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## CHAPTER 2

# The Expansive Phenotype of VCFS

*E*ssentially every organ, bodily function, and behavior can be affected in VCFS. The syndrome exhibits craniofacial, heart, brain, neurologic, limb, internal organ, genitourinary, skeletal, ocular, ear, vascular, glandular, dental, and muscle anomalies. These result in impairments of development, cognition and learning, mental health, speech and language, the immune system, the respiratory system, the endocrine system and growth, and the digestive system. It is possible that the reason that the large array of specific phenotypes has been reported in association with VCFS is that many people from many separate disciplines have studied the disorder. It is also possible that the deletion that causes the syndrome involves genes that are critical to embryonic development and postnatal function. Of course, these two factors are not mutually exclusive and both may be true. What is easy to understand is that by studying VCFS, clinicians and scientists may be able to unlock some of the mysteries of how specific genomic elements result in some common human illness, both physical and mental.

The first step in the process is to understand the full expanse of the phenotype in VCFS. This next section of the text will detail the phenotype of VCFS by categories of anomalies that occur in VCFS with a frequency higher than would be expected in the general population. To date, 190 distinct anomalies or patterns of anomalies have been described.

Because VCFS has so many clinical findings, referrals to care providers tend to be based on presenting symptoms. A pediatric cardiologist and cardiothoracic surgeon are often the first contact for babies with the syndrome. Developmental delay may prompt referral to a variety of early intervention specialists including speech pathologists, physical therapists, and occupational therapists. Developmental pediatricians may be also be in the picture,

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and if seizures present, a child neurologist. Immune disorders will result in an immunology evaluation and hypocalcemia an endocrine workup. Hypernasality and articulation impairment will bring the patient to a speech pathologist and perhaps a cleft palate team and an otolaryngologist and reconstructive surgeon. If the syndrome is not known to them, each of these specialists will manage these disorders in the manner they might for others who do not have VCFS. They would also not refer the patient for additional investigations to rule out other problems associated with VCFS, such as renal anomalies, tethered spinal cord, and vascular anomalies. Each specialist would take care of his or her corner of the syndrome and may not appreciate the bigger picture. The purpose of this chapter is to describe in great detail the phenotypes associated with VCFS and how they may interrelate with other anomalies associated with the syndrome. The categories and specific anomalies associated with VCFS will be used as a template for quick referral. We will number each anomaly consecutively and the entire list will be available in the Appendix.

### CRANIOFACIAL ANOMALIES

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The following craniofacial malformations and variants have been reported in association with VCFS:

1. Palate anomalies, including overt cleft palate, submucous cleft palate, occult submucous cleft palate, deficient muscle, and asymmetric palate
2. Asymmetric pharynx
3. Platybasia
4. Retrognathia
5. Asymmetric crying facies (infancy)
6. Functional facial asymmetry
7. Structural facial asymmetry
8. Straight facial profile
9. Hypotonic facies
10. Vertical maxillary excess
11. Small primary teeth
12. Enamel hypoplasia (primary dentition)
13. Downturned oral commissures
14. Microstomia

15. Microcephaly
16. Small posterior cranial fossa
17. Cleft lip

### Palatal Anomalies

It has been reported that approximately 75% of individuals with VCFS have structural anomalies of the palate (Shprintzen, 1999; Shprintzen, 2005a) and essentially the same percentage has velopharyngeal insufficiency (Shprintzen, 1999). The anomalies of the palate in VCFS can be divided into the following types.

#### ***Overt Cleft Palate***

Overt clefts of the palate are the least common type of palate anomaly in VCFS. In a sample of 815 individuals with VCFS ascertained from our own clinical cases and from members of The Velo-Cardio-Facial Syndrome Educational Foundation, Inc. in response to a questionnaire study, we found that only 18% had overt palatal clefts (Figure 2-1), and of those, the majority were clefts of the soft palate only. Moreover, a large number of the overt clefts were part of the Robin sequence because of the association of cleft palate with retrognathia and upper airway obstruction (Williams, Shprintzen, & Goldberg, 1985).



**FIGURE 2-1.** An overt cleft of the velum.

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### ***Submucous Cleft Palate***

Nearly half of individuals with VCFS have submucous clefts of the palate (Golding-Kushner, 1991; Shprintzen, 1999) that could be detected orally by the presence of a bifid uvula with or without other stigmata such as a notch in the posterior border of the hard palate and zona pellucida (Figure 2-2). Very few individuals with VCFS have the classic triad of submucous cleft palate (bifid uvula, zona pellucida, and notched hard palate). Most have bifid uvulas or even notched or boxy uvulas (Figure 2-2) without other palatal stigmata detectable on oral examination.

### ***Occult Submucous Cleft Palate***

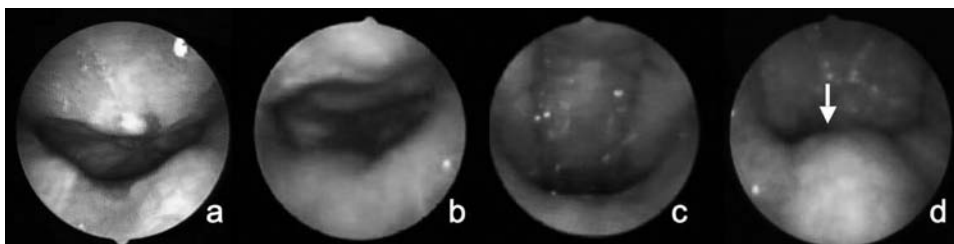
As described earlier in Chapter 1, occult submucous cleft palate was originally described in individuals obviously affected with VCFS although the syndrome had not yet been delineated (Kaplan, 1975). Occult submucous cleft palate cannot be detected without an endoscopic view of the nasal surface of the velum and this can be problematic in children with VCFS who are often



**FIGURE 2-2.** Examples of submucous cleft palate in individuals with VCFS.

fearful of nasopharyngoscopy. Because of the behavioral patterns of VCFS that can include generalized anxiety, impulsivity, and phobias, many clinicians may choose to defer, delay, or even forego nasopharyngoscopy because of the difficulty involved or their fear that they may traumatize the child. However, the importance of endoscopic examination cannot be emphasized enough. Besides showing the midline depression of the palate representing absence of the musculus uvulae, the examination can also show severely ectopic internal carotid arteries and laryngeal anomalies (Video 2-1).

