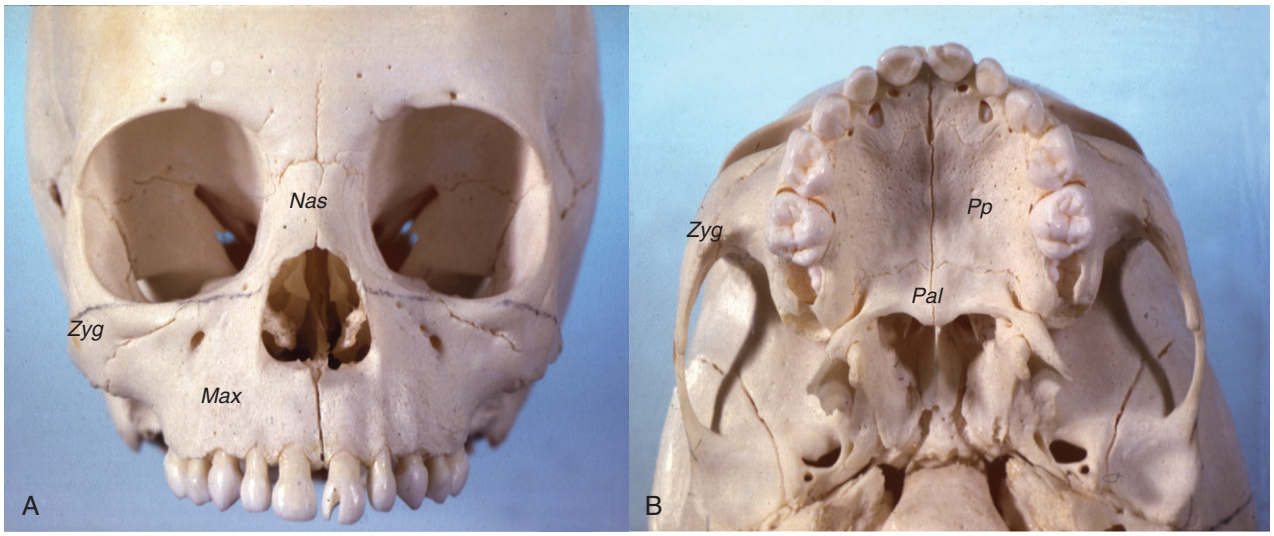


Fig. 2.18 A, Frontal and (B) basal views of a juvenile human indicating the bones comprising the midface. *Max,* Maxilla; *Nas,* nasal bones; *Zyg,* zygomatic bones; *Pal,* palatine bones; *Pp,* palatal processes of the maxillary bones.

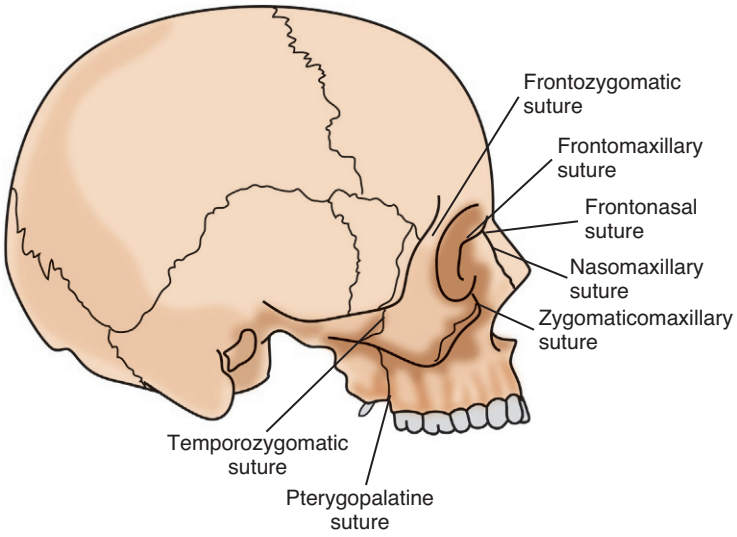


Fig. 2.19 Location of the Circummaxillary Suture System Articulating the Midface with the Neurocranium.

component is derived from two embryonic structures. The first is an inferior extension of the frontonasal prominence, which extends toward the oral opening, or stomodeum, to form nasal structures and the philtrum of the upper lip. The second is the paired maxillary processes of the first branchial arch. Differential growth of the right and left maxillary processes results in their apparent migration medially until they come into contact with the medial nasal process of the frontonasal prominence.

The skeletal elements comprising the midfacial complex arise almost exclusively from neural crest cells within the maxillary process of the first branchial arch. The primary palate, which gives rise to the four maxillary incisors, is derived from the frontonasal prominence. Only the facial ethmoid and inferior turbinate are derived from the cartilaginous component of the midface. Like the bones of the cranial vault, because the bones composing the nasomaxillary complex have no cartilaginous precursors, they rely on intramembranous ossification for their development. However, the exact process by which initial bone formation occurs differs from that of the cranial vault bones. Whereas the bones of the cranial vault arise within a desmocranial membrane, centers of ossification for the nasomaxillary bones develop as blastemas directly within the mesenchyme of the first branchial arch. These blastemas of bone are then surrounded by a periosteum that provides the source of new osteoblastic cells and thus for enlargement of the skeletal element. Molecular signaling mechanisms associated with the development, growth, and maintenance of the facial sutures are dependent on the presence of the nasal capsular cartilage, which appears to play a role similar to the dura mater in sutures of the cranial vault in the expression of *TGF-β1*, *TGF-β2*, *TGF-β3*, and *Msx2*.[48] It has also been shown that *Fgf8* plays a significant role in the integration and coordination of the frontonasal prominence with the nasal and optic regions.[49]

Virtually all of the major centers of ossification within the midface can be seen at approximately 7 to 8 weeks' gestation. At 6 weeks' gestation, the palatal shelves, which are mesenchymal tissue extensions of the embryonic maxillary processes of the first branchial arches, elevate within the oral cavity, where they will give rise to the hard and soft palates. The palatal shelves begin to ossify at 7 to 8 weeks' gestation, with the two bone fronts of the palatal processes each extending medially to form the secondary palate, composed of processes from the maxillary bones and from the palatine bones, as they meet in the midline, where they form the midpalatal suture.

The molecular mechanisms associated with the development of the palate are among the most studied in all of craniofacial growth and development because of the obvious problem of cleft lip and palate, which is the most common craniofacial deformity (~1:1000 for children of European descent).[50,51] Genes that have been identified specifically for a significant role in the genesis of cleft lip and palate now include isoforms of *BMP, Dlx, Fgf-8, Msx, Pitx, Sho2, Shh, Sox9,* and *TGF-β*, among others. It is also well documented that epigenetic factors, such as anoxia resulting from cigarette smoking and alcohol use, have a major impact on nonsyndromal cleft lip and palate.

Development of the nasomaxillary complex proceeds laterally and anteroposteriorly with expansion of the brain and cranial cavity and expansion of the oral cavity and oronasal pharynx. Also throughout the fetal period, anterior and inferior growth of the nasal septal cartilage, which is an extension of the anterior cranial base, is most prominent. The cartilaginous nasal capsule, which envelops the nasal cavity laterally, is primarily structural and contributes little to the overall growth of the nasomaxillary complex other than possible expression of growth factors that support the facial sutures (Fig. 2.20). Thus the primary factors influencing the growth of the nasomaxillary complex from the late embryonic period and throughout the fetal period and the juvenile period postnatally are an expansion of the brain and cranial vault and growth of the anterior cranial base, including in particular anterior and inferior growth of the nasal septum, as well as expansion of the nasal cavity and oronasal pharynx.

Postnatal Growth of the Midface

At the time of birth, the midface is well developed but diminutive relative to the neurocranium. The circummaxillary and intermaxillary sutures are all present and active as sites of bone growth. The nasal capsule and midline nasal septum are still primarily cartilaginous and continuous with the rest of the chondrocranium from the anterior cranial base. The septum is also very actively growing by means of interstitial cartilaginous growth, leading to significant anterior and vertical growth of the midface, especially during the first 3 to 4 years of life.

With the exception of the nasal septum, postnatal development of the nasomaxillary complex occurs by intramembranous ossification. Growth at the circummaxillary and intermaxillary sutures occurs in response to midfacial displacements, the result principally of growth of the anterior cranial base and nasal septum. Inferior, anterior, and lateral displacements of the midface result in concomitant compensatory sutural growth to account for the majority of vertical, anteroposterior, and transverse changes that occur during both childhood and

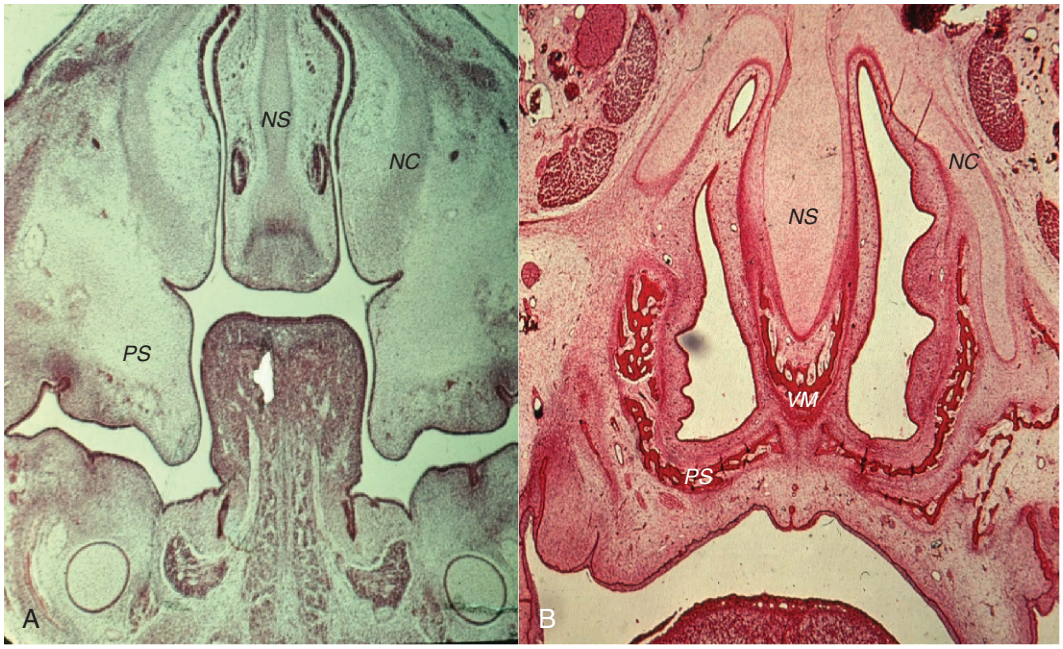


Fig. 2.20 Frontal histologic sections of human fetuses at approximate ages of 5 weeks' gestation **(A)** and 11 weeks' gestation **(B)** (hematoxylin and eosin–stained). *NC,* Nasal capsular cartilage; *NS,* nasal septal cartilage; *V,* vomer; *PS,* palatal shelves.

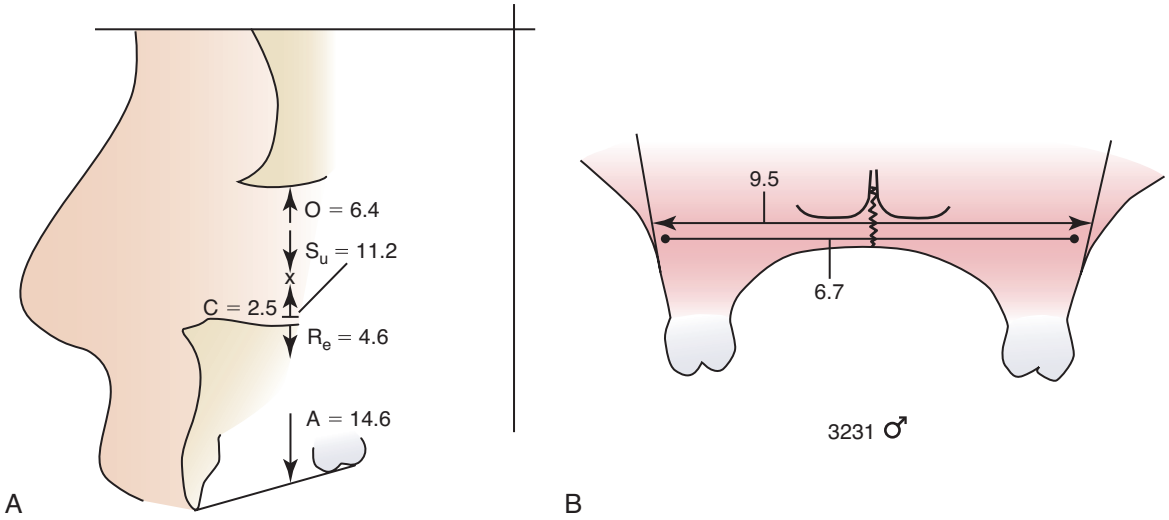


Fig. 2.21 **A,** Sutural displacement *(S_u),* apposition of the orbital floor *(O),* resorption of the nasal floor *(R_e),* apposition at the infrazygomatic crest *(C),* and dentoalveolar development *(A)* from 4 years of age through adulthood in nine boys. **(B)** Width changes (mm) of the maxilla and lateral implants between 3.9 and 17.7 years of age. (From Björk A, Skieller V. Postnatal growth and development of the maxillary complex. In: McNamara JA Jr, ed. *Factors Affecting the Growth of the Midface,* Ann Arbor, MI: Center for Human Growth and Development, Michigan Craniofacial Growth Series; 1976:61-100.)

adolescence (Fig. 2.21). Along with displacements, extensive surface modeling takes place over the entire nasomaxillary complex, especially along its posterior and superior aspects.

As long as the midface undergoes displacement, sutural growth occurs, with the amounts of bony apposition being related directly to amounts of sutural separation. Growth continues until the sutures are no longer separating. The premaxillary/maxillary suture fuses at approximately 3 to 5 years of age.[52] The midpalatal and transpalatal maxillary sutures, which are the major intermaxillary growth sites associated with transverse and anteroposterior maxillary growth, have been reported to close between 15 and 18 years of age[53] and 20 to 25 years of age,[54] respectively, depending on the criteria on which closure is based. More recent studies suggest only limited amounts of sutural obliteration (i.e., the development of bony bridges, or spicules, running across the suture after growth has ceased) in adult midpalatal sutures.[55,56] The increasing complexity that characterized sutures during childhood and adolescence appears to be functionally related rather than age related.[57] Although data are limited, it appears that closure of the circummaxillary sutures occurs somewhat later than closure of the intermaxillary sutures.

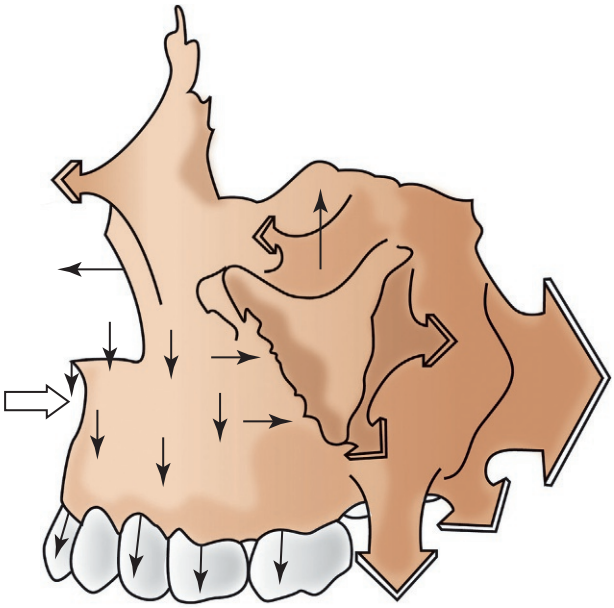


Fig. 2.22 Maxillary remodeling, with the sizes of the arrows indicating relative amounts of change and with *dark* and *light arrows* indicating resorption and apposition, respectively. (Redrawn from Enlow DH, Bang S. Growth and remodeling of the human maxilla. *Am J Orthod.* 1965;51:446-464.)

