



CHAPTER 4

Differential Diagnosis of Waardenburg Syndrome

Chapter 1 described several ways that scientists diagnose genetic syndromes. This chapter addresses the specific application of these diagnostic methods to Waardenburg syndrome, and compares the characteristics of WS to those of similar conditions and syndromes. It also reviews diagnostic techniques for assessing the problems associated with WS. After reading this chapter you should be able to:

- Explain why individuals and families of individuals with WS may be unaware of a genetic basis for their WS-related physical problems