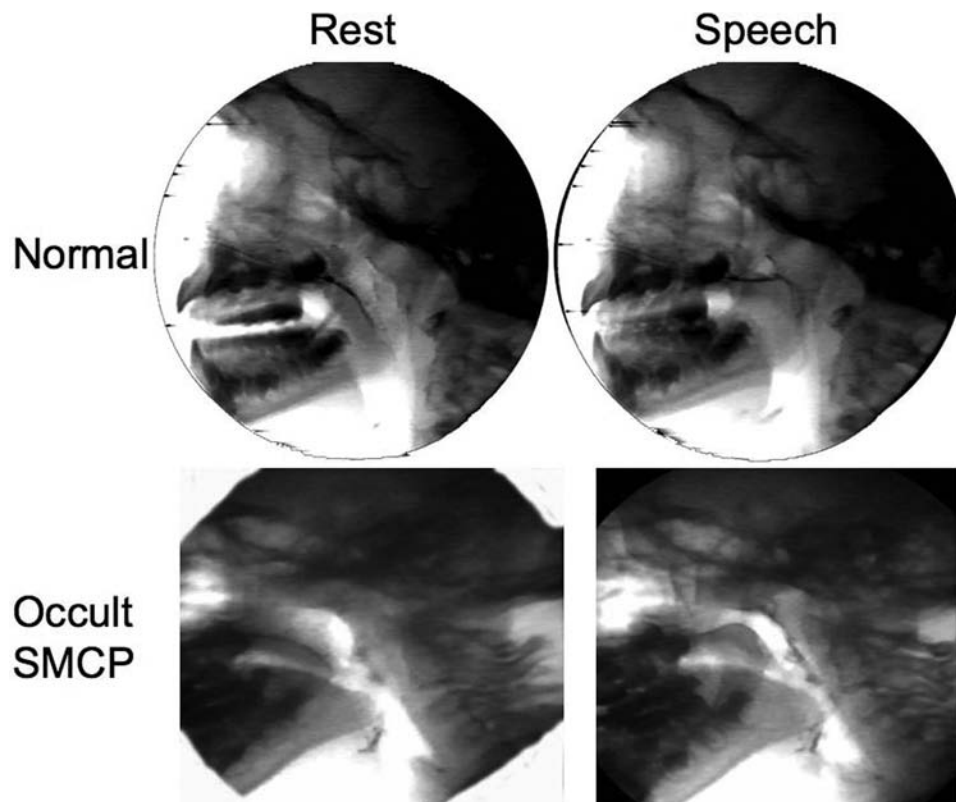
The anomalies of the velum in occult submucous cleft can be subtle, ranging from a prominent midline depression to a gentle concavity to a flat nasal surface of the velum (Figure 2-3). When seen in a lateral view videofluoroscopy, the velum is short and thin (Golding-Kushner, 1991; Shprintzen, 1982), and during speech, it does not thicken, as would a normal palate (Figure 2-4). In the normal palate, the thickening of the velum during speech is caused by the presence of the musculus uvulae (Figure 2-5). The contraction of the musculus uvulae causes it to thicken at its belly because it has no firm attachment at its distal end where it ends in the blind sac of the uvula. In VCFS, the musculus uvulae is absent so that there is no thickening of the velum with palatal motion. The shortness of the velum plus increased volume in the pharynx (to be discussed later) makes the palate appear very short and thin (Golding-Kushner et al., 1991) within the confines of a large pharynx (Video 2-2). It is also possible that the thinness of the palate often observed in VCFS (Golding-Kushner, 1991; Shprintzen, 1982) is related to generalized thinning of the pharyngeal muscles (Golding-Kushner, 1991) caused by abnormalities of the muscle fibers at the cellular level (Zim et al., 2003), rather than to a cleft, *per se*.



**FIGURE 2-3.** Endoscopic view of the nasal surface of the velum in three patients with VCFS compared to a normal individual (*right*). At the *far left* (**a**) is a child with VCFS and occult submucous cleft palate showing a deep midline groove in the velum. At *middle left* (**b**), the nasal surface of the velum in a child with VCFS and occult submucous cleft showing a gentle midline concavity, and at *middle right* (**c**) is a child with VCFS and occult submucous cleft palate with a flat velum. The normal (**d**) shows a prominent convexity in the midline of the velum (*arrow*) representing the musculus uvulae.



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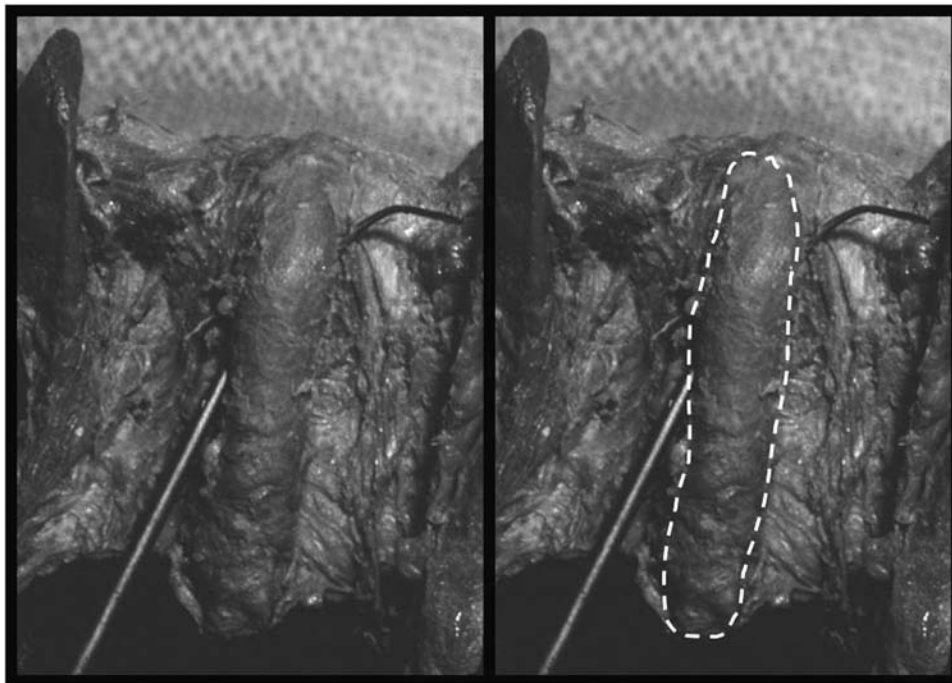


**FIGURE 2-4.** Lateral view videofluoroscopy in a 5-year-old with a normal palate (*top row*) and a 5-year-old with VCFS who has an occult submucous cleft palate (*bottom row*) at rest and during phonation of /pa-pa-pa/. Note that the normal palate thickens considerably during phonation, whereas the palate with an occult submucous cleft elevates but does not thicken at all.

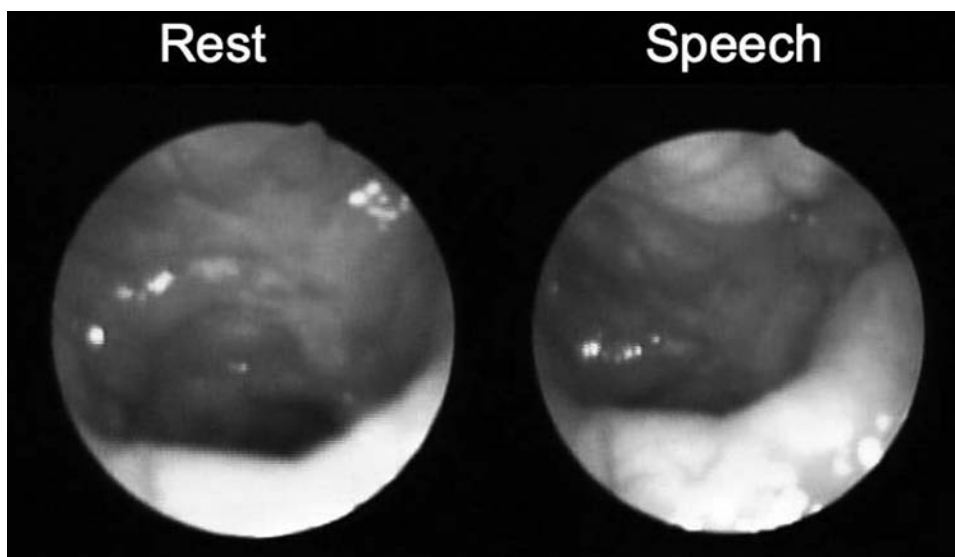
### ***Asymmetric Palate***

A more recently reported structural and functional anomaly of the palate (and pharynx) is asymmetry (Chegar, Tatum, Marrinan, & Shprintzen, 2006). In an endoscopic and fluoroscopic study of 121 subjects with VCFS, 67% were found to have asymmetric elevation (Video 2-3) of the velum during speech and the position, length, and size of the levator veli palatini was found to be asymmetric in many cases. The velar midline was also found shifted to one side or the other (Figure 2-6).

One study suggested that structural palatal anomalies occur in only 14% of cases, 9% cleft palate and 5% submucous cleft palate (Ryan et al., 1997), a clear error probably based on ascertainment parameters and a failure to recognize more subtle anomalies of velar structure. Data for the Ryan et al. study



**FIGURE 2-5.** A normal musculus uvulae in a cadaver dissection.



**FIGURE 2-6.** Asymmetric palate at rest and during speech in an individual with VCFS and occult submucous cleft palate.