The midface undergoes a complex modeling pattern throughout childhood and adolescence (Fig. 2.22).[58] As the midface is displaced anteriorly, compensatory bony deposition occurs along the posterior margin of the maxillary tuberosity, resulting in an increase in the length of the entire maxilla and of the dental arches.[59] The posterior maxilla is a major modeling site that accounts for most of the increases in maxillary length. The anterior periosteal surface of the maxilla is slightly resorptive, while the buccal surfaces undergo substantial bony deposition. From the sagittal perspective, the area of the anterior nasal spine drifts inferiorly; the A-point also drifts inferiorly and slightly posteriorly. For every 4 mm that the posterior nasal spine drifts posteriorly, it drifts approximately 3 mm inferiorly. Associated with inferior displacement of the midfacial complex, bony resorption occurs along the floor of the nasal cavity, whereas apposition occurs on the roof of the oral cavity (i.e., palate) and orbital floor. Implant studies suggest that for every 11 mm of inferior midfacial displacement, the orbital floor drifts superiorly 6 mm and the nasal floor drifts inferiorly 5 mm.[60] Thus midfacial height increases because of the combined effects of inferior cortical drift and inferior displacement (see Fig. 2.21). The height of the midface is further increased by continued development of the dentition and alveolar bone. The lack of naturally stable structures on the surface of the midfacial complex makes superimposition difficult.

The width of the midface at the time of birth is proportionately large because of the precocious development of the eyes, which are the central features of the neonatal midface. Growth in width during the first 2 to 3 years after birth is associated with expansion of the brain laterally and anteroposteriorly, which brings the eyes laterally with it. As this occurs, the sutures separating the two halves of the frontal bone (metopic suture), the two nasal bones (internasal suture), the two maxillae (intermaxillary suture), and the two palatine bones (midpalatal suture) are positioned to respond by secondary, compensatory bone formation. It has been estimated that the midalveolar and bijugale widths of the maxilla increase approximately 5 and 6 mm, respectively, between 7.6 and 16.5 years of age; rates of growth in width diminish slightly with increasing age.[61]

At the same time that the midface is increasing in width, it is increasing even more dramatically in depth (anteriorly) and height (vertically). The midface increases most in height, next in depth, and least in width. As the brain and eyes grow anteriorly relative to the middle cranial base, the orbits increase in depth and the anterior cranial base lengthens, primarily as a result of growth at the sphenoethmoidal synchondrosis. Concomitantly, the nasal septum grows vertically as the midface is displaced inferiorly relative to the anterior cranial base. The combination of these two growth processes—growth in a vertical direction associated with interstitial cartilaginous growth within the nasal septum and growth in an anterior direction associated with interstitial cartilage growth within both the nasal septum and synchondroses of the cranial base—results in the typical downward and forward growth of the entire midface relative to the anterior cranial base. Surface deposition cannot account for the downward and forward midfacial growth that occurs during childhood and adolescence.

The age of approximately 7 years is something of a benchmark for growth of the midface. Growth of the CNS—the brain and eyes—is essentially complete at about 7 years of age. Concomitantly, the cartilage of the sphenoethmoidal synchondrosis ossifies and a suture is formed between the sphenoid and ethmoid bones at about that time. As a result, a relatively stable anterior cranial base is established extending from the sella turcica to the foramen cecum. Also at about 7 years of age, the growth of the cartilages of the nasal capsule and nasal septum changes significantly. The cartilaginous nasal capsule becomes ossified, and the nasal septum, which remains cartilaginous throughout life in humans, decreases significantly in growth activity. Despite these important developmental changes in the growth processes of the midface, downward and forward skeletal growth continues to be significant over the next decade or so, particularly in males during adolescence.

Growth of the nasomaxillary complex continues throughout childhood and adolescence, with substantially greater vertical than anteroposterior growth potential (Fig. 2.23). By 4.5 years of age, palatal length (anterior nasal spine–posterior nasal spine) and anterior facial height

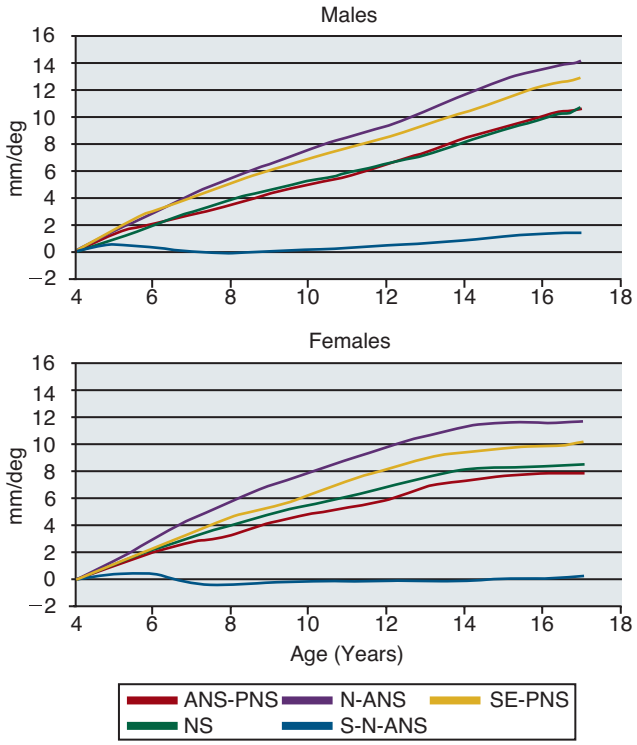
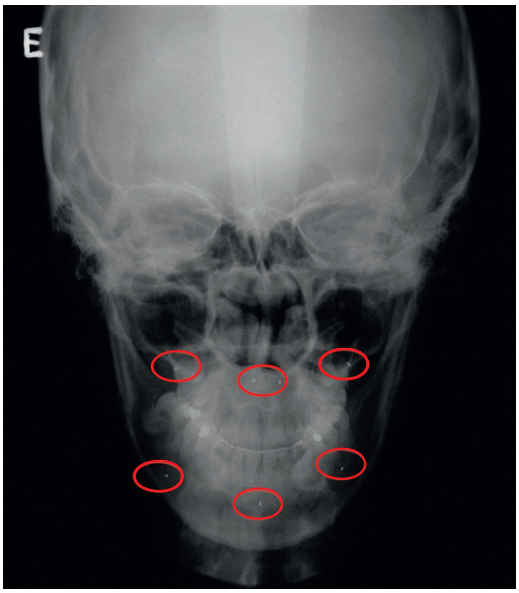


Fig. 2.23 Maxillary Growth Changes between 4 and 17 Years of Age of Males and Females. (Adapted from data provided by Bhatia SN, Leighton BC. *A Manual of Facial Growth: A Computer Analysis of Longitudinal Cephalometric Growth Data.* New York: Oxford University Press; 1993.)

(nasion–anterior nasal spine) have attained approximately 80% and 73% of their adult size, respectively (see Fig. 2.17). In terms of absolute growth, midfacial heights should be expected to increase 10 to 12 mm in females and 12 to 14 mm in males between 4 and 17 years of age. Palatal length should be expected to increase 8 to 10 mm over the same period. Because nasion drifts anteriorly at approximately the same rate as the midface is displaced anteriorly, the sella-nasion-anterior (SNA) nasal spine angle shows little or no change during childhood or adolescence. Although vertical maxillary growth rates peak during adolescence, at approximately the same time as stature, anteroposterior maxillary growth remains more or less constant, with no distinct adolescent spurt.

Because the displacements are not parallel, the midface undergoes varying amounts of vertical and transverse true rotation. True rotation is independent of surface modeling and refers to changes that occur over time in the positions of basal bone; it is commonly assessed with metallic implants placed into the mandibles and maxillae of growing children.[62] From the sagittal perspective, most children undergo true forward or counterclockwise (subject facing to the right) rotation of the midface, due to greater inferior displacement of the posterior than anterior maxilla. The true rotation that occurs tends to be covered up or hidden by the resorption that occurs on the nasal floor. For example, true forward rotation is associated with greater resorption in the anterior than posterior aspect of the nasal floor. Because of greater transverse displacements posteriorly than anteriorly, the midfacial complex also exhibits transverse rotation around the midpalatal suture (Fig. 2.24). As a result, there is greater sutural growth in the posterior than anterior aspect of the midpalatal suture. Cephalometric analyses using metallic implants have shown that the posterior maxilla expands approximately 0.27 to 0.43 mm/yr, with greater expansion occurring during childhood than during adolescence.[60]



References	Ages (Years)	*Mx*	*Md*
Björk and Skieller, 1977	4-21	.42	N/A
Korn and Baumrind, 1990	8.5-15.5	.43	.28
Gandini and Buschang, 2000	13.9-16.7	.27	0.19
Iseri and Solow, 2000	7-12	N/A	.22
	13-18	N/A	.13

Fig. 2.24 Transverse expansion (mm/yr) of metallic bone markers inserted into the maxillary *(Mx)* and mandibular *(Md)* basal structures.

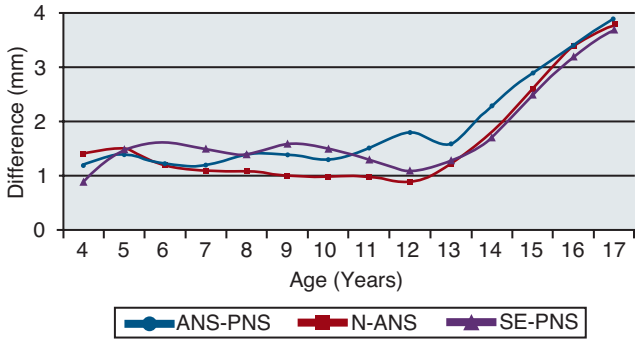


Fig. 2.25 Sex Differences (Male Minus Female) in Maxillary Size. (Adapted from data provided by Bhatia SN, Leighton BC. *A Manual of Facial Growth: A Computer Analysis of Longitudinal Cephalometric Growth Data.* New York: Oxford University Press; 1993.)

There are definite sex differences in maxillary postnatal growth (Fig. 2.25), with males being larger and growing more than females. Size differences, averaging between 1 and 1.5 mm, are small but consistent during infancy and childhood. Sexual dimorphism increases substantially throughout the midfacial complex during adolescence, with differences of approximately 4 mm in maxillary length (anterior nasal spine to posterior nasal spine [ANS-PNS]) and upper facial height (nasion to anterior nasal spine [N-ANS]) at 17 years of age. Males also have significantly wider midfaces than females, with differences approximating 5 to 7 mm during late adolescence.[63] The primary reason that adult males are larger than adult females is the extra 2 years of childhood growth that males have; males enter the adolescence phase of growth at approximately 12 years of age, whereas females enter around 10 years. Males are also larger than females because they experience a more intense adolescent spurt, but this contributes less to the sex differences observed.

MANDIBLE

Development of the Mandible

The mandible develops bilaterally within the mandibular processes of the first branchial arch. Each embryonic mandibular process contains a rodlike cartilaginous core, Meckel's cartilage, which is an extension of the chondrocranium into the viscerocranium. Throughout its course, distally Meckel's cartilage is accompanied by the mandibular division of the trigeminal nerve (cranial nerve V), as well as the inferior alveolar artery and vein. Proximally, Meckel's cartilage articulates with the cartilaginous cranial base in the petrous region of the temporal bone, where it gives rise to the malleus and incus bones of the inner ear.

By 6 weeks' gestation, a center of ossification appears in the perichondrial membrane lateral to Meckel's cartilage.[46] It is critical to note that ossification of the mandible takes place in membrane *lateral* and *adjacent* to Meckel's cartilage, and *not within* Meckel's cartilage itself (Fig. 2.26). Therefore it is clear that the mandible develops and subsequently grows by means of intramembranous ossification and not through endochondral ossification and replacement of Meckel's cartilage. The only portion of the developing lower jaw that appears to be derived from endochondral ossification of Meckel's cartilage is the mental ossicles, which are two very small sesamoid bones that are

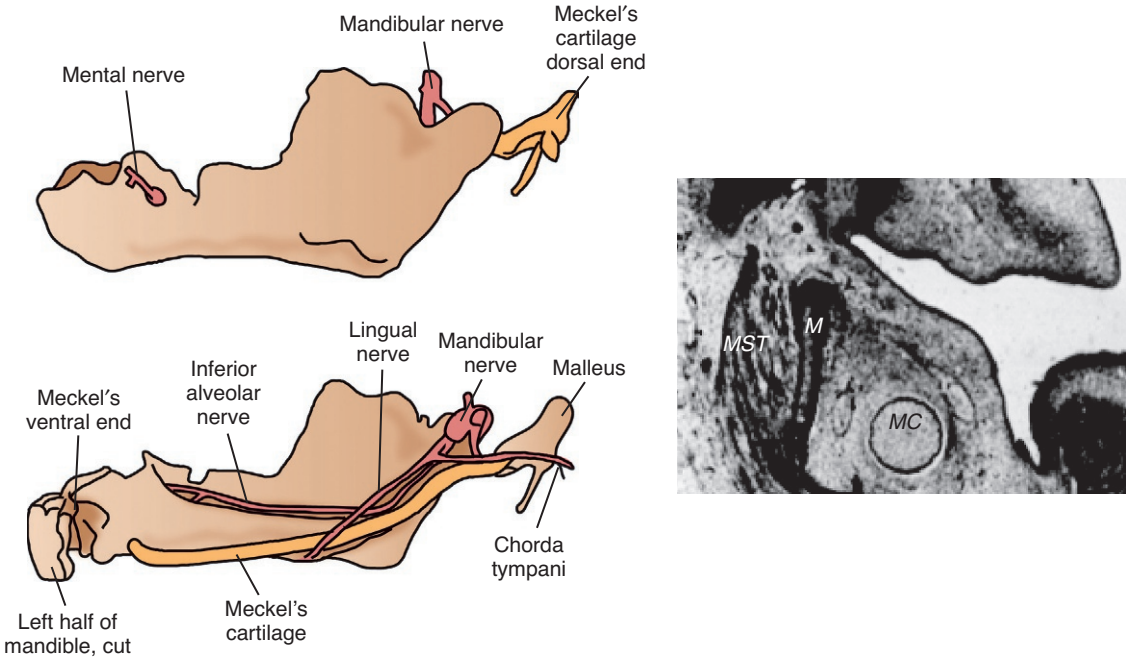


Fig. 2.26 Drawings of a Fetal Mandible with Lateral *(top left)* and Medial *(bottom left)* Views. *Right,* Photomicrograph of coronal view of human fetus indicating Meckel's cartilage medial to the mandible *(M). MST,* Masseter muscle. (Drawings adapted from Warwick R, Williams PL, eds. *Gray's Anatomy*. 35th ed. Philadelphia: WB Saunders; 1973.)

formed in the inferior aspect of the mandibular symphysis.[65] These bones are no longer present at the time of birth.

Intramembranous ossification of the body of the mandible proceeds distally toward the mental symphysis and proximally up to the region of the mandibular foramen. As it does so, Meckel's cartilage begins to degenerate and involute as the inferoalveolar neurovascular bundle becomes progressively enveloped by the intramembranously developing mandibular bone. Meckel's cartilage completely disappears by approximately 24 weeks' gestation, remaining in remnant form as the dense sphenomandibular ligament and giving rise to the malleus and incus ear ossicles.