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were obtained from more than 20 centers in Europe. There was no reported attempt to confirm examiner reliability or validity. Occult submucous cleft palate was not a recognized clinical finding in any cases, although it was noted that 32% had velopharyngeal insufficiency. The structural findings were not discussed. A major percentage of the sample was children ranging in age from 0 to 5 years. It is not known how many of these subjects were infants and were therefore not speaking so that velopharyngeal insufficiency could not be determined. Asymmetry of the palate was also not mentioned as a clinical finding in this study, which preceded the report of Chegar et al. (2006).

### Asymmetric Pharynx

Chegar et al. (2006) also reported that the pharynx was commonly asymmetric in VCFS. Asymmetric structure of the posterior pharyngeal wall or movement of the lateral pharyngeal walls was seen in 76% of people with VCFS (Video 2-4). Endoscopic observation showed that one side of the pharynx had more fullness than the other with the right side showing that increased fullness more frequently than the left. The increased unilateral fullness often compromised the pyriform sinus tract on that side, potentially resulting in restriction of the flow of liquids and food to the cricopharyngeus, resulting in coughing or choking. Asymmetric lateral pharyngeal wall motion (Video 2-5) is also common among cases in which there is any degree of active medial movement (most individuals with VCFS have little or no lateral wall movement).

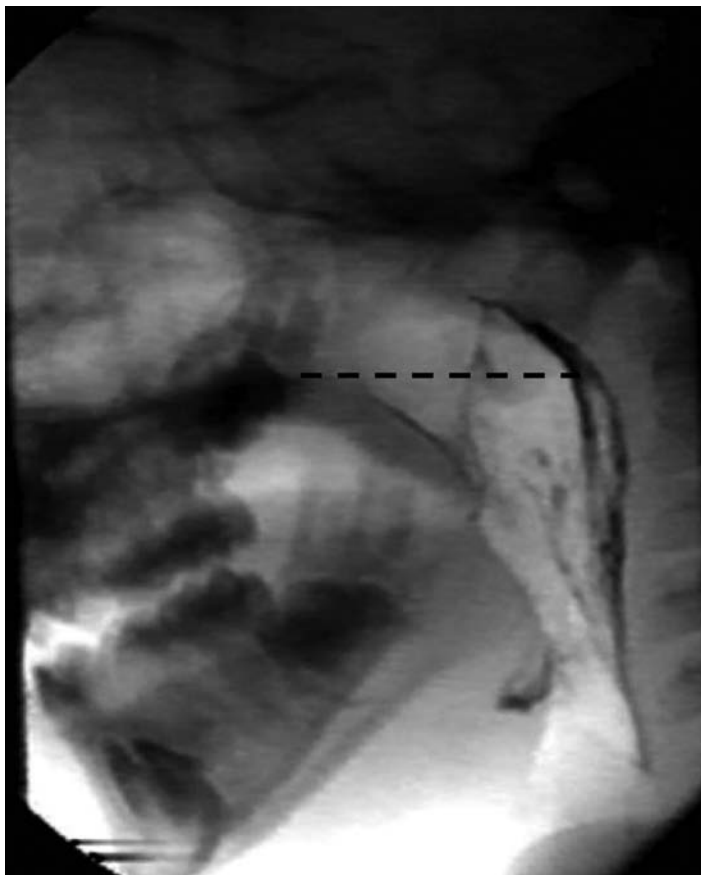
### Platybasia

Platybasia refers to an abnormally obtuse angle of the skull base. The human cranium has a flexion along the skull base that differentiates the anterior portion of the cranium that supports the facial bones and the posterior aspect that contains the posterior portions of the brain and the junction with the spinal cord (Figure 2-7). The angulation of the skull base is typically analyzed by measuring the angle from the nasion (the junction of the nasal bones to the frontal bone of the calvarium) to the sella turcica (the bony projection containing the pituitary gland) to the basion (the anteriormost point of the foramen magnum). This angle is typically about  $128^\circ$  with a standard deviation of approximately  $4^\circ$ . The implications of platybasia cut across several of the anomalies associated with VCFS by creating secondary anomalies that may not be primary gene effects. Arvystas and Shprintzen (1984) found that the skull base angulation in VCFS was significantly more obtuse than in normals and that the resulting effect on craniofacial structure is that the glenoid fossa and the temporomandibular joint are more posteriorly located than in the normal (Figure 2-7), so that the mandible is retropositioned (retrognathia). Retrognathia can lead to Robin sequence, malocclusion, and possible airway



**FIGURE 2-7.** Drawing of the human cranium showing the flexion point in the skull base.

obstruction in infancy. Arvystas and Shprintzen (1984) also found that the obtuse angulation of the skull base caused the posterior skull base to move backwards with resulting deepening of the pharynx, because the posterior pharyngeal wall is attached to the prevertebral fascia and suspended from the posterior skull base. The increase in pharyngeal depth is an additional factor in the frequency and severity of velopharyngeal insufficiency in VCFS (Figure 2-8). The posterior rotation of the skull base also causes a secondary anterior displacement of the forehead because of the counterclockwise rotation of the cranium around the flexion point at the base (Figure 2-9). With the forehead displaced anteriorly, the upper eyelids become stretched in the same direction making them look “puffy” or hooded in relation to the globe. Although the malar bones and maxillary basal bone are actually normal in VCFS, the cheeks look flat because the forehead is in a more anterior position in relation to the malar eminences. Therefore, the reported flattening of the midface in VCFS is actually an optical illusion of relative projection of structures in the profile view (Figure 2-9). At this point, it is not known if the flattening of the skull base is a primary feature of skeletal formation in VCFS or secondary

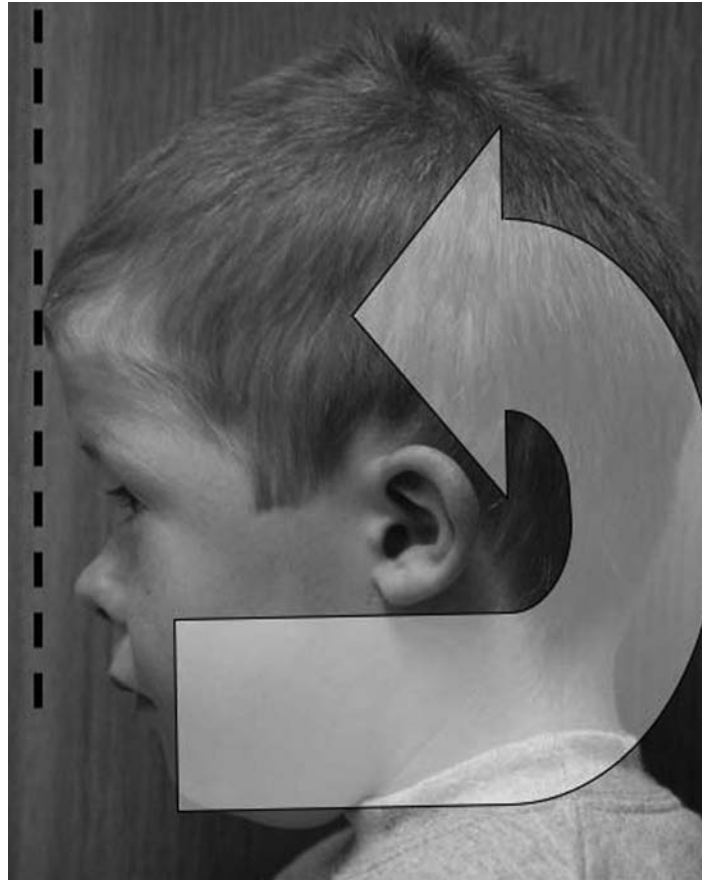
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**FIGURE 2-8.** Increased pharyngeal depth in VCFS related to platybasia.

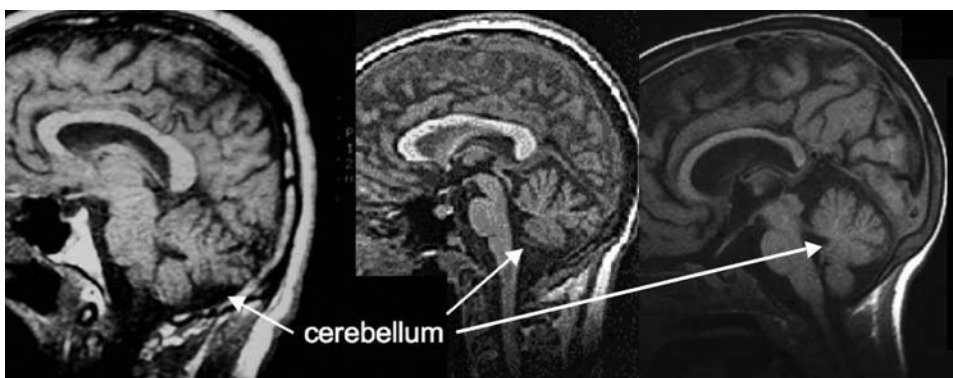
to reduced volume of the cerebellum. It is possible that cerebellar hypoplasia results in decreased pressure on the embryonic and postnatal skull base so that there is reduced mechanical force driving it forward (Figure 2-10). Skull growth is driven in part by bone growth potential, but also by the internal forces of a growing brain that are pushing the cranium from within, therefore driving growth of the bones and remodeling of their architecture based on the needed size for the brain within the cranial fossa.

### **Retrognathia**

Abnormal position of the mandible and retrusion of the chin can be caused by three different factors: micrognathia, retrognathia, and microretrognathia. Micrognathia refers to a small or hypoplastic mandible. Micrognathia can be caused by a small body of the mandible, by a short ascending ramus, or both.



**FIGURE 2-9.** Counterclockwise rotation of the cranium in VCFS resulting in anterior displacement of the forehead.



**FIGURE 2-10.** Cerebellar hypoplasia may reduce pressure on the skull base, therefore decreasing anterior movement of the posterior basicranium.

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Individuals with VCFS do not typically have micrognathia. They have retrognathia, an abnormal retruded position of the mandible. The size and architecture of the mandible are normal in VCFS (Arvystas & Shprintzen, 1984), although the chin looks retrusive. In VCFS, the abnormal position of the mandible is related to retrognathia secondary to platybasia as discussed above. Microretrognathia is the combination of a small mandible and retrognathia. Although micrognathia is not a syndromic feature of VCFS, one must keep in mind that children with VCFS also inherit all of the other genes from their parents. Their physical appearance is not completely related to the deletion. It is therefore possible for micrognathia to be inherited as a separate trait from one or both parents who may have it. It is important to distinguish between micrognathia and retrognathia because of the prognosis for future growth of the lower jaw. Micrognathia implies that the mandible has fewer cells to begin with and with time the amount and pattern of growth will remain the same or get worse. It will certainly not be normal. In retrognathia with a structurally normal mandible, normal growth should be anticipated.

### Asymmetric Crying Facies

The majority of diagnoses of VCFS are being made because there is routine screening of children born with severe conotruncal heart anomalies such as interrupted aortic arch type B, tetralogy of Fallot, and truncus arteriosus. Although individuals with VCFS constitute a large percentage of each of these major heart anomalies (50% of interrupted aortic arches, 25% of tetralogies, and over 50% of truncus cases), the majority of children with VCFS do not have these serious heart anomalies. The most common heart malformation in VCFS is ventricular septal defect, and many children with VCFS will have other more minor heart anomalies, such as atrial septal defect, aortic valve anomalies, or other aortic arch anomalies. It is also true that approximately 25–30% of children with VCFS have no congenital heart disease. Therefore, a question that is often asked is if there are any clinical features that should present as diagnostic “red flags” for VCFS in the neonatal period. One such red flag is asymmetric crying facies (Figure 2-11). Asymmetric crying facies typically refers to an abnormal lack of movement of one side of the mouth, usually the lower lip and corner of the mouth on the same side, during crying when it is most obvious. The combination of asymmetric crying facies with congenital heart disease has been referred to by some as Cayler syndrome (Cayler, 1969). It has since been learned that the association of asymmetric crying facies and congenital heart disease is most often associated with VCFS and that patients previously diagnosed with Cayler syndrome have the same 22q11.2 deletion (Bawle, Conard, Van Dyke, Czarnecki, & Driscoll, 1998). If a newborn is noted to have asymmetric crying facies in addition to chronic nasal regurgitation, VCFS becomes a highly probable diagnosis and these findings would be sufficient to warrant a FISH study.



**FIGURE 2-11.** An infant with VCFS and asymmetric crying facies.

### **Functional Facial Asymmetry**

Although asymmetric crying facies can be easy to detect in neonates, facial asymmetry may manifest itself in a more subtle manner in VCFS. Asymmetric crying facies involves an obvious lack of movement in the lower part of the face on one side. Some individuals with VCFS do not have an obvious asymmetric face during crying, but do have asymmetry of smile or normal facial animation during speech and emotional expression (Figure 2-12). Because facial expression is something that evolves over time, such minor asymmetries may not become obvious until early childhood.

### **Structural Facial Symmetry**

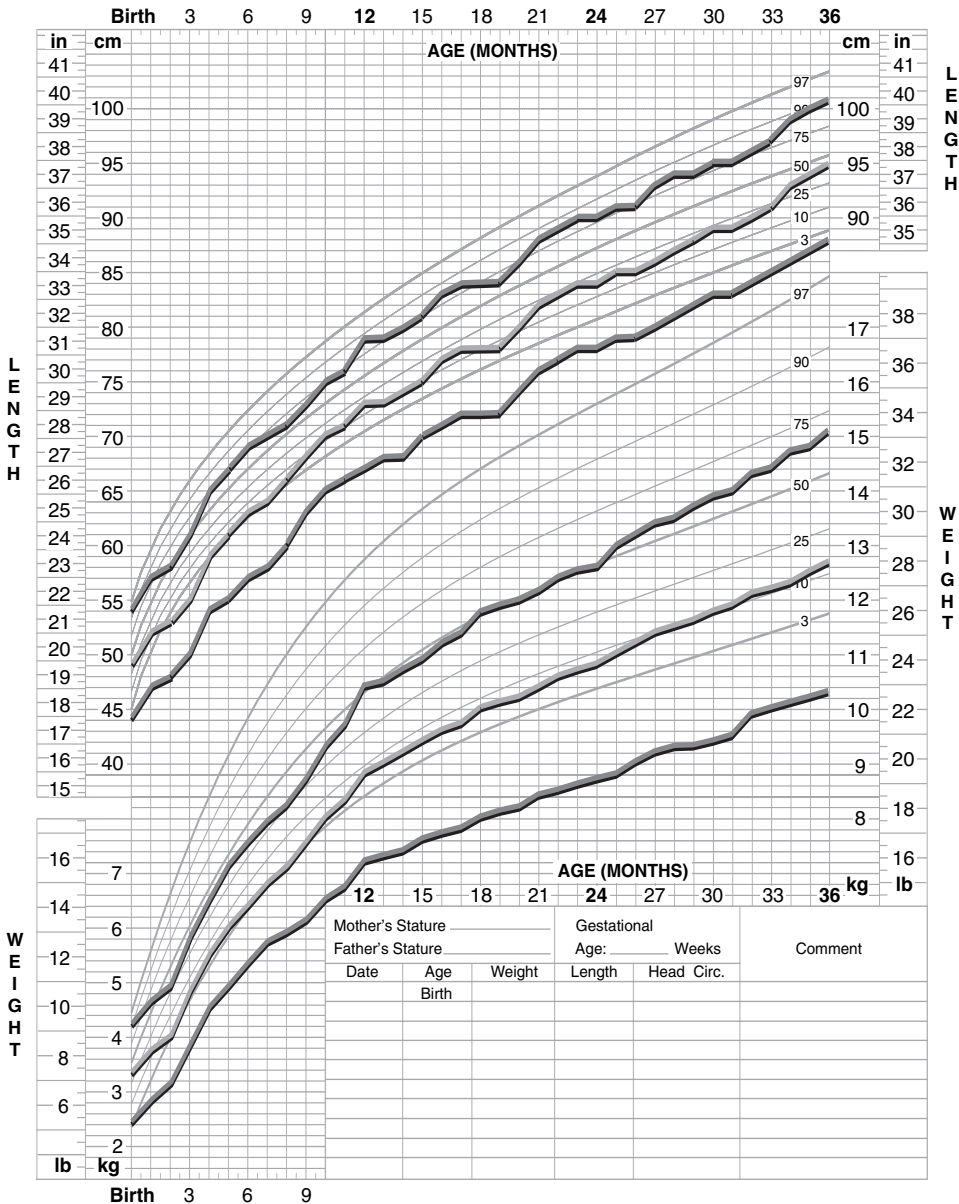
A small percentage of individuals with VCFS have asymmetry of the face that is based on skeletal growth (Figure 2-13). Although structural facial asymmetry is not a common feature of VCFS, it does occur in approximately one fifth of affected individuals (Shprintzen, 1999). Facial asymmetry is a common cranio-facial malformation and is found in oculo-auriculo-vertebral spectrum (also