Initial evidence of the formation of the temporomandibular joint (TMJ) is seen on expression of the Barx-1 homeobox gene. By approximately 8 weeks' gestation, the condylar process appears as a separate carrot-shaped blastema of cartilage extending from the ramus proximal to the mandibular foramen and extending up to articulate with the squamous (membranous) portion of the developing temporal bone. Formation of the joint cavity between the condylar process and the squamous portion of the temporal bone is essentially completed as the TMJ by about 12 weeks' gestation (Fig. 2.27).

Because the cartilage composing the mandibular condyle arises "secondarily" within a skeletogenic membrane and apart from the primary embryonic cartilaginous anlagen, it is referred to as a *secondary cartilage* (Fig. 2.28). Secondary cartilage is a unique type of skeletal tissue that has the characteristics of both intramembranous bone and certain histologic and functional features of hyaline growth cartilage. Secondary cartilage is formed in areas of precocious stresses and strains within intramembranous bones, as well as in areas of rapid development and growth of bone.[65,66] Within the craniofacial complex, the angular and the coronoid processes of the mandible also may exhibit the presence of secondary cartilage because these are sites of very rapid bone growth associated with the function of the muscles of mastication. In addition, secondary cartilage may be found in areas

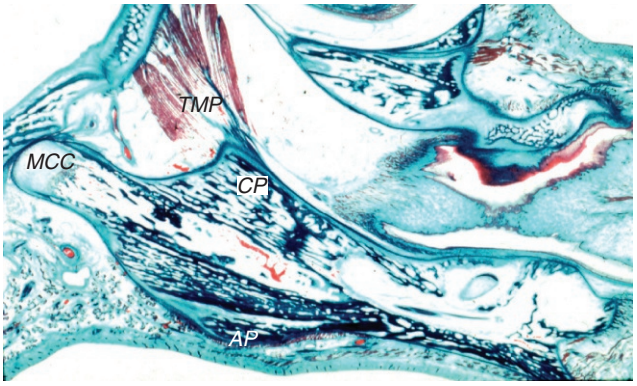


Fig. 2.27 Parasagittal histologic section of human fetus (~12 weeks' gestation) (hematoxylin and eosin–stained). *MCC,* Mandibular condylar cartilage; *CP,* coronoid process; *AP,* angular process; *TMP,* temporalis muscle.

of sutures characterized by rapid intramembranous bone growth and biomechanical load associated with separation and bending at the articular surfaces.

At birth, the two halves of the mandible are separated in the midline by a fibrous articulation, the mental symphysis, which will fuse by the end of the first year of life. Each half of the mandible is characterized anatomically by (1) a *condyle* and *condylar process,* which articulates with the temporal bone to make up the TMJ; (2) a *ramus,* which extends roughly vertically–inferiorly from the condylar process and provides insertions for the muscles of mastication; and (3) a *corpus,* or body, which extends roughly horizontally–anteriorly to provide a base for the mandibular dental arch and house the inferior alveolar–neurovascular bundle. Each of these anatomic structures also can be considered in terms of overlapping functional units (Fig. 2.29). The mandibular condyle and condylar processes obviously are essential for

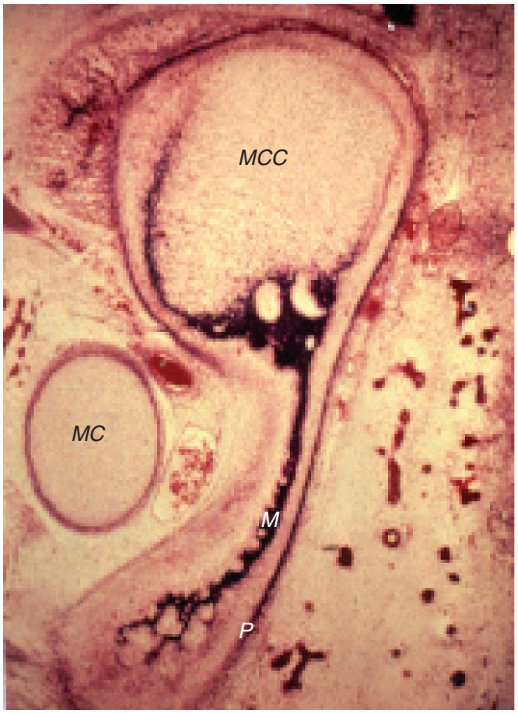


Fig. 2.28 Frontal histologic section of a human fetus (~8 weeks' gestation) (hematoxylin and eosin–stained). The bone comprising the body and ramus of the mandible *(M)* originates in the membrane lateral to Meckel's cartilage *(MC)*. The periosteal membrane enveloping the mandible gives rise secondarily to the mandibular condylar cartilage *(MCC)*.

normal articular function of the TMJ and movements of the mandible, while at the same time playing a significant role in mandibular growth for most of the first two decades of life.[67] Variation in the function of the TMJ, such as might occur in association with differences in mastication, jaw movements, and jaw position, for example, is highly likely to affect its growth and form. The gonial region of the mandible, at the inferior aspect of the ramus, is related to the function of the masseter and medial pterygoid complex of muscles, and the coronoid process is primarily related to the temporalis muscle. Variation in the growth and form of each of these regions is due in large part to variation in the function of the muscles of mastication. The alveolar process of the mandible functions to provide support for the dentition. Finally, the body of the mandible, extending from the mandibular foramen to the mental process, provides support and structural connection between the various functional components of the mandible.

Growth of the Mandibular Condyle

Just as a suture can be considered to be a specialization of an osteogenic membrane (i.e., periosteum and dura mater), the condylar cartilage can also best be considered to be a specialization of periosteum. As with sutures, growth of the mandibular condyle tends to be relatively highly responsive to mechanical, functional, and hormonal stimuli both at the time of development and throughout the growth period, similar to intramembranous bone development elsewhere.

Histomorphology of the Growing Condyle

A number of similar but somewhat different terms have been used to describe the histomorphology of the growing mandibular condyle.[68] These are summarized according to their equivalencies in E-Table 2.2.

The secondary cartilage composing the condyle during growth can be divided into two general layers: an articular layer and a growth layer. The more superficial *articular layer* is continuous with the outer fibrous layer of the bilaminar periosteum, encapsulating the condylar neck and temporal bone, respectively. Deep to the articular layer is a subarticular *growth layer*. The growth layer of the condylar cartilage is organized into an additional series of layers or zones typical of growing cartilage that blend into each other (Fig. 2.30). Each of these zones is present in the neonate and remains in the condyle through maturity. However, their absolute and relative size as well as their growth-related activity may vary considerably, depending on the overall rate and amount of condylar growth and on the functional requirements placed on the condyle and TMJ.[69,70]

Articular layer. The articular layer of the joint surface of the mandibular condyle and temporal portion of the TMJ consist of an avascular dense fibroelastic connective tissue whose collagen fibers are oriented parallel to the articular surface. The articular layer varies in thickness along the condylar head and temporal joint surface, increasing in thickness in the superior aspect of the condyle and on the articular eminence of the glenoid fossa, where compressive forces associated with mastication are greatest.[71] The fibrous articular layer of the mandibular condyle and that found in the glenoid fossa and articular eminence are identical functionally to the articular cartilage found in the diarthroidial joints of the postcranial long bones, but their origin and histologic composition are completely different. Articular cartilage is derived from the primary cartilaginous anlagen at the ends of long bones; the articular tissue of the TMJ is a specialization of the fibrous layer of periosteum that covers the mandible and temporal bone.

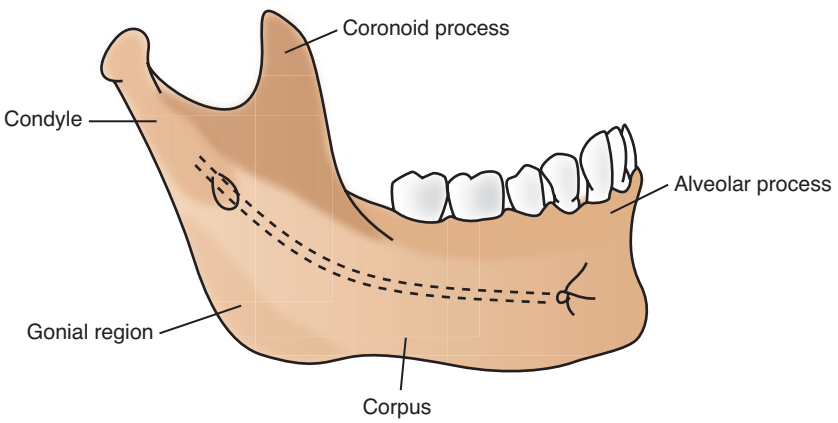


Fig. 2.29 Major Functional Units of the Mandible.

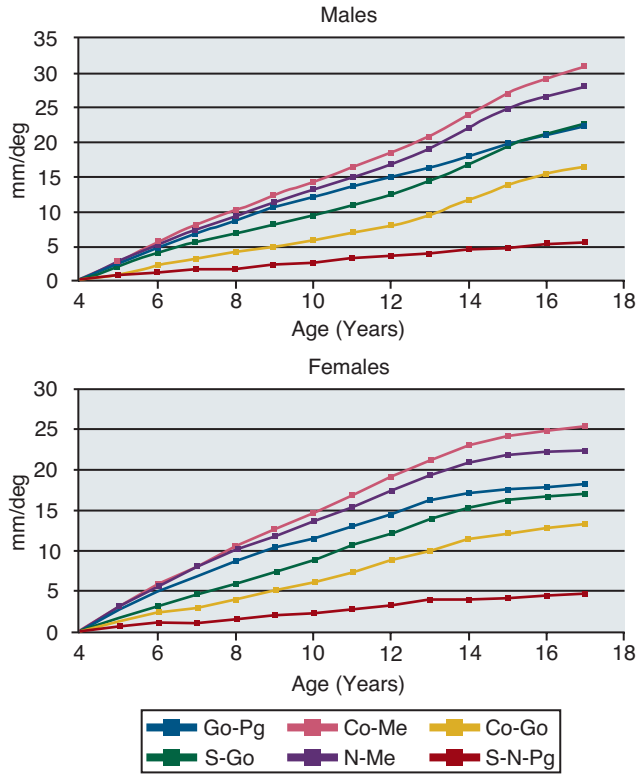


Fig. 2.34 Mandibular growth changes between 4 and 17 years of age of males and females. (Adapted from data provided by Bhatia SN, Leighton BC. *A Manual of Facial Growth: A Computer Analysis of Longitudinal Cephalometric Growth Data*. New York: Oxford University Press; 1993.)

pronounced spurt for the anteroposterior and transverse growth has not been established.

The mandible undergoes substantial amounts of true vertical rotation and more limited, but definite, transverse rotation. Although the maxilla exhibits more transverse rotation, the mandible exhibits more vertical rotation than the maxilla. The typical pattern of vertical rotation is forward (counterclockwise with the subject facing to the right), as a result of greater inferior displacements of the posterior than anterior aspects of the mandible.[101] Rates of vertical mandibular rotation have been estimated to range between 0.4 and 1.3 degrees/yr, with significantly greater rates of rotation during childhood than adolescence (Fig. 2.36). Although relatively few (< 10%) children are "true" posterior rotators, up to 25% of adolescents have been reported to be posterior rotators.[80] Greater amounts of true mandibular rotation occur during the transition to the early mixed dentition than at any time thereafter.[102,103]

The mandible also rotates transversely because of greater expansion of the posterior than of the anterior aspects of the two corpora. This type of rotation has been demonstrated repeatedly in subjects with metallic implants and represents expansion of basal bone. It has also been shown that, when viewed from frontal projects, the right and left mandibular nerves are displaced laterally throughout growth. Transverse rotation is also age related, with greater amounts occurring during childhood than adolescence. The posterior aspect of the mandible expands approximately 65% to 70% as much as the posterior maxilla expands at the posterior aspect of the midpalatal suture (see Fig. 2.20).

As in the rest of the craniofacial complex, sex differences in mandibular growth are evident at the earliest ages and become pronounced during adolescence. At birth, males have significantly larger mandibles than do females. Sex differences, which are greatest for overall length, followed by corpus length and ramus height, respectively, range from 0 to 2 mm between 1 and 12 years of age, when males initiate their adolescent phase of growth. Mandibular dimorphism increases to 4 to 8 mm by the end of the adolescent growth phase (Fig. 2.37). There are no sex differences in vertical rotation during childhood or adolescence.

In summary, the mandible increases in size as a result of the combined processes of proliferation of secondary cartilage at the condyle and differential formation and modeling of bone along the entire surface of the mandible, particularly along its superior and posterior aspects. Growth of the mandible is expressed in a downward and forward direction relative to the cranium and cranial base. The mandible is typically displaced downward more than the maxilla, with the resulting space being taken up by the erupting dentition. Because of the geometry of the craniofacial complex, normal, coordinated growth of the jaws and a normal relationship of the associated occlusal arches require that the relative rate and amount of growth of the maxilla and mandible differ.

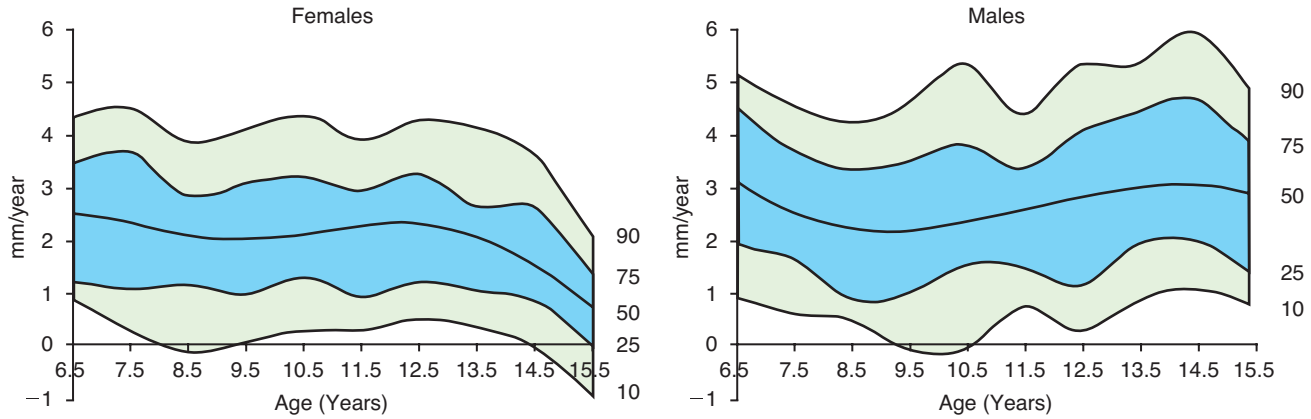
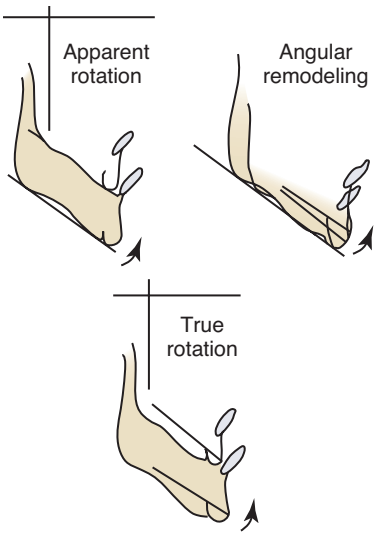


Fig. 2.35 Percentile Curves for Condylar Growth of Females and Males. (Adapted from Buschang PH, Santos Pinto A. Condylar growth and glenoid fossa displacement during childhood and adolescence. *Am J Orthod Dentofac Orthop*. 1998;113:437-442.)