**Birth to 36 months: Boys**  
**Length-for-age and Weight-for-age percentiles**

NAME \_\_\_\_\_

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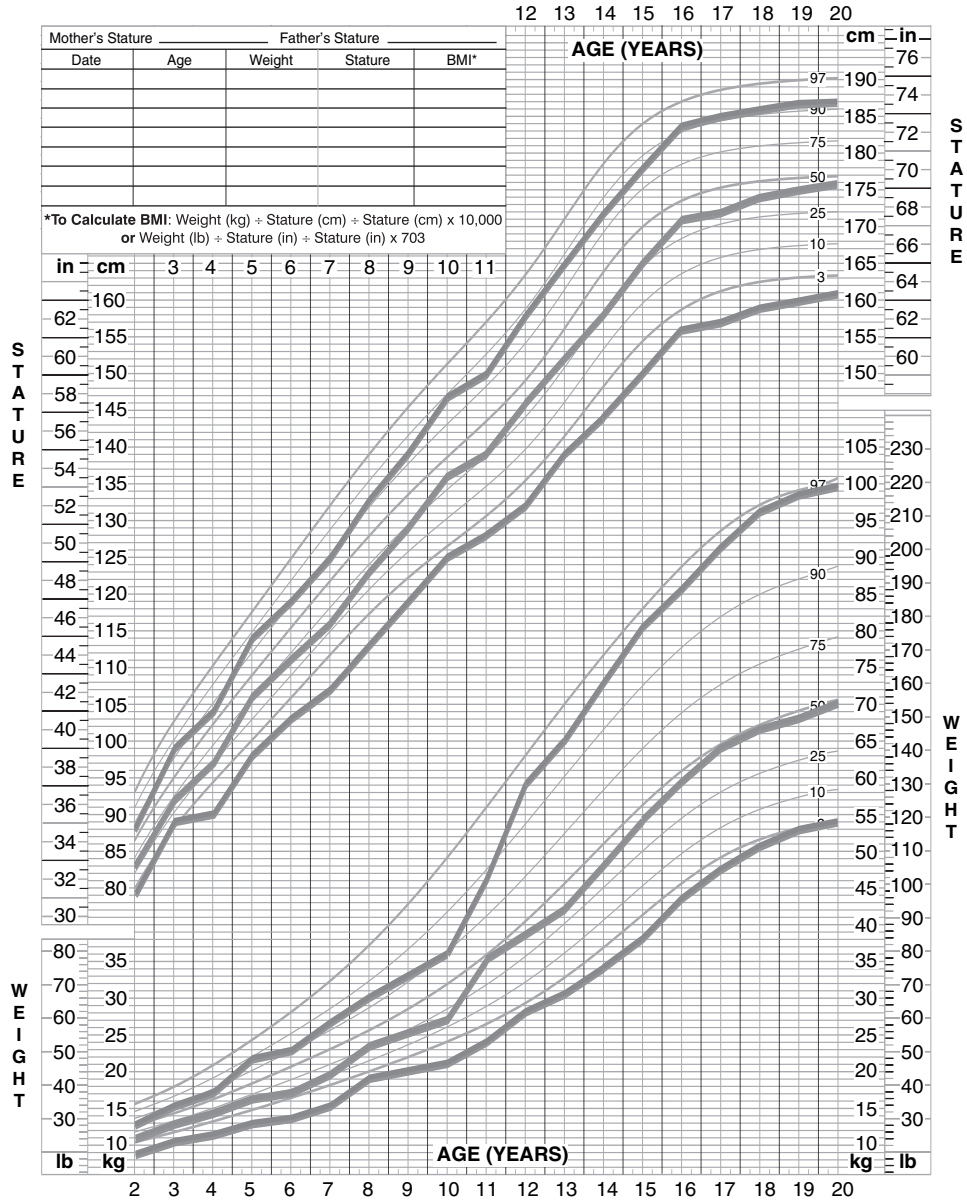
Published May 30, 2000 (modified 4/20/01).  
 SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).  
<http://www.cdc.gov/growthcharts>



**FIGURE 5-3.** Growth curves from birth to 20 years for males with VCFS superimposed over the same curves for the general population as published by the CDC. The lines for VCFS include the 50th (*middle line*), 97th (*top line*), and 3rd centiles (*bottom line*). *Note.* From National Center for Health Statistics, 2000. Available from <http://www.cdc.gov/growthcharts> *continues*

**2 to 20 years: Boys**  
**Stature-for-age and Weight-for-age percentiles**

NAME \_\_\_\_\_  
 RECORD # \_\_\_\_\_



Published May 30, 2000 (modified 11/21/00).  
 SOURCE: Developed by the National Center for Health Statistics in collaboration with  
 the National Center for Chronic Disease Prevention and Health Promotion (2000).  
<http://www.cdc.gov/growthcharts>

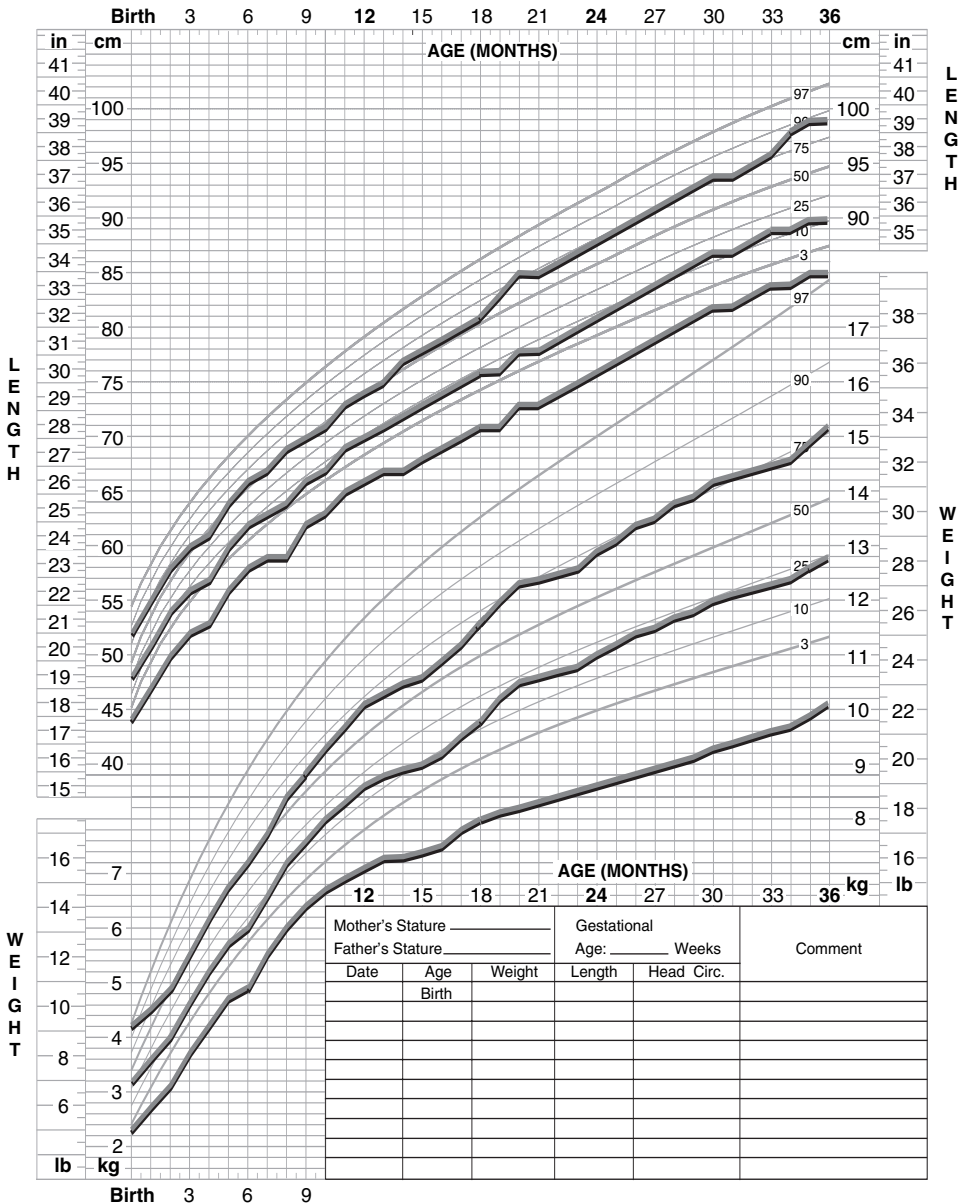


**FIGURE 5-3.** *continued*

**Birth to 36 months: Girls**  
**Length-for-age and Weight-for-age percentiles**

NAME \_\_\_\_\_

RECORD # \_\_\_\_\_



Published May 30, 2000 (modified 4/20/01).  
 SOURCE: Developed by the National Center for Health Statistics in collaboration with  
 the National Center for Chronic Disease Prevention and Health Promotion (2000).  
<http://www.cdc.gov/growthcharts>

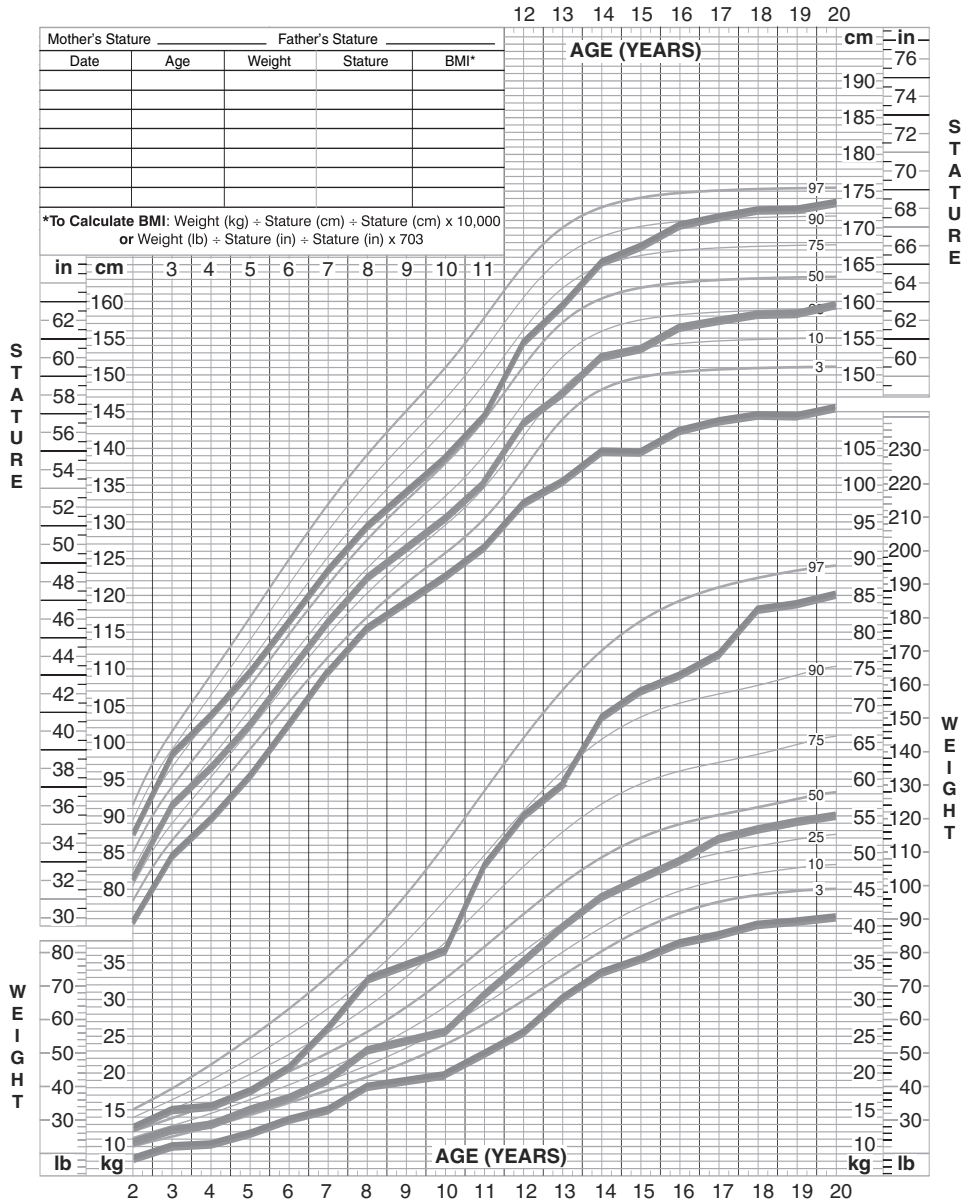


**FIGURE 5-4.** Growth curve from birth to 20 years for females with VCFS superimposed over the same curves for the general population as published by the CDC. *Note.* From National Center for Health Statistics, 2000. Available from <http://www.cdc.gov/growthcharts> *continues*

**2 to 20 years: Girls**  
**Stature-for-age and Weight-for-age percentiles**

NAME \_\_\_\_\_

RECORD # \_\_\_\_\_



Published May 30, 2000 (modified 11/21/00).  
 SOURCE: Developed by the National Center for Health Statistics in collaboration with  
 the National Center for Chronic Disease Prevention and Health Promotion (2000).  
<http://www.cdc.gov/growthcharts>