References	Ages	deg/yr
Odegaard, 1970	7-14	0.8
Lavergne and Gasson, 1977	7-19	0.9
Skieller et al., 1984	Adolescence	1.0
Spady et al., 1992	Childhood	0.9
	Adolescence	0.4
Miller and Kerr, 1992	5-10	1.3
	10-15	0.8
Karlsen, 1995	6-12 (high angle)	0.7
	6-12 (low angle)	1.3
	12-15 (high angle)	0.7
	12-15 (low angle)	1.3
Wang et al., 2009	5.6-8.5	1.3
	8.5-15.5	0.7

Fig. 2.36 True Mandibular Rotation (Degrees per Year) During Childhood and Adolescence.

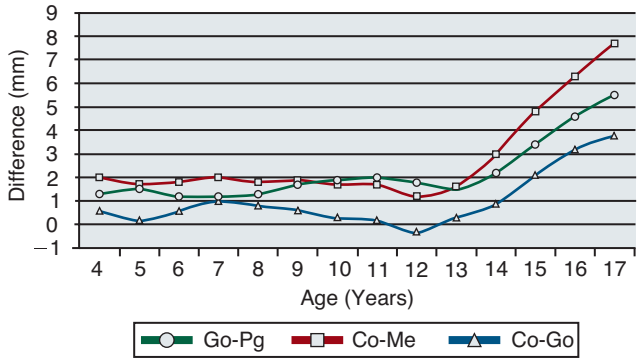


Fig. 2.37 Sex Differences (Male Minus Female) in Mandibular Size. (Adapted from Bhatia SN, Leighton BC. *A Manual of Facial Growth: A Computer Analysis of Longitudinal Cephalometric Growth Data.* New York: Oxford University Press; 1993.)

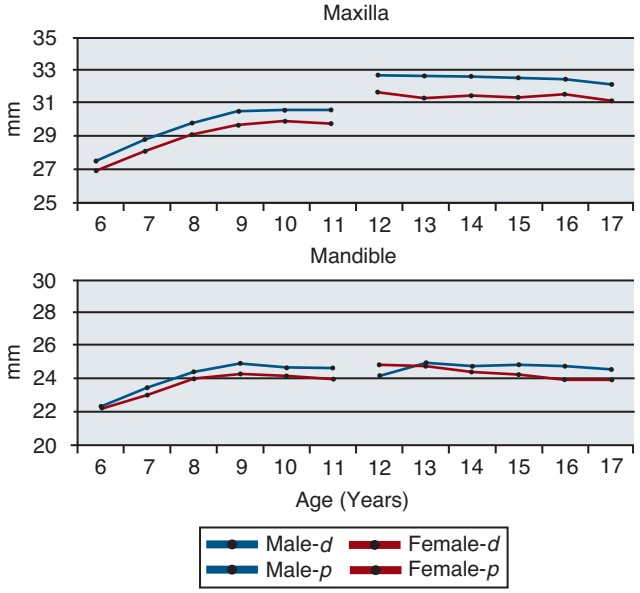


Fig. 2.38 Maxillary and mandibular intercanine widths of males and females based on measurements taken from the deciduous *(d)* and permanent *(p)* canines. (Data from Moyers RE, van der Linden PGM, Riolo ML, et al. *Standards of Human Occlusal Development*. Ann Arbor, MI: Center for Human Growth and Development; 1976.)

ARCH DEVELOPMENT, TOOTH MIGRATION, AND ERUPTION

The oral apparatus is the region of the craniofacial complex that holds the greatest potential for adaptive changes. Dental arch width and perimeter change dramatically, especially during the transitions to the early mixed and permanent dentitions.[104] Maxillary intercanine width increases approximately 3 mm during the transition to the early mixed dentition and an additional 2 mm with the emergence of permanent canines (Fig. 2.38).[105] Mandibular intercanine width increases approximately 3 mm during initial transition but shows little or no change with the eruption of the permanent canines. Intermolar widths progressively increase during childhood and adolescence, approximately 4 to 5 mm for the maxilla and 2 to 3 mm for the mandible between 6 and 16 years of age (Fig. 2.39). Maxillary arch depth (incisors to molars) decreases slightly during the transition to the early mixed dentition, increases 1 to 2 mm with the emergence of permanent incisors, and then decreases approximately 2 mm with loss of the deciduous first and second molars. Mandibular arch depth decreases slightly during the transition to mixed dentition, maintains its dimension during most of the mixed dentition, and then decreases 2 to 3 mm with the loss of the deciduous first and second molars. Maxillary arch perimeter from first molars to first molars increases 4 to 5 mm during early mixed dentition and then decreases approximately 4 mm during late mixed dentition, resulting in only a slight overall increase between 5 and 18 years of age (Fig. 2.40). Mandibular arch perimeter, from first molar to first molar, on the other hand, increases approximately 2 mm during early mixed dentition and decreases 4 to 6 mm during late mixed dentition, resulting in overall decreases of 3.5 and 4.5 mm in males and females, respectively. Most of the dental arch changes represent dentoalveolar compensations associated with incisor liability during the early mixed dentition, Leeway space during the late mixed dentition, and growth changes.

Perhaps most important from a clinical perspective, the teeth continue to migrate and erupt throughout childhood and adolescence, even after they have attained functional occlusion. The posteruptive movements of teeth are directly related to the spaces created by growth displacements and movements of other teeth. Dentoalveolar

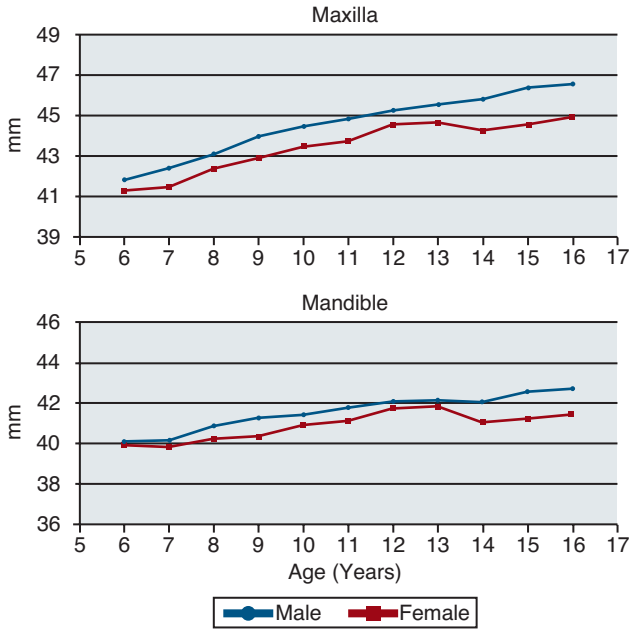


Fig. 2.39 Maxillary intercanine width of males and females based on measurements taken from the deciduous and permanent canines. (Data from Moyers RE, van der Linden PGM, Riolo ML, et al. *Standards of Human Occlusal Development*. Ann Arbor, MI: Center for Human Growth and Development; 1976.)

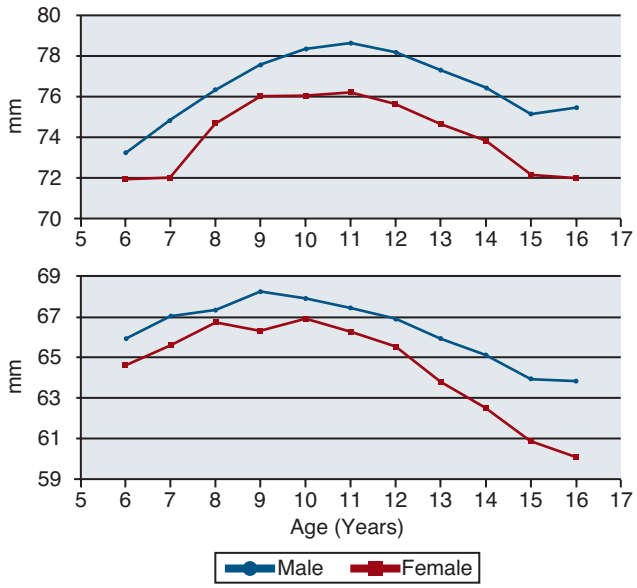


Fig. 2.40 Maxillary and Mandibular Arch Perimeter of Males and Females. (Data from Moyers RE, van der Linden PGM, Riolo ML, et al. *Standards of Human Occlusal Development*. Ann Arbor, MI: Center for Human Growth and Development; 1976.)

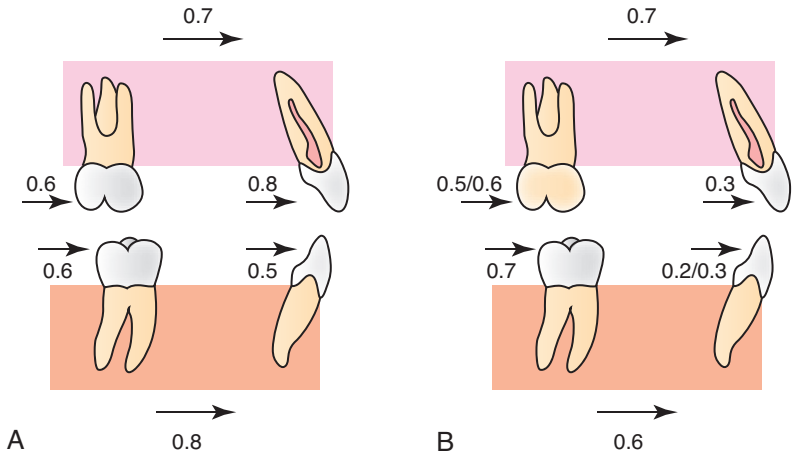


Fig. 2.41 Approximate maxillary and mandibular AP displacements and tooth migration (mm/yr) during (A) childhood and (B) adolescence (female/male).

compensation is the mechanism that coordinates their eruption and migration relative to their jaw bases; it maintains the relationships of teeth within and between the upper and lower dental arches. Dentoalveolar compensation depends on a normal eruptive system, dental equilibrium, and influences of neighboring teeth.[105] During childhood, the maxillary incisor drifts anteriorly at a greater rate than the maxillary molar (0.8 vs. 0.6 mm/yr, respectively), which accounts for the arch-depth increases evident with the eruption of the incisors (Fig. 2.41). In contrast, the mandibular molars drift anteriorly at a slightly greater rate than the incisors. Between 10 and 15 years of age, the molars (0.5–0.7 mm/yr) show significantly greater amounts of anterior drift than the incisors (0.3 mm/yr).

Substantial amounts of eruption occur throughout growth. During childhood, the maxillary first molars and incisors erupt at a rate of approximately 1.0 mm/yr, whereas their mandibular counterparts erupt at a rate of approximately 0.5 mm/yr (Fig. 2.42). During adolescence, the maxillary molars and incisors erupt at rates of 1.2 to 1.4 mm/yr and 0.9 mm/yr, respectively. The mandibular molars and incisors erupt at a rate of 0.5 to 0.9 mm/yr, with little or no differences between incisor and molar eruption. The amounts of eruption that occur are associated closely with the inferior displacements of the midface and, especially, the mandible.

During childhood, there is little or no evidence of sexual dimorphism in the migration and eruption of teeth. In contrast, there is a relatively high degree of dimorphism during adolescence in mandibular eruption, with boys showing almost twice as much eruption as girls. The maxillary teeth show only limited sex differences, pertaining primarily to the molars.

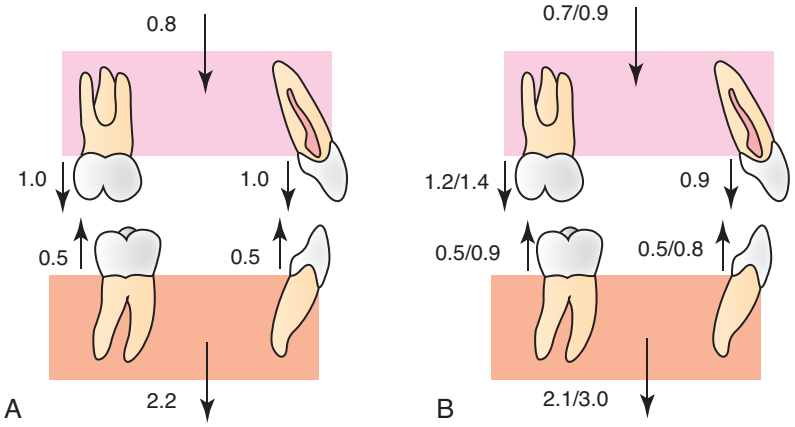


Fig. 2.42 Approximate maxillary and mandibular vertical displacements (mm/yr) and tooth eruption during (A) childhood and (B) adolescence (female/male).

ADULT CHANGES IN CRANIOFACIAL FORM

The size and shape of the craniofacial complex continue to change throughout a considerable part of adulthood. Over 90% of the 70 cephalometric distances and 70% of the 69 angles evaluated by Behrents[106] showed changes after 17 years of age; 61% of the distances and 28% of the angles showed changes after 35 years of age. In particular, the mandibular plane angle increases in adult females and decreases in adult males, which explains why males 25 to 46 years of age exhibit greater chin projection than females, who undergo increases in the angle Nasion-Sella-Gnathion (NSGn).[107]

Adult soft tissues undergo the more pronounced changes than the skeletal structures. The nose grows substantially during adulthood, with the tip moving down and forward approximately 3 mm after 17 years of age. Males exhibit significantly more nasal growth than females. Upper lip length increases (~2–3 mm) in both males and females after 17 years of age, resulting in decreases in upper incisor display over time. Lower lip length also increases, but less than upper lip length. The lips straighten and flatten during adulthood, but the most pronounced changes occur after 50 years of age. The soft tissue profile angle increases over time, with smaller increases when the nose is included than when it is excluded. Adult profile changes are limited to 2 to 3 degrees and 4 to 6 degrees when the nose is included and excluded, respectively.

POSTNATAL INTERRELATIONSHIPS DURING CRANIOFACIAL GROWTH

Postnatal craniofacial growth follows a gradient of relative growth that ranges between the neural and general somatic patterns. Vertical growth and modeling of the viscerocranium, as well as dental eruption, exhibit mid-childhood and pubertal growth spurts. Anteroposterior growth and tooth migration, which do not exhibit mid-childhood or pubertal growth spurts, change more or less regularly—except for the accelerated migration associated with the loss of teeth—throughout childhood and adolescence.

Generally, most displacements and rotations of the maxillomandibular complex are controlled epigenetically through growth of the chondrocranium, soft tissue growth, and expansion of the oronasal capsule. The cartilaginous growth centers play a particularly important role in the primary displacement of the chondrocranium, as well as in the secondary displacement of the viscerocranium. The anterior displacement of the midface has been associated with growth of the anterior cranial base and expansion of the anterior cranial fossa; mandibular displacements are more closely associated with growth of the posterior cranial base and middle cranial fossa. Anteroposterior length changes of the anterior cranial base, measured from sella to foramen cecum, coincide closely with expansion of the frontal lobes and growth at the sphenoethmoidal synchondrosis. Angular changes of the cranial base have been associated with growth gradients within the synchondroses, complex interactions with the growth of the brain, as well as facial growth. The cranial base angle decreases as a result of greater chondrogenesis in the superior than in the inferior aspects of the sphenoethmoidal and, especially, spheno-occipital synchondroses. Changes in cranial base angulation also appear to be related to changes in brain size, especially to the dramatic changes that occur during the first 2 postnatal years.

Cranial base growth influences the displacement and rotation of the viscerocranium. Growth of the posterior cranial base (i.e., spheno-occipital synchondrosis) is directly related to inferior and posterior displacements of the glenoid fossa; growth of the anterior cranial base is associated with midfacial displacement. Consequently, cranial base growth changes partially explain individual and population differences in anteroposterior skeletal relationships. Most studies show that individuals with larger cranial base angles and/or larger anterior and posterior cranial base lengths tend to be retrognathic (i.e., Class II), whereas those with the smaller lengths and angles tend to be prognathic (i.e., Class III).

Structures within the midfacial complex also affect its displacement and rotation. Growth of the eyeball is associated with both the anterior and lateral displacements of the midface, which explains why enucleation of the eyeball results in anterior and lateral growth deficiencies of the midface.[108] The nasal septum also plays important roles in nasomaxillary growth, displacement, and rotation. However, although the anterior cranial fossa, cranial base, eyeball, and nasal septum play important roles in the early displacement and rotation of the midface, their growth potentials are limited after 7 to 8 years of age. Soft tissue growth and other factors leading to the expansion of the oronasal capsule are relatively more important in explaining the midfacial rotation and displacement during later childhood and adolescence.

In turn, mandibular displacement and rotation are greatly influenced by midfacial displacement and rotation, growth of the posterior cranial base, soft tissue growth, expansion of the oronasal capsule, and development of occlusion. Posture appears to have a profound effect on mandibular growth and remodeling. There is also a direct relationship

between the true rotation of the maxilla and mandible. Both jaws usually rotate forward; individuals showing greater amount of forward rotation of the maxillary also tend to show greater forward rotation of the mandible (Fig. 2.43). Midfacial growth and the associated changes in the position of the maxillary dentition are also thought to play an important role in mandibular growth displacements. Major insults to maxillary growth can inhibit mandibular growth. Cranial growth disturbances can also influence mandibular growth indirectly through their effects on the midface and on the positional changes of the glenoid fossa, especially during infancy and early childhood. For example, it has been shown that craniosynostosis, if left untreated for a sufficiently long period, can produce significant asymmetry of the mandible.

The anterior and, especially, inferior displacements of the maxilla and mandible have direct effects on the growth at the sutures, condylar growth, modeling patterns, dental eruption, and dental migration. Although there is an upper threshold, the amount of bony apposition that occurs at sutures is related to the amount of sutural separation. For example, larger expansion forces produce greater sutural separation, which in turn results in greater sutural bone formation (Fig. 2.44). Such growth potential is essential during periods of greater sutural separation, which require concomitantly greater bone formation. The condyle also undergoes a growth spurt that closely coincides with the increased rates of inferior displacement of the mandible that occur during adolescence.[109] Because the mandible's modeling patterns are directly related to the amounts of vertical and horizontal displacement that take place,[110] individuals with greater inferior displacement show greater superior drift of bone along the entire surface of the ramus (i.e., greater apposition superiorly and greater resorption along the lower border) than do individuals who undergo less inferior displacement. Because of the close association between mandibular displacement and rotation, individuals showing greater or lesser amounts of anterior displacement of the mandible tend to exhibit lesser or greater amounts of posterior drift of the superior aspect of the ramus, respectively. The amounts of inferior displacement of the mandible that occur are also positively related to the amount of eruption that occurs, especially of the posterior teeth. Importantly, it is the displacement that determines the amounts of eruption that occur during growth, rather than vice versa. Displacements of the mandible also influence the anteroposterior compensations of the teeth. Individuals showing relatively greater anterior displacement of the mandible than maxilla tend to exhibit greater mesial displacement of the maxillary molars and counterclockwise rotation of the occlusal plane; those who undergo relatively greater anterior maxillary displacements display greater mesial displacement of the mandibular molars and minimal mesial displacement of maxillary molars.

The morphologic correlates with true rotation are numerous and hold important clinical implications.[111] Vertical rotation has been related to changes in tooth position, with true forward rotators showing greater amounts of lower incisor proclination during eruption; backward rotators show retroclination of the incisors and loss of arch space. True rotation is also related to the modeling pattern that occurs on the lower mandibular border; subjects who undergo greater amounts of true forward rotation also exhibit the greatest amounts of posterior resorption and anterior bony deposition. Ramus modeling in general depends on the rotational pattern of the mandible. Individuals who undergo greater amounts of true forward rotation also exhibit greater amounts of condylar growth, oriented in a more superoanterior direction (Fig. 2.45). Perhaps the most important clinical correlate is the relationship between true rotation and chin position. Most mandibles are displaced back during growth because of greater posterior

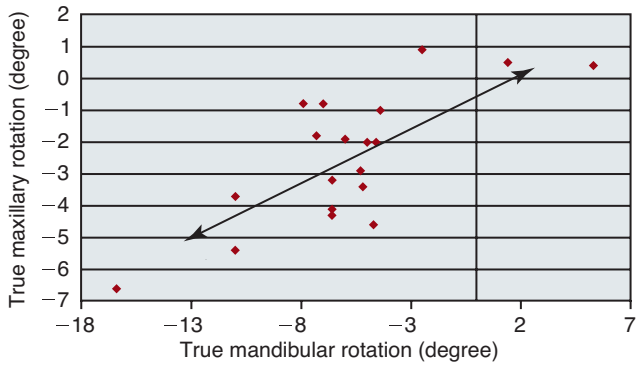


Fig. 2.43 Relationship of True Mandibular and True Maxillary Rotation (r = .75). (Data from Björk A, Skieller V. Facial development and tooth eruption. An implant study at the age of puberty. *Am J Orthod.* 1972;62:339–383.)

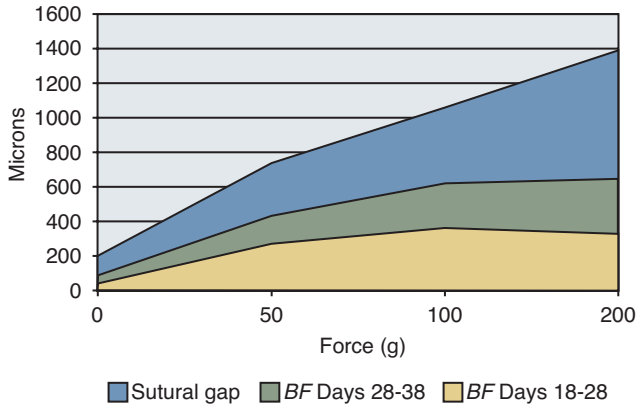


Fig. 2.44 Relationships of Bone Formation *(BF),* Sutural Gap Width, and Amounts of Force Applied to Separate Sutures.

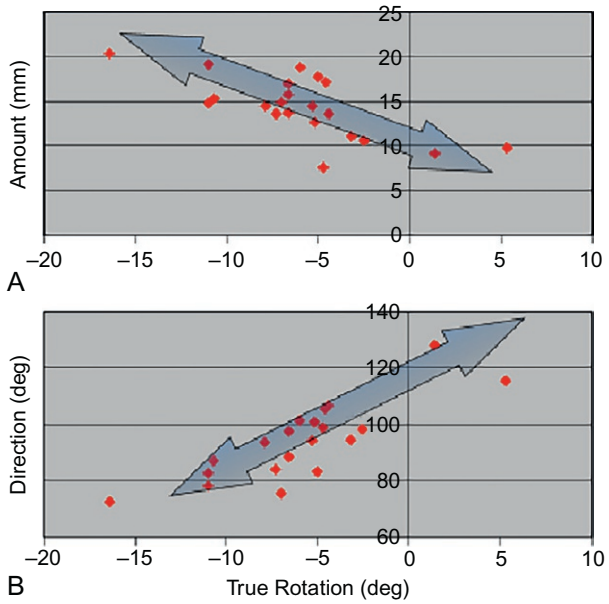


Fig. 2.45 Relationships between true mandibular rotation and **(A)** the total amount of condylar growth and **(B)** the direction of condylar growth. (Data from Björk A, Skieller V. Facial development and tooth eruption. An implant study at the age of puberty. *Am J Orthod.* 1972;62:339-383.)

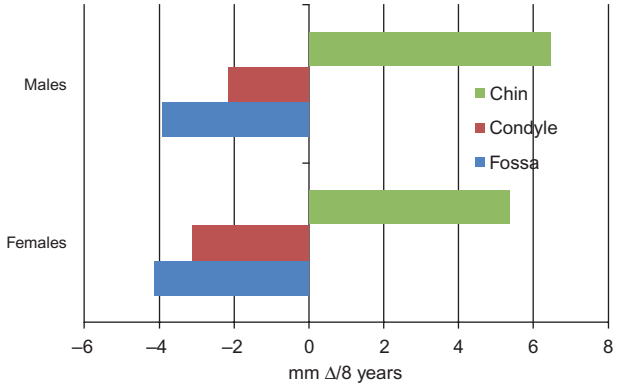


Fig. 2.46 Anteroposterior changes in chin, condylar and glenoid fossa positions in untreated children and adolescents showing backward displacement of the mandible and forward rotation of the chin.

displacement of the glenoid fossa than posterior condylar growth (Fig. 2.46). However, the chin typically comes forward as a result of true mandibular forward rotation. True rotation of the mandible explains more of the individual variation in chin position than condylar growth or changes in glenoid fossa position.

SIGNIFICANCE OF UNDERSTANDING CRANIOFACIAL GROWTH FOR ORTHODONTICS

To be most effective as clinicians, it is essential that orthodontists understand the development, growth, and adaptive potentials of the craniofacial structures. Along with orthodontic biomechanics, knowledge of how the craniofacial complex develops and grows provides the foundation for understanding the cause of the various dental and skeletal malocclusions, the best of all possible treatment approaches, and how patients might be expected to respond after treatment. A thorough understanding of growth provides the basis for knowing which craniofacial components should be expected to respond to treatment and how great the response might be expected to be. Because a structure's response potential to stress is directly related to its relative growth potential, and the vertical aspects of the mandible have the greatest relative growth potential, it follows that skeletal malocclusions might be expected to relate to vertical mandibular growth. Class II and Class III skeletal malocclusion both pertain primarily to the mandible.[112,113] These individuals are often retrognathic as a result of limited true forward rotation of the mandible, which is in turn related to deficient inferior growth displacement of the posterior mandible and/or excessive inferior displacement of the anterior aspect of the mandible.

Knowledge of growth is also important because, whenever possible, orthodontists should try to mimic growth when planning treatment. An understanding of growth provides the biological limits within which treatments can be performed. As previously indicated, the viscerocranium is made up almost entirely of intramembranous bone and is predominantly under epigenetic and environmental control. It is programmed to adapt, and adaptation should be expected whenever it is stressed. The biological system cannot distinguish between stresses imposed by the orthodontist and those imposed during normal growth; it simply responds depending on its growth potential. Continuing with the previous example, individuals who exhibit good growth patterns tend to be true forward rotators with condyles that grow in a more anterior direction. Based on this knowledge, hyperdivergent retrognathnic patients would best be served by treatments that focus on rotating the mandible rather than stimulating or redirecting condylar growth in a posterior direction.[114]

Finally, an understanding of growth makes it possible to estimate morphologic changes that should be expected to occur during and after orthodontic treatment. Unless it is intentionally disrupted, an individual's growth path before treatment might be expected to continue during and after treatment. Knowing how the maxilla and mandible rotated and/or were displaced during treatment provides an understanding of the modeling and consequent shape changes that might be expected to occur. Moreover, vertical growth after treatment is problematic in terms of posttreatment crowding, because of its relationship with tooth eruption. It has been shown that the best predictors of mandibular crowding of the permanent dentition, both after treatment and without treatment, are the inferior displacement of the mandible and superior eruption of the incisors.[86]

As understanding of craniofacial development, growth, and adaptation continues to improve in the future, orthodontists can look forward to even more therapeutic advances that can be used to influence growth and posttreatment stability. This understanding will facilitate greater clinical control of craniofacial growth changes and compensatory adaptation of tissues after treatment. Understanding normal craniofacial growth and especially that of the complex network of underlying molecular factors responsible for craniofacial growth and treatment will also be of immeasurable benefit in assisting the orthodontist in understanding what may or may not be possible, not only with respect to diagnosing a patient's underlying abnormality but also in determining the best treatment approach for its correction.[17,18,115-120]

REFERENCES

1. Carlson B. *Human Embryology and Developmental Biology.* Philadelphia: Elsevier; 2014.
2. Sperber GH, Sperber SM. *Craniofacial Embryogenetics and Development.* Raleigh NC: PMPH USA; 2018.
3. Carlson DS, Ribbens KR. Craniofacial Growth during Adolescence. In: *Craniofacial Growth Series.* Ann Arbor, MI: Center for Human Growth and Development; 1987:20.
4. Scammon RE. The measurement of the body in childhood. In: Harris JA, Jackson CM, Scammon RE, eds. *The Measurement of the Body in Childhood.* Minneapolis, MN: University of Minneapolis Press; 1930.
5. Buschang PH, Hinton RJ. A gradient of potential for modifying craniofacial growth. In: Carlson DS, ed. *Control Mechanisms of Craniofacial Development and Growth*. Semin Orthod; 2005;11(4):219–226.
6. Buschang PH, Tanguay R, Demirjian A, LaPalme L, Turkewicz J. Mathematical models of longitudinal mandibular growth for children with normal and untreated Class II, division 1 malocclusion. *Eur J Orthod.* 1988;10:227–234.
7. Malina RM, Bouchard C, Beunen G. Human growth: selected aspects of current research on well-nourished children. *Ann Rev Anthrop.* 1988;17:187–219.
8. Lewis AB, Roche AF, Wagner B. Pubertal spurts in cranial base and mandible. Comparisons within individuals. *Angle Orthod.* 1985;55:17–30.
9. Buschang PH, Jacob HB, Demirjian A. Female adolescent craniofacial growth spurts: real or fiction? *Eur J Orthod.* 2013;35:819–825.
10. Tanner JM. Growth at adolescence: an introduction. In: Carlson DS, Ribbens KR, eds. *Craniofacial Growth during Adolescence.* Ann Arbor, MI: Center for Human Growth and Development; 1987:1–22. Craniofacial Growth Series; 20;.
11. Grave KC, Brown T. Skeletal ossification and the adolescent growth spurt. *Am J Orthod.* 1976;69:611–624.
12. Fishman LS. Radiographic evaluation of skeletal maturation. *Angle Orthod.* 1982;52:88–112.
13. Baccetti T, Franchi L, McNamara Jr JA. The cervical vertebral maturation (CVM) method for the assessment of optimal treatment timing in dentofacial orthopedics. *Semin Orthod.* 2005;11:119–129.

14. Massoud MI, Masoud I, Kent Jr RL, Gowharji N, Hassan AH, Cohen L. Relationship between blood-spot insulin-like growth factor 1 levels and hand-wrist assessment of skeletal maturity. *Am J Orthod Dentofac Orthop.* 2009;136(1):59–64.
15. Wilkie AOM, Morriss-Kay GM. Genetics of craniofacial development and malformation. *Nat Rev Genet.* 2001;2:458–468.
16. Hefer T, Jaochims HZ, Carlson DS, Finnell RH. Factors associated with the etiology of congenital craniofacial anomalies: an update Part I. *J Israeli Med Assoc.* 1998;135(209–213):286–291.
17. Carlson DS. Growth modification: from molecules to mandibles. In: McNamara JA, ed. *Growth Modification: What Works, What Doesn't, and Why.* Ann Arbor, MI: Center for Human Growth and Development; 1999:17–65. Craniofacial Growth Series;.
18. Carlson DS. Toward a new synthesis for craniofacial biology: a genomic-epigenomic basis for dentofacial orthopedic treatment. In: JA McNamara, ed. *The 40th Moyers Symposium. Looking Back—Looking Forward.* Ann Arbor, MI: Center for Human Growth and Development; 2014:193–247. Craniofacial Growth Series; ;50;.
19. D'Souza RN, Dunnvald M, Frazier-Bowers S, et al. Translational genetics: advancing fronts for craniofacial health. *J Dent Res.* 2013;92(12):1058–1064.
20. Eng G, Chen A, Vess T, Ginsburg GS. Genome technologies and personalized dental medicine. *Oral Dis.* 2012;18:223–235.
21. Pritchard JJ, Scott JH, Girgis FG. The structure and development of cranial and facial sutures. *J Anat.* 1956;90:73–86.
22. Scott JH. The growth of the human face. *Proc R Soc Med.* 1954;47:91–100.
23. Baer MJ. Patterns of growth of the skull as revealed by vital staining. *Hum Biol.* 1954;26:80–126.
24. Rice DPC. Craniofacial anomalies: from development to molecular pathogenesis. *Curr Mol Med.* 2005;5:699–722.
25. Chai Y, Maxson Jr RE. Recent advances in craniofacial morphogenesis. *Dev Dyn.* 2006;235:2353–2375.
26. Kim HJ, et al. FGF-, BMP- and Shh-mediated signalling pathways in the regulation of cranial suture morphogenesis and calvarial bone development. *Devel.* 1998;125(7):1241–1251.
27. Rice DP, Kim HJ, Thesleff I. Apoptosis in murine calvarial bone and suture development. *Eur J Oral Sci.* 1999;107(4):265–275.
28. Carver EA, Oram KF, Gridley T. Craniosynostosis in Twist heterozygous mice: a model for Saethre-Chotzen syndrome. *Anat Rec.* 2002;268(2):90–92.
29. Warren SM, et al. The BMP antagonist noggin regulates cranial suture fusion. *Nature.* 2003;422(6932):625–629.
30. Veistinen L, Takatolo M, Tanimoto Y, Kesper D, Vortkamp A, Rice DPC. Loss-of-function of *Gli3* in mice causes abnormal frontal bone morphology and premature synostosis of the interfrontal suture. *Front Physiol.* 2012;3:1–6.
31. Jabs EW, et al. A mutation in the homeodomain of the human *MSX2* gene in a family affected with autosomal dominant craniosynostosis. *Cell.* 1993;75(3):443–450.
32. el Ghouzzi V, et al. Mutations of the *TWIST* gene in the Saethre-Chotzen syndrome. *Nat Genet.* 1997;15(1):42–46.
33. Howard TD, et al. Mutations in TWIST, a basic helix-loop-helix transcription factor, in Saethre-Chotzen syndrome. *Nat Genet.* 1997;15(1):36–41.
34. Moss ML, Salentijn L. The primary role of functional matrices in facial growth. *Am J Orthod.* 1969;55:566–577.
35. Martinez-Abadias N, Heuze Y, Wang Y, Jabs EW, Aldridge K, Richtmeier J. FGF/FGFR signaling coordinates skull development by modulating magnitude of morphological integration: evidence from Apert syndrome mouse models. *PLoS One.* 2011;6(10).
36. Heuze Y, Martinez-Abadias N, Stella JM, et al. Quantification of facial skeletal shape variation in fibroblast growth factor receptor-related craniosynostosis syndromes. *Birth Def Res (A).* 2014;100:250–259.
37. Di Ieva A, Bruner E, Haider T, et al. Skull base embryology: a multidisciplinary review. *Childs Ner Syst.* 2014;30:991–1000.
38. Lei WY, Wong RWK, Rabie ABM. Factors regulating endochondral ossification in the spheno-occipital synchondrosis. *Angle Orthod.* 2008;78(2):215–220.
39. Balczerski B, Zakaria S, Tucker AS, et al. Distinct spatiotemporal roles of hedgehog signaling during chick and mouse cranial base and axial skeletal development. *Dev Biol.* 2012;371:203–214.
40. Kuhn JL, Ciarelli MJ. The biomechanics of the growth plate. In: Carlson DS, Goldstein SA, eds. *Bone Biodynamics in Orthodontic and Orthopedic Treatment.* Ann Arbor, MI: Center for Human Growth and Development; 1992:93–110. Craniofacial Growth Series;.
41. Opperman LA, Gakunga PT, Carlson DS. Genetic factors influencing morphogenesis and growth of sutures and synchondroses in the craniofacial complex. In: Carlson DS, ed. *Control mechanisms of craniofacial development and growth*; 2005:199–208. Semin Orthod; 11(4).
42. Baume LJ. Principles of cephalofacial development revealed by experimental biology. *Am J Orthod.* 1961;47(12):881–901.
43. Buschang PH, Baume RM, Nass GG. A craniofacial growth maturity gradient for males and females between 4 and 16 years of age. *Am J Phys Anthrop.* 1983;61:373–382.
44. Melsen B. The cranial base: the postnatal development of the cranial base studied histologically on human autopsy material. *Acta Orthod Scand Suppl.* 1974;62:1–126.
45. Latham RA. The sella point and postnatal growth of the cranial base in the human skull. *Am J Orthod.* 1972;61:156–162.
46. Powell TV, Brodie AG. Closure of the spheno-occipital synchondrosis. *Anat Rec.* 1963;147:15–23.
47. Ford HER. Growth of the human cranial base. *Am J Orthod.* 1958;44:498–506.
48. Adab K, Sayne JR, Carlson DS, Opperman LA. Tgf-β1, Tgf-β 2, Tgf- β 3 and Msx2 expression is elevated during frontonasal suture morphogenesis and during active postnatal facial growth. *Orthod Craniofac Res.* 2002;5(4):227–237.
49. Griffin JN, Compagnucci C, Hu D, et al. *Fgf8* dosage determines midfacial integration and polarity within the nasal and optic capsules. *Dev Biol.* 2013;374:185–197.
50. Greene RM, Pisano MM. Palate morphogenesis: current understanding and future directions. *Birth Defects Res (Part C).* 2010;90:133–154.
51. Bush JO, Jiang R. Palatogenesis: morphological and molecular mechanisms of secondary palate development. *Devel.* 2012;139:231–243.
52. Behrents RG, Harris EF. The premaxillary-maxillary suture and orthodontic mechanotherapy. *Am J Orthod Dentofac Orthop.* 1991;99:1–6.
53. Melsen B. Palatal growth studied on human autopsy material. A histologic microradiographic study. *Am J Orthod.* 1975;68:42–54.
54. Persson M, Thilander B. Palatal suture closure in man from 15 to 35 years of age. *Am J Orthod.* 1977;72:42–52.
55. Korbmacher H, Schilling A, Puschel K, Amling M, Kahl-Nieke B. Age-dependent three-dimensional microcomputed tomography analysis of the human midpalatal suture. *J Orofac Orthop.* 2007;68:364–376.
56. Knaup B, Yildizhan F, Wehrbein H. Age-related changes in the midpalatal suture. A histomorphometric study. *J Orofac Orthop.* 2004;65:467–474.
57. Herring SW, Mucci RJ. In vivo strain in cranial sutures: the zygomatic arch. *J Morphol.* 1991;207:225–239.
58. Björk A, Skieller V. Postnatal growth and development of the maxillary complex. In: McNamara Jr JA, ed. *Factors Affecting the Growth of the Midface.* Ann Arbor, MI: Center for Human Growth and Development; 1976:61–100. Craniofacial Growth Series;.
59. Enlow DH, Bang S. Growth and remodeling of the human maxilla. *Am J Orthod.* 1965;51:446–464.
60. Björk A, Skieller V. Growth of the maxilla in three dimensions as revealed radiographically by the implant method. *Br J Orthod.* 1977;4:53–64.
61. Hersby RM, Marshall SD, Dawson DV, et al. Transverse skeletal and dentoalveolar changes during growth. *Am J Orthod Dentofac Orthop.* 2006;130:721–731.
62. Solow B, Houston WJ. Mandibular rotations: concepts and terminology. *Eur J Orthod.* 1988;10:177–179.
63. Lux CJ, Conradt C, Burden D, et al. Transverse development of the craniofacial skeleton and dentition between 7–15 years of age: a longitudinal postero-anterior cephalometric study. *Eur J Orthod.* 2004;26:31–42.
64. Shibata S, Sakamoto Y, Yokohama-Tamaki T, Murakami G, Cho BH. Distribution of matrix proteins in perichondrium and periosteum during incorporation of Meckel's cartilage into ossifying mandible: an immunohistochemical study. *Anat Rec.* 2014;297:1208–1217.

65. Hall BK. Immobilization and cartilage transformation into bone in the embryonic chick. *Anat Rec.* 1972;173:391–404.
66. Vinkka H. Secondary cartilages in the facial skeleton of the rat. *Proc Finn Dent Soc.* 1982;78:36–39.
67. Copray JCVM, Dibbets JMH, Kantomaa T. The role of condylar cartilage in the development of the temporomandibular joint. *Angle Orthod.* 1988;58:369–380.
68. Carlson DS. Growth of the temporomandibular joint. In: Zarb GA, Carlsson GE, Sessle BJ, Mohl ND, eds. *Temporomandibular Joint and Masticatory Muscle Disorders.* Copenhagen: Munksgaard; 1994:128–155.
69. Hinton RJ, Carlson DS. Regulation of growth in the mandibular condylar cartilage. In: Carlson DS, ed. *Control mechanisms of craniofacial development and growth*; 2005:209–218. Semin Orthod; ;11(4).
70. Enomoto A, Watahiki J, Nampo T, Ichikawa Y, Tachikawa T, Maki K. Mastication markedly affects mandibular condylar cartilage growth, gene expression, and morphology. *Am J Orthod Dentofac Orthop.* 2014;146(3):355–363.
71. Hinton RJ, Carlson DS. Histological changes in the articular eminence and mandibular fossa during growth of the rhesus monkey (*Macaca mulatta*). *Am J Anat.* 1983;166:99–116.
72. Carlson DS, McNamara Jr JA, Jaul DH. Histological analysis of the growth of the mandibular condyle in the rhesus monkey (*Macaca mulatta*). *Am J Anat.* 1978;151:103–117.
73. Wright DM, Moffett BC. The postnatal development of the human temporomandibular joint. *Am J Anat.* 1974;141:235–250.
74. Hinton RJ, Serrano M, So S. Differential gene expression in the perichondrium and cartilage of the neonatal mouse temporomandibular joint. *Ortho Craniofac Res.* 2009;12:168–177.
75. Hinton RJ. Genes that regulate morphogenesis and growth of the temporomandibular joint: a review. *Dev Dyn.* 2014;243:864–874.
76. Öberg T, Carlsson GE, Fajers CM. The temporomandibular joint. A study on human autopsy material. *Acta Odontol Scand.* 1971;29:349–384.
77. Carlsson GE, Öberg T. Remodeling of the temporomandibular joint. *Oral Sci Rev.* 1974;6:53–86.
78. Lubsen CC, Hansson TL, Nordstrom BB, et al. Histomorphometric analysis of cartilage and subchondral bone in mandibular condyles of young human adults at autopsy. *Arch Oral Biol.* 1985;30:129–136.
79. Lubsen CC, Hansson TL, Nordstrom BB, et al. Histomorphometry of age and sex changes in mandibular condyles of young human adults. *Arch Oral Biol.* 1987;32:729–733.
80. Dibbets JMH, Carlson DS. Implications of temporomandibular disorders for facial growth and orthodontic treatment. *Semin Orthod Temporomandibular Jt Disord: Facts Fallacies.* 1995;1(4):258–272.
81. Dechow PD, Carlson DS. Development of mandibular form: phylogeny, ontogeny and function. In: McNeill C, ed. *Science and Practice of Occlusion.* New Malden, UK: Quintessence; 1997:3–22.
82. Petrovic A, Stutzmann J, Oudet C. Control processes in the postnatal growth of the condylar cartilage. In: McNamara Jr JA, ed. *Determinants of Mandibular Form and Growth.* Ann Arbor, MI: Center for Human Growth and Development; 1975:101–154. Craniofacial Growth Series;.
83. Petrovic A. Control of postnatal growth of secondary cartilages of the mandible by mechanisms regulating occlusion. Cybernetic model. *Trans Eur Orthod Soc.* 1974;69–75.
84. McNamara JA, Carlson DS. Quantitative analysis of temporomandibular joint adaptations to protrusive function. *Am J Orthod.* 1979;76:593–611.
85. Petrovic A. Experimental and cybernetic approaches to the mechanism of action of functional appliances on mandibular growth. In: McNamara Jr JA, Ribbens KA, eds. *Malocclusion and the Periodontium.* Ann Arbor, MI: Center for Human Growth and Development; 1985:213–268. Craniofacial Growth Series;.
86. Carlson DS. Theories of craniofacial growth in the postgenomic era. In: Carlson DS, ed. *Control Mechanisms of Craniofacial Development and Growth*; 2005:172–183. Semin Orthod; ;11(4).
87. Visnapuu V, Peltomaki T, Ronning O, et al. Distribution of fibroblast growth factors (FGFR-1 and -3) and platelet-derived growth factor receptors (PDGFR) in the rat mandibular condyle during growth. *Orthod Craniofac Res.* 2002;5:147–153.
88. Ramirez-Yanez GO, Young WG, et al. Influence of growth hormone on the mandibular condylar cartilage of rats. *Arch Oral Biol.* 2004;49:585–590.
89. Visnapuu V, Peltomaki T, Ronning O, et al. Growth hormone and insulin-like growth factor-I receptors in the temporomandibular joint of the rat. *J Dent Res.* 2001;80:1903–1907.
90. Rabie ABM, She TT, Hägg U. Functional appliance therapy accelerates and enhances condylar growth. *Am J Orthod Dentofacial Orthop.* 2003;123(1):40–48.
91. Chu FT, Tang GH, Hu Z, Qian YF, Shen G. Mandibular functional positioning only in vertical dimension contributes to condylar adaptation evidenced by concomitant expressions of L-Sox5 and type II collagen. *Arch Oral Biol.* 2008;53:567–574.
92. Owtad P, Park JH, Shen G, Potres, Darendelier MA. The biology of TMJ growth modification: a review. *J Dent Res.* 2013;92(4):315–321.
93. Xue F, Wong RWK, Rabie ABM. Genes, genetics, and Class III malocclusion. *Orthod Craniofac Res.* 2010;13:69–74.
94. Fuentes MA, Opperman LA, Buschang P, et al. Lateral functional shift of the mandible: Part II. Effects on gene expression in condylar cartilage. *Am J Orthod Dentofac Orthop.* 2003;123:160–166.
95. Hajjar D, Santos MF, Kimura ET. Propulsive appliance stimulates the synthesis of insulin-like growth factors I and II in the mandibular condylar cartilage of young rats. *Arch Oral Biol.* 2003;48:635–642.
96. Rabie ABM, Hagg U. Factors regulating mandibular condylar growth. *Am J Orthod Dentofac Orthop.* 2002;122:401–409.
97. Tang GH, Rabie ABM, Hagg U. Indian hedgehog: a mechanotransduction mediator in condylar cartilage. *J Dent Res.* 2004;83:434–438.
98. Enlow DH, Harris DB. A study of the postnatal growth of the human mandible. *Am J Orthod.* 1964;50:25.
99. Buschang PH, Julien K, Sachdeva R, et al. Childhood and pubertal growth changes of the human symphysis. *Angle Orthod.* 1992;62:203–210.
100. Buschang PH, Santos Pinto A. Condylar growth and glenoid fossa displacement during childhood and adolescence. *Am J Orthod Dentofac Orthop.* 1998;113:437–442.
101. Björk A, Skieller V. Facial development and tooth eruption. An implant study at the age of puberty. *Am J Orthod.* 1972;62:339–383.
102. Spady M, Buschang PH, Demirjian A, et al. Mandibular rotation and angular remodeling during childhood and adolescence. *Am J Hum Biol.* 1992;4:683–689.
103. Wang M, Buschang PH, Behrents R. Mandibular rotation and remodeling changes during early childhood. *Angle Orthod.* 2009;79:271–275.
104. Moorrees CFA, Grøn AM, Lebret LML, et al. Growth studies of the dentition: a review. *Am J Orthod.* 1969;55:600–616.
105. Moyers RE, van der Linden PGM, Riolo ML, et al. *Standards of Human Occlusal Development.* Ann Arbor, MI: Center for Human Growth and Development; 1976.
106. Behrents RG. Growth in the Aging Craniofacial Skeleton. In: *Craniofacial Growth Series.* Ann Arbor, MI: Center for Human Growth and Development, University of Michigan; 1985. Monograph #17.
107. Bishara SE, Treder JE, Jakobsen JR. Facial and dental changes in adulthood. *Am J Orthod Dentofacial Orthop.* 1994;106:175–186.
108. Sarnat BG. Eye and orbital size in the young and adult. *Ophthalmologica.* 1982;185:74–89.
109. Kim YE, Nanda RS, Sinha PK. Transition of molar relationships in different skeletal growth patterns. *Am J Orthod Dentofac Orthop.* 2002;121:280–290.
110. Buschang PH, Gandini Jr LG. Mandibular skeletal growth and modeling between 10–15 years of age. *Eur J Orthod.* 2002;24:69–79.
111. Dibbets JMH. Mandibular rotation and enlargement. *Am J Orthod Dentofac Orthop.* 1990;98(1):29–32.
112. McNamara Jr JA. Components of class II malocclusion in children 8–10 years of age. *Angle Orthod.* 1981;51:177–202.