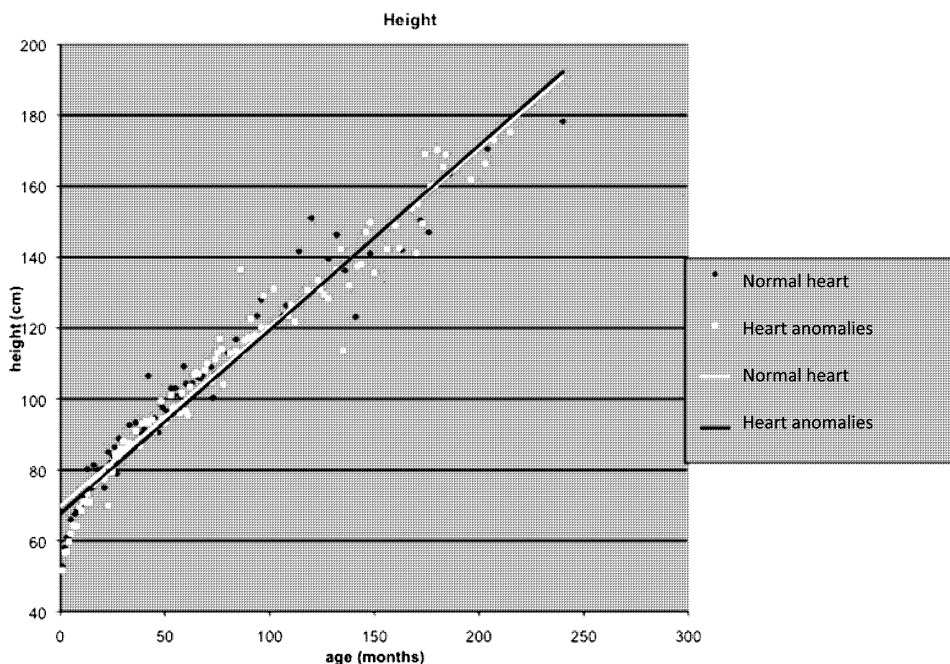
**FIGURE 5-4. continued**

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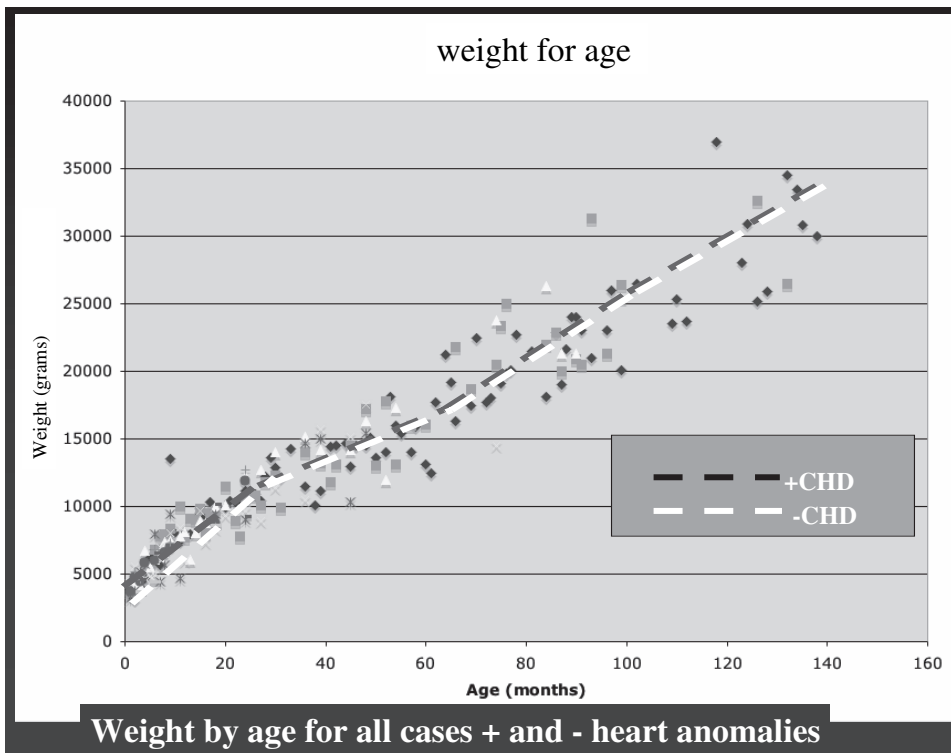
The separation of the growth data for those with and without congenital heart disease compared these two subpopulations for both growth velocity and eventual growth outcomes. With the exception of those individuals who had pulmonary atresia or stenosis, the growth velocities and expected heights were the same as for their peers with VCFS who did not have heart anomalies, except for the time prior to definitive heart repair. Prior to heart repair, those cases with more severe heart anomalies such as large ventricular septal defects lagged behind other babies with VCFS, but only until surgery. The majority of cases of tetralogy of Fallot, interrupted aortic arch, and truncus arteriosus had definitive heart surgery in the neonatal period so that there was not a long period of time with significantly abnormal perfusion.

Figure 5-5 and Figure 5-6 show height and weight profiles for children with and without heart disease. Although there is some early distance between the two samples, these are no longer present by 3 years of age when the pulmonary atresia cases are deleted from the sample.

We then asked if early feeding difficulties were predictive of growth problems and if those cases treated with alternative feeding methods such as gastrostomies or gavage feedings grew at an accelerated pace compared to other VCFS children who had feeding problems but who were only fed by mouth. Feeding problems were reported in 74% of the sample. Of those,



**FIGURE 5-5.** Height and weight profiles for males with VCFS with and without heart disease. Note that the trends for both coincide.



**FIGURE 5-6.** Height and weight profiles for females with VCFS with and without heart disease. Note that the trends for both coincide.

approximately one quarter were fed by gavage (nasogastric tubes) or gastrostomy (and its variations, including J-tubes). Almost all of these procedures were implemented for at least a year, and those with gastrostomies had them for a mean period of 3 years, ranging from 1 to 7 years. When the growth velocities of the children with alternative feeding procedures were compared to the rest of the sample, there was no difference in growth velocity or eventual outcome. We also looked at the cases with reported failure to thrive or feeding difficulties and compared them to the entire VCFS sample and also found no differences in growth velocity.

We then assessed the expected heights for the 127 adults. We found that 92% of the males in the sample were within 3 cm of their calculated expected heights. The distribution of those above expected height was essentially the same as those slightly below; three cases were within 3 cm below expected height, two were above. Of the remaining five males in the sample, one was 15 cm taller than expected, and four were between 3 cm and 7 cm shorter than expected. Of these shorter cases, three had no heart disease, and three had histories of long-term G-tube placement.

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The females in the sample did not reach expected height with the same frequency as the males and tended to be a bit shorter than their peers, but less than one standard deviation. Of the 67 females in the adult sample, 74% were within 3 cm of calculated expected height, and of those who were not, the majority were shorter than expected height. None were of severe short stature (below the 3rd centile), but a sizeable portion of the sample, 10%, were at or below the 10th centile for general population norms and were well below their predicted heights.

### **SIGNIFICANCE OF THESE DATA AND THE GROWTH CURVE**

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We have seen many children with VCFS who have had life-altering operative procedures in infancy and childhood that have had a major impact on quality of life. Major traumatic procedures seen repeatedly in children with VCFS are gastrostomies and jejunostomies, Nissen fundal plications, and long-term gavage feedings by nasogastric tubes. Application of these procedures is based on a number of incorrect assumptions about VCFS. The first and most important relates to the growth curve for VCFS constructed from our sample. Low weight does not equate with failure to thrive. Weight in VCFS falls substantially below the normative data for the general population reflected by the CDC growth charts for infants and children, although it approximates it in the general population by teen years. Height is also less for boys and girls with VCFS until adolescence, although not as low as weight when compared to general population norms. Of course, it is always important to measure linear growth in children every time they are weighed, but weight-to-height ratios for VCFS are not comparable to population normal. Children with VCFS have primary hypotonia and have less muscle mass than children who do not have the deletion. Muscle is a very heavy tissue both because of its cellular density and because of its rich blood supply. It is much heavier than fat and connective tissue per cubic centimeter. When muscle mass is reduced, body weight is very low. We have seen many children labeled as having failure to thrive or poor weight gain yet who have fat on their abdomens, thighs, arms, and necks (Figure 5-7). Children do not deposit fat under their skin unless they are getting enough calories to support linear growth. Excess calories are stored as fat. Therefore, regardless of the numerical values on a scale and a stadiometer, clinicians must use their eyes and common sense to determine if a child is not getting enough calories to support growth.

Often, when a child refuses more food during a feeding, it is because his stomach is full and he has consumed all of the calories he wants and needs. Putting more food into him will only induce spitting up, emesis, and discomfort. Overfeeding is particularly problematic in VCFS because the chronic constipation encountered in many children with VCFS prevents the stomach from emptying at a normal pace. The discomfort will lead to an unhappy feed-



**FIGURE 5-7.** Photos of a 6-month-old child with VCFS labeled as having failure to thrive because of low weight and low weight to height proportion. Note that he has significant subcutaneous fat, including fat on his hands, on his arms, and around his belly.

ing situation and stress on both the parents and the child. If these findings result in the recommendation for a fundal plication or G-tube, the child is then made medically dependent, and the entire dynamic of the family is changed by removing pleasant mealtimes from the daily routine. Moreover, babies who are fed by tube never learn that the way to satiate hunger is to eat something. They are fed by a tube on schedule and never have the pleasurable experience of tasting food and pairing the act of eating with eliminating hunger pangs. The longer they stay on tube feedings, the more difficult it is to teach them to eat and to allow them the pleasure of eating. Also, clinicians must be aware that the family interaction that happens during mealtimes is one that is filled with conversation, language stimulation, social interaction, and a great deal of happiness for most families. An enormous amount of learning happens during family meals, including the art of conversation. Could the absence of these times in a child's life further impair language development?

Another misconception is that frequent emesis in infancy and childhood is actually reflux and that nasal reflux (which is simply emesis coming through the nose) puts a child at risk for aspiration and pneumonia. Carried one step further, pneumonia in VCFS is presumed to be aspiration pneumonia,



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especially when the child is having feeding difficulties and persistent emesis. Nasal emesis is not correlated in any way to aspiration. Furthermore, in most instances, pneumonia in children with VCFS is related to immune issues and not to aspiration. Unfortunately, the language used to describe spitting up (emesis) as “reflux” leads the clinician to believe that the problem is one of GER or GERD, which leads to specific treatments. When medications fail, fundal plications are often recommended. If the child also has low weight in relation to the CDC norms and it is not possible to increase weight with oral feedings, and if the child feeds to a point and then refuses more food, gastrostomies are often recommended. Hyperalimentation is then attempted through a G-tube or J-tube, and with the Nissen fundal plication in place, the child is unable to vomit when the stomach is overfilled. When this occurs, the child experiences persistent episodes of retching, often violent retching. The stomach empties slowly, especially with most children with VCFS being constipated, causing significant abdominal discomfort; the child does not want to eat by mouth because he does not feel hunger and in fact feels abdominal discomfort.

Although these issues were discussed within the context of specific anomalies in Chapter 2, they deserve repetition in the context of growth and the data presented here. Clinicians must be aware that the problems observed in children with VCFS cannot be equated with symptoms present in the general population. When problems go unexplained in VCFS, clinicians may be tempted to seek exotic explanations and exotic treatments that are major disruptions in the life of the patient and the family. If clinical experience showed us that these explanations were accurate and the treatments were effective, then they could be supported. However, just the opposite is true. The first step is the careful assessment of the patient’s phenotype, followed by the inferential and deductive analysis of the symptoms in relation to these anomalies. In other words, before recommending a fundal plication for persistent emesis, ask why it is occurring in relation to the phenotypic findings. Try to be certain that the treatment is not worse than the disease, and try to be certain that the assessment of risk is real.

### POSSIBLE FLAWS IN THE DATA

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Assembling the growth curve presented in this chapter was a complicated process involving years of data collection. That being said, there are some possible flaws in the curves that are related to the data used and how they were obtained. The most obvious problem is the lack of standardization in obtaining heights and weights. There is enormous variation in how anthropometric data are obtained, the accuracy of equipment, and the amount of clothing the child has on when weighed. Obviously, there are many variables that would affect the data collection process. We do not have any reason to suspect that the number of overestimates of weight outnumber the underes-

timates, but there certainly might be an effect on each individual data point and the standard deviation calculation for that age range.

Although these data represent a large data set for a rare disorder, the sample is still relatively small for constructing a growth curve. For many of the months of age we had hundreds of data points. For birth weight, we had over 1000 data points and the early years of life provided large numbers per month of age. Late adolescent and adult measures were lower in number, with some months having only a dozen or so data points, which makes the calculations less robust and standard deviations larger. When dealing with retrospective data of this type, we have to take what is available. We may also be dealing with a biased sample. It is possible that the mildest cases of VCFS, in other words, the most normal people, are never diagnosed, or if they are diagnosed but are not symptomatic for any major problems, they may have no reason to visit our center and therefore would be excluded from the study. Another issue that could affect linear growth is scoliosis. Scoliosis occurs in approximately 30% of individuals with VCFS, although it is often mild. Scoliosis will reduce linear growth measurements. Although our sample of individuals with scoliosis was essentially equally divided between males and females, we cannot calculate relative severity and effect on height. However, if anything, the sample may be skewed to a lower growth velocity than in the general population because of some degree of loss of height in approximately 30% of the sample.

## IMPLICATIONS

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It is now clear that the reason earlier reports cited short stature as a feature of VCFS was because individual cases were compared in a cross-sectional manner to normative data for the general population. Growth velocity differs for VCFS in terms of the timing and periodic velocity, but not in terms of total growth. People with VCFS are not abnormally small when they reach adult life; they simply reach their adult height at a different pace than other people. This points out the need to follow populations of rare conditions over time in order to understand eventual outcomes and prognoses.

Except in early infancy until definitive heart surgery, the presence of CHD was not a factor in long-term growth, with the exception of severe cases of pulmonary atresia or stenosis. The poor peripheral perfusion that occurs with pulmonary atresia limits growth because there is not sufficient drive to stimulate the formation of new peripheral blood vessels. Definitive repair of heart anomalies did not impair the long-term outcome in relation to expected height. Males reached expected heights, females tended to fall slightly short by comparison, but severe short stature was not seen in either males or females.

In childhood, weight was low compared to height (typically between the 10th to 25th centile) for individuals with VCFS. However, this discrepancy

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was common and independent of eating habits or diagnosis of failure to thrive. Many children had weight-to-height proportions at or below the 10th centile yet still had normal or even excessive amounts of body fat. Evidence indicates that muscle mass is reduced in VCFS (Zim et al., 2003) and that muscle fibers are smaller than normal. It seems likely that the weight-to-height and body mass indices calculated for children in the general population are not relevant to children with VCFS. After puberty, weight increased relative to height, but examination of these children showed that many appear overweight with disproportionate amounts of body fat. The reason for this is not clear. It may be related to hypotonia and lower activity levels or perhaps to hypothyroidism, a common finding in adolescence. It may also be that changes in the endocrine system may prompt weight gain more than in the general population.

Early feeding difficulties were not predictive of short stature or low weight as an adolescent or adult. More important, the use of alternative feeding in infancy did not increase linear growth velocity. Those individuals who had major surgical procedures related to feeding such as fundal plication and gastrostomy did not have an advantage in long-term or short-term growth over those who struggled with feeding but did not have surgery.

The conclusion drawn from these data is simple. The one factor that had an effect on how children with VCFS grow is the deletion. Feeding difficulties, heart anomalies (with the exception of pulmonary atresia), treatments, diet, history of illness, and all other factors did not have an effect on long-term outcome. VCFS is not a syndrome of short stature. This should not come as a surprise. Children with many, if not most, multiple anomaly syndromes have abnormal growth patterns compared to the general population. The overwhelming majority of people with chromosomal rearrangements involving multiple genes have abnormal growth patterns, and the large majority of them have deficient growth velocity. Comparing these people to growth charts based on the general population in order to recommend treatment is not appropriate. Once the diagnosis of VCFS is made, all treatment decisions and all parameters of growth and development need to be placed within the context of the diagnosis. Treatments need to be implemented based on outcomes, especially treatments that will have a major impact on quality of life.

### FEEDING THERAPY

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Unfortunately, when clinicians feel they have no other option, or they are unable to understand the issues related to how VCFS affects feeding, they recommend surgical alternatives to feeding and placement of tubes in the stomach or jejunum for feeding and to allow the baby to gain weight. On occasion, this approach may be an expedient approach to having children discharged from hospitals so that they are not inpatients for a protracted period of time