113. Buschang PH, Martins J. Childhood and adolescent changes of skeletal relationships. *Angle Orthod.* 1998;68:199–208.
114. Driscoll-Gilliland J, Buschang PH, Behrents RG. An evaluation of growth and stability in untreated and treated subjects. *Am J Orthod Dentofac Orthop.* 2001;120:588–597.
115. Carlson DS. Biological rationale for early treatment of dentofacial deformities. *Am J Orthod Dentofac Orthop.* 2002;121(6):554–558.
116. Buschang PH. Chapter 6, Section I: The development, phenotypic characteristics and etiology of Class II malocclusion. In: Araujo EA, Buschang PH, eds. *Recognizing and Correcting Development Malocclusions – A Problem-Oriented Approach to Orthodontics.* Hoboken, New Jersey: Wiley Blackwell; 2015.
117. Buschang PH. Chapter 7. Section I:The development, phenotypic characteristics and etiology of Class III malocclusion. In: Araujo EA, Buschang PH, eds. *Recognizing and Correcting Development Malocclusions – A Problem-Oriented Approach to Orthodontics.* Hoboken, New Jersey: Wiley Blackwell; 2015.
118. Driscoll-Gilliland J, Buschang PH, Behrents RG. An evaluation of growth and stability in untreated and treated subjects. *Am J Orthod Dentofac Orthop.* 2001;120:588–597.
119. Carlson DS. Biological rationale for early treatment of dentofacial deformities. *Am J Orthod Dentofac Orthop.* 2002;121(6):554–558.
120. Carlson DS. Evolving concepts of heredity and genetics in orthodontics. *Am J Orthod Dentofac Orthop.* 2015;148(6):922–938.

3

Genetics and Orthodontics

James Kennedy Hartsfield, Jr. and Lorri Ann Morford

OUTLINE

Malocclusion arises from the combined interactions of genetic and environmental factors on the developmental pathway(s) involved in the formation of the orofacial region. Orthodontists can become best equipped to understand why some patients develop certain occlusions when they gain a solid foundational understanding of genetics. This will be especially important in the future application of genome information to patient care.[1] The consideration of family history and known genetic factors in the diagnosis and treatment planning of malocclusion is essential; especially because there are genetic influences on virtually all aspects of dental and facial growth and development. Therefore to maximize the chance of successful treatment outcomes, there are two key considerations: (1) properly identify the cause of the problem before attempting treatment and/or (2) identify the factors that will influence the treatment outcome. The factors involved in the cause of a malocclusion may not be the same factors that would influence the treatment outcome. Knowing whether the cause of the problem is "genetic" has been cited as a factor in eventual outcome; that is, if the problem is genetic, then orthodontists may be limited in what they can do (or change).[2-4] However, this concept has often been misapplied. In the orthodontic literature, for example, there are many inappropriate uses of heritability estimates as a proxy for evaluating whether a malocclusion or some anatomic morphology is of "genetic origin." As will be explained in this chapter, heritability estimates have no relevance to the question of the genetic influence on a specific malocclusion in a particular patient. The greatest concern for the clinician should be how specific genetic factors will influence a patient's responsiveness to environmental factors (including orthodontic treatment and the long-term stability of its outcome) as determined by studies of genetic markers, or gene sequences, and their impact on the proteins they encode or influence.[1,5]

ETIOLOGY

Consideration of the potential cause(s) of a malocclusion requires careful contemplation of the following:

1. Most problems in orthodontics (or any outcome of growth and development), unless acquired by trauma, are not strictly the result of only genetic or only environmental factors.[6] Growth is the result of the interaction of genetic and environmental factors over time.[7,8]
2. Many studies examining the genetics of craniofacial growth are analyses of heritability. Heritability studies estimate the proportion of the total phenotypic variation, for a quantitative trait, that can be attributed to genetic differences among individuals within the specific population being examined up to the time of the analysis. Heritability studies *do not* determine the type of genetic influences or their mode of inheritance, that is, whether the trait is a single gene (monogenic) trait or a complex trait[5] with the effects of multiple genetic and environmental factors.
3. Even if a patient's craniofacial growth is influenced heavily by one gene (i.e., monogenic in familial skeletal Class III) as opposed to multiple genetic factors, there is no guarantee that future growth will necessarily or absolutely be predetermined. Nor does it mean that growth will proceed on a particular immutable track, although traits with a monogenic influence may be less amenable to environmental (treatment) intervention than traits influenced by multiple genes. Orthodontic treatment itself is an environmental factor that can move the teeth within the hard and soft tissue envelope, but to what extent it can influence growth is difficult to determine. This is because it is impossible to really know exactly how much growth would have happened in the individual without treatment, even if compared with an untreated identical twin.

4. A patient's biological responsiveness to a particular environmental factor (e.g., orthodontic treatment) does not necessarily depend on any prior interactions of genetic and environmental factors, but rather on the individual's biological responsiveness to the orthodontic treatment. The final outcome of orthodontic treatment will be a function of the overall interactions among: the gene products generated from genetic factors that are expressed (or not expressed) during the treatment time, combined with any other environmental factors present during the treatment time, against the backdrop of the developmental maturity of the individual.[9-12] The most important and practical questions regarding orthodontics and genetics, however, lay in the determination of whether different patients respond to a specific type of orthodontic treatment in dissimilar ways because of the influence of their "unique" genetic makeups.[1]

BACKGROUND AND BASIC DEFINITIONS

Before proceeding, a few basic genetic definitions and concept descriptions are required. An organism's *genome* is defined as the complete set of genetic instructions for that organism. The Human Genome Project (HGP), completed in April 2003, was instrumental in helping us understand more about the overall size and complexity of the human genome. We learned that the human genome is made up of a double helix of deoxyribonucleic acid (DNA) composed of ~3.2 billion chemical nucleotide base pairs within nearly every cell of the body.[13] The genetic instructions, or DNA code(s), are created by the linear pattern, order, and number of adenine (A), thymine (T), cytosine (C), and guanine (G) bases along the paired double helix, where A base pairs with T in the double-helical structure and C base pairs with G (Fig. 3.1). This genetic information is normally organized into smaller units (ranging in length from ~50 to 250 million base pairs each) called *chromosomes.*[13] A chromosome is made up of a continuous stretch of the double-helical DNA that is wrapped around proteins that are called *histones. Histones* enable the DNA units to be tightly packed into the nucleus of our cells, and they play an important role in regulating when and where our cells will use portions of the genetic information contained in the genome.[14]

Altogether, we each inherit a total of 46 chromosomes: 22 *homologous pairs* of chromosomes called *autosomes* that are numbered by size and other characteristics, along with one pair of *sex chromosomes* that are homologous (X, X) in females and only partly homologous (X, Y) in males (Fig. 3.2). *Homologous chromosomes* are units of genetic material that are similar in size and structural features. Upon conception, a person inherits all 46 chromosomes (22 autosomal pairs total and one pair of sex chromosomes) that make them a unique individual; one chromosome for each autosomal pair is contributed by each parent and one sex chromosome originates from each parent. Chromosomes in all subsequent cells are copies of the original maternal or paternal chromosomes.

Looking closer at the chromosomes, they are further organized into smaller units called *genes,* which represent the smallest physical and functional unit of inheritance. A *gene* can be defined as the complete DNA sequence that codes for the synthesis of a specific polypeptide (protein) via a messenger RNA intermediate (mRNA) (Fig. 3.3) or the synthesis of a specific RNA molecule, such as transfer RNA (tRNA), ribosomal RNA (rRNA), and noncoding regulatory RNA molecules such as microRNA (miRNA), or long noncoding RNA (lncRNA).[15] Each person normally inherits two copies of every gene within the genome: one gene copy on the autosome or sex chromosome of maternal origin, and the other gene copy on the autosome or sex chromosome of paternal origin, although the X chromosome has more genes than the Y chromosome. Based on the findings of the HGP, we have learned that: (1) there are an estimated 20,500 to 25,000 genes in the human genome; (2) our genes only make up 2% of the whole genome; and (3) the average gene is 3000 nucleotide base pairs in length.[13]

Within the human genome, every gene resides in a specific location referred to as a *locus* (Fig. 3.4). The term *locus* is used when describing a single genetic region or location, while the term *loci* is the plural form. Genes at the same locus on a pair of homologous chromosomes are called *alleles.* One allele would be a copy of the maternal allele, and the other would be a copy of the paternal allele. If these alleles are not identical, they can produce different polypeptide (protein) sequences and possibly diverse effects. When a pair of alleles are identical in DNA

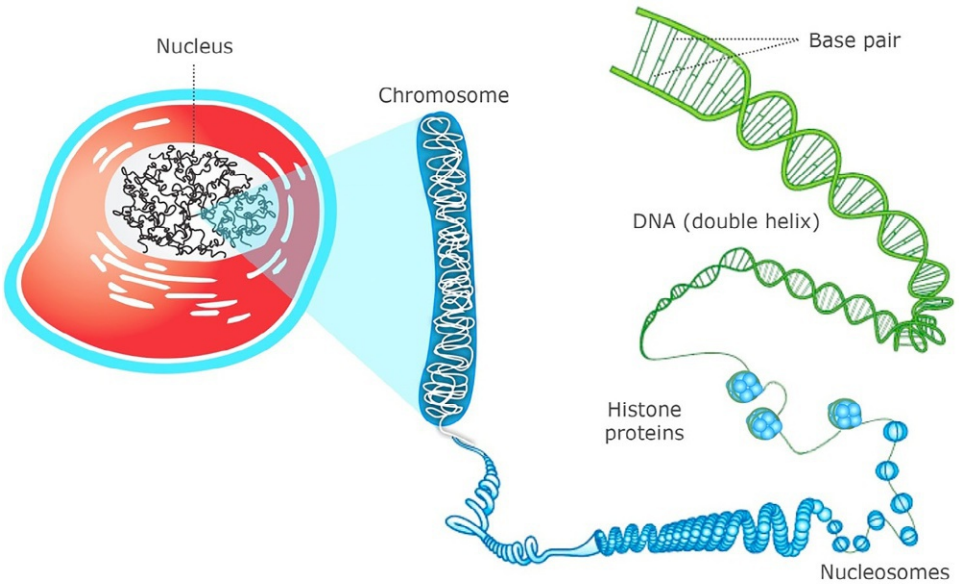


Fig. 3.1 Diagram of a human cell, enlarged chromosome, DNA wrapped around histones, the DNA double helix structure, and base pairing, such that adenine *(A)* pairs with thymine *(T),* and cytosine *(C)* pairs with guanine *(G).* (From The University of Waikato Te Whare o Wāikato | *www.sciencelearn.org.nz*. With permission.)

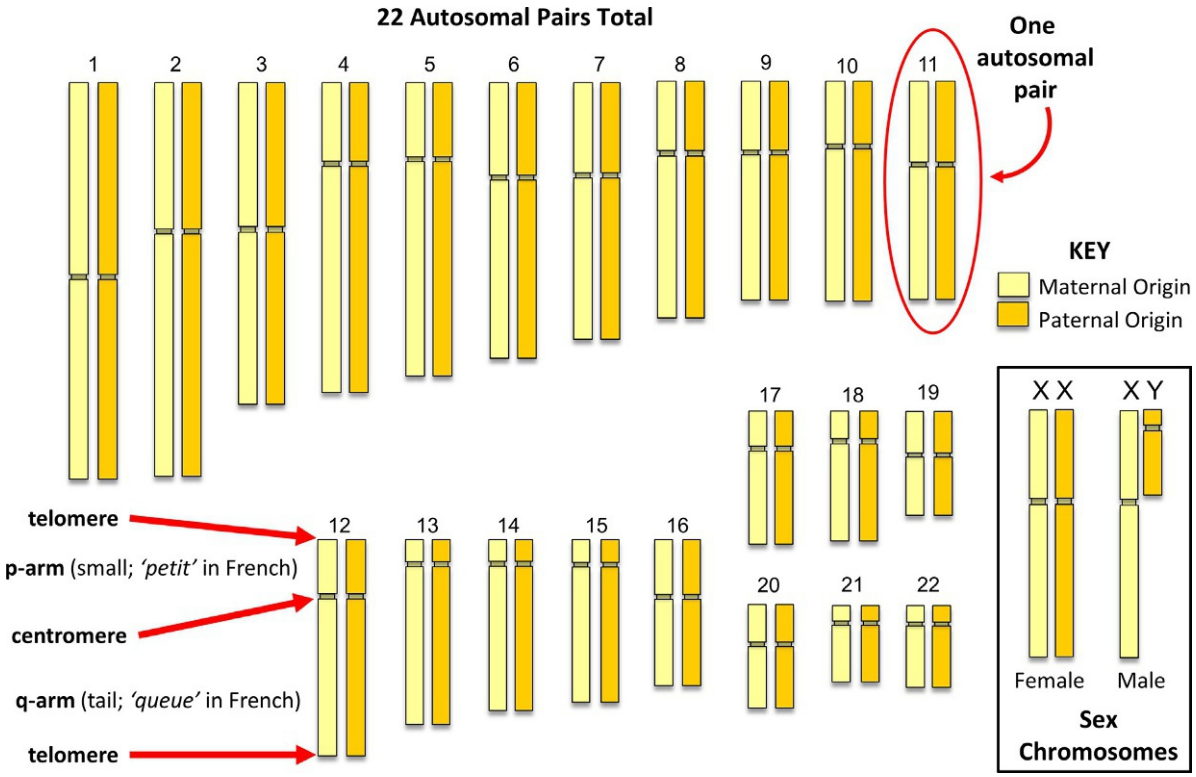


Fig. 3.2 Diagram of human chromosomes.

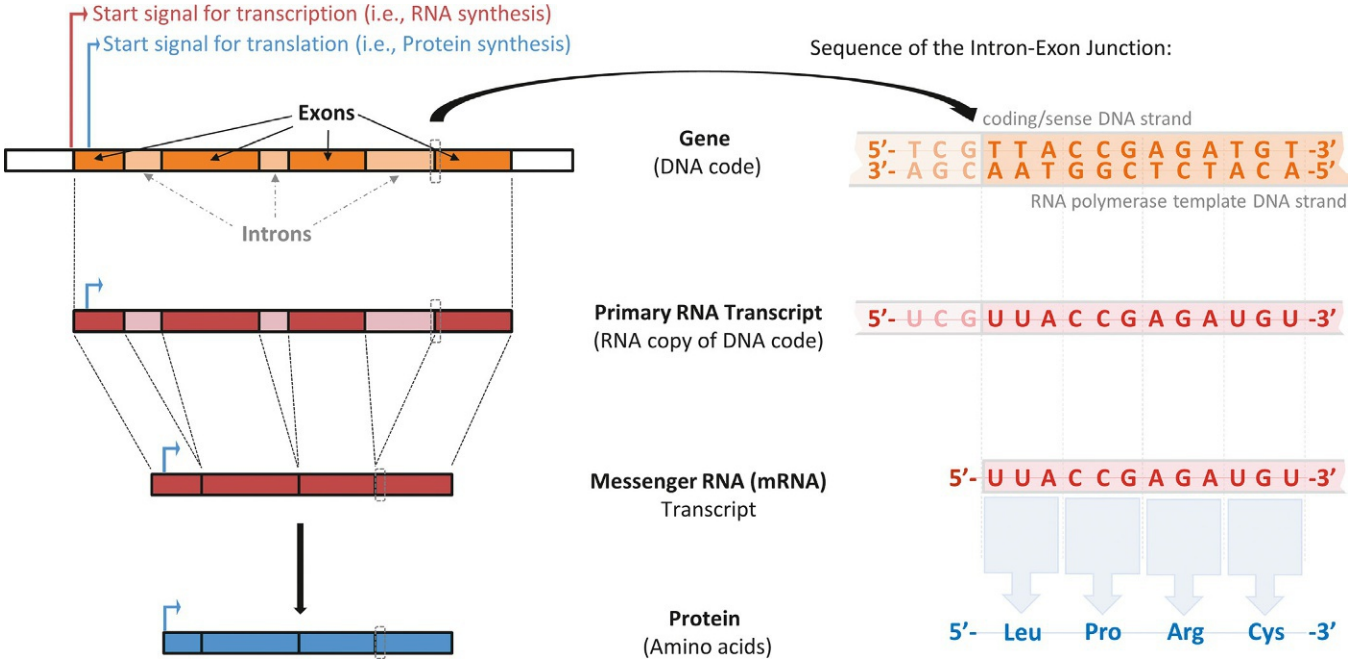


Fig. 3.3 **An illustration of how protein is synthesized from DNA.** A gene contains all of the instructions in the DNA code to make a protein. Within our cells, the DNA instructions are transcribed (copied) into a primary RNA transcript by an enzyme called *RNA polymerase*. The RNA transcript is processed to form a messenger RNA (mRNA) template that contains only the information that was originally coded in the gene's exon sequences (i.e., removal of the intron information). Then, the code for the mRNA template is read (translated) by ribosome complexes in our cells, and protein is synthesized out of amino acids based on the information found in the mRNA.

sequence (e.g., allele *A* and allele *A*), the individual is said to be *homozygous* for that locus. However, when the two alleles have one or more differences in the DNA sequence (e.g., allele *A* and allele *a*), the individual is said to be *heterozygous* for that locus. A *genotype* generally refers to the combination of alleles at a given locus within the genome (e.g., *AA*, *Aa*, or *aa*). A person's *genotype* cannot be seen with our eyes but must be determined with the use of a genetic test or analysis.

According to the information gained in the HGP, we now know that the human genome is ~99.9% identical from one person to another.[13] Thus there is only an estimated 0.1% variation within the entire DNA

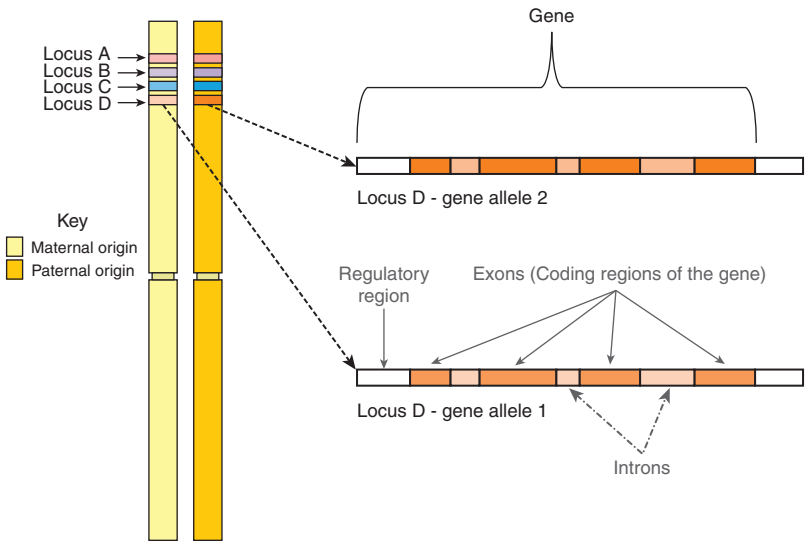


Fig. 3.4 One autosomal pair of chromosomes illustrating the concepts of four unique gene loci contained on the autosomal pair, multiple alleles, and the general structure of a gene.

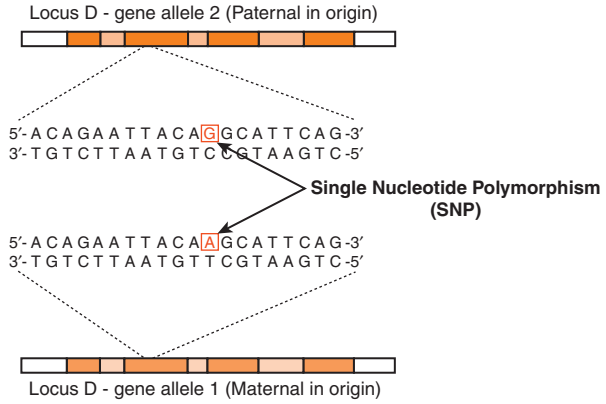


Fig. 3.5 An example of a single-nucleotide polymorphism (SNP).

code between two people that makes each individual unique. So how does this translate to the level of the gene or individual nucleotide? Homologous genes that exhibit more than one allele will vary from each other at the DNA sequence level as a result of either normal inherited variations or sporadic mutations. The most common inherited variation or sporadic mutation in the human genome is called a *single-nucleotide polymorphism* (SNP; pronounced *Snip*) (Fig. 3.5). The term *SNP* describes the occasion when more than one nucleotide base (A, T, C, or G) can be inherited at a specific location in the DNA code upon comparing the DNA codes at that same position among many individuals. There are over 10 million SNPs that have been identified in the human genome to date, with ~1 SNP occurring every 300 nucleotides.[13,16] Three basic categories of SNPs exist: (1) intergenic SNPs located in between genes, (2) intragenic SNPs located within the intron regions of a gene, and (3) gene coding region SNPs, which lie within an amino acid coding (exon) region of a gene. Coding region SNPs are further divided into (a) synonymous SNPs in which the variation does not lead to an amino acid change in the protein encoded by the gene, and (b) nonsynonymous SNPs in which the variation results in an amino acid change. More in-depth information on the three basic categories of SNPs; how SNPs and other genetic variations and mutations affect protein coding; and linkage disequilibrium (how DNA is inherited) can be found in the online supplement section. Additional information pertaining to genes, SNP location, SNP minor allele frequency (MAF) by ethnic group, and the biological impact of gene variations is also available online at the National Center for Biotechnology Information (NCBI) website (http://www.ncbi.nlm.nih.gov/gene/) and the Genome Data Viewer that incorporated the previous 1000 Genomes Browser (https://www.ncbi.nlm.nih.gov/genome/gdv/browser/genome/?id=GCF_000001405.25). Different types of sporadic or inherited variations in the DNA code can also arise as a result of variable number tandem repeats (VNTRs; i.e., microsatellites, simple sequence repeats, short tandem repeats), gene or region duplications, insertions or deletions of a small segment of DNA sequence, inversions of the DNA sequence, translocation of a segment of the DNA sequence, or base-pair changes.

DNA variations are examined and analyzed using numerous methodologies. Large abnormalities in chromosome structure can be studied via karyotyping or genomic hybridization, which are methods that can detect insertions, deletions, translocations, and whole chromosome deletions or duplications. Smaller-scale variations can be studied: (1) within families by linkage analysis or association analysis (i.e., trios of mother, father, and child), and (2) within large populations of unrelated individuals of the same ethnic background by association analysis. Because there is some natural variation in the occurrence of genetic polymorphisms among groups of people, control groups should be from individuals with a similar ethnic background so differences between affected and nonaffected individuals may reflect an association of the genetic variant with the phenotype of interest and not a difference in ethnicity. Thus population stratification (or population structure) may confound the results of genetic association studies, although there are methods to adjust for this. This consideration may be important when comparing an affected sample from a minority group to a nonminority control group, or vice versa.[17] Additional information on different inheritance patterns of genetic information by race or ethnicity can be found in the online supplement section. These types of studies may specifically (1) assay a limited number of genetic markers within a candidate gene/loci; (2) assay millions of genetic markers (i.e., SNPs or VNTRs that have also been termed *microsatellite markers*) in genome-wide association study (GWAS) arrays; or (3) involve different forms of next-generation (Next-Gen) sequencing such as targeted DNA sequencing, whole exome sequencing (WES), or whole genome sequencing (WGS).[1] Although the cost of generating DNA sequence data has decreased dramatically, facilitating the use of large-scale

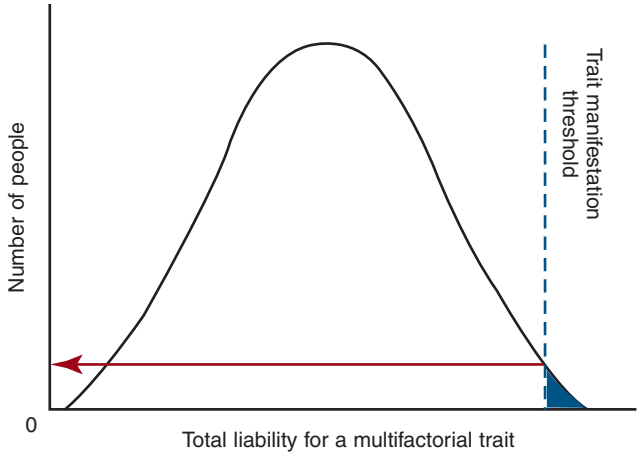


Fig. 3.6 The liability to have a multifactorial trait is influenced by multiple genes and environmental factors that are distributed throughout a population. However, if some of the population members do not have the trait and others do, then there is a threshold on which a member of the population who has a particular susceptibility to the trait will manifest it. If the genetic liability, environmental liability, or both increases, then the liability distribution curve shifts to the right, increasing the number of persons who are affected.

sequencing technologies for clinical care and/or research purposes, the demand for experienced bioinformaticians has grown significantly. As such, the costs of data *cleansing*, sequence analysis, and bioinformatics should also be taken into account when using these large-scale sequencing technologies.[18] Illustrations of several of these types of studies are included in the online supplement section.

In contrast with genotypes, *phenotypes* are the observable properties, measurable features, and physical characteristics of an individual.[19] A phenotype is generated by the summation of the effects arising from an individual's genotype and the environment in which the individual is developing over a period of time. A *trait* is a particular aspect or characteristic of the phenotype. Examples of traits include eye color, hair color, mandibular jaw size, and stature. When considering genetic influences on traits, it is convenient to think of two types of influence: monogenic (predominately a single gene with the possibility of other smaller genetic and environmental factors) and complex (many genetic and environmental factors). Information from a numbered database/catalog of human traits, syndromes, and genetic disorders associated with monogenic influence is available at the Online Mendelian Inheritance in Man (OMIM) website (http://omim.org/). Complex traits that are or are not visibly expressed and are not associated with a monogenic syndrome (e.g., nonsyndromic cleft lip-palate, neural tube defects such as spina bifida and anencephaly, or congenital hip dislocation) are also referred to as multifactorial traits where the combination of genetic and environmental factors must reach a threshold for the trait to be present in that individual (Fig. 3.6).[20] For further information, the reader is referred to the reviews by Mossey,[3,21] Abass and Hartsfield,[22] Lidral et al.,[20] and Hartsfield and Morford.[23]

TYPES OF GENETIC EFFECTS AND MODES OF INHERITANCE

It is important to understand that it is the *trait, not the gene that influences the trait,* that can be described as having a specific mode of inheritance (e.g., dominant or recessive). Why is this so? A *coding* gene is simply a set of instructions for a polypeptide (protein) sequence. Hence, a single gene could be "turned on" (i.e., *expressed*) to produce a protein that affects the development of one trait in a given tissue or area of the body at a specific time. The same gene could also be "turned on" to produce the same exact protein in a different area of the body that affects the development of a very different trait in another tissue. Any one gene or a specific gene allele, therefore, is technically not dominant or recessive; it is simply a set of instructions to be used in response to factors that influence protein production. As mentioned earlier, the same gene allele in an individual can influence more than one trait in that person, and each trait may have a different mode by which it is inherited. For example, the melanocortin 1 receptor gene (*MC1R,* OMIM *155555) produces a protein that is involved in the pigmentation of our skin, hair, and eyes. This gene is known to play an important role in the development of two different traits: freckles and red hair. Freckles (ephelides) are inherited as a dominant trait because a person only needs to have one causative copy of the *MC1R* gene to develop them.[24] On the other hand, red hair can be inherited as an autosomal recessive trait where you have two causative copies of the *MC1R* gene to develop red hair[24] or as a compound heterozygous trait that acts like a recessive trait.[25] In addition, as an example of its involvement in a complex trait, *MC1R* gene variants and their phenotype red hair color are associated with increased dental care–related anxiety, fear of dental pain, and avoidance of dental care.[26]

Monogenic Traits

As already noted, traits that develop primarily as a result of the influence of a single gene locus are termed *monogenic* traits. The traits associated within the peas that Mendel described in his inheritance studies happened to be monogenic; thus monogenic traits sometimes are called *Mendelian* traits. They can have autosomal recessive or dominant inheritance or X-linked recessive or dominant inheritance. These types of traits also tend to be described as *discrete* or *qualitative* (dichotomous or yes/no) in occurrence. However, if they are present, these traits still may be variable and quantifiable in some cases.

Autosomal Dominant Traits and Penetrance

When a trait is present as the result of only one copy of a particular allele (e.g., *A*) in a heterozygous allele pair (e.g., *Aa*), then the trait has an *autosomal dominant* inheritance. If the trait is only present when *both* alleles at the locus are the same (e.g., *aa;* in other words, the individual is homozygous for *a*), then the trait has an *autosomal recessive* inheritance. Although it is the phenotype that is dominant or recessive, and not the gene itself, the terms *dominant gene/dominant allele* and *recessive gene/recessive allele* are used commonly to describe the genes associated with these types of inherited traits in families.

The nature of these family-based (familial) traits can be studied by constructing family trees called *pedigrees* in which males are denoted by squares and females by circles, noting who in the family has the trait and who does not. Constructing a pedigree as a part of the patient's medical history is indicated when more than one member of the immediate family is affected by the trait. The practitioner should solicit and record the family history in first-degree relatives of the patient (siblings and parents), second-degree relatives (half-siblings, aunts, uncles, and grandparents), and third-degree relatives (first cousins). From this information, a pedigree like those shown in Figs. 3.7 to 3.9, 3.11, and 3.12 may be drawn. A pedigree can be used to help understand the approximate likelihood that the patient or a sibling may also develop the same trait. This can be particularly useful for monogenic traits including Class III malocclusion, hypodontia, primary failure of eruption (PFE), and developmental dental dysplasias such as types of dentinogenesis and amelogenesis imperfecta. A family history may also be useful for complex traits such as Class II/division 2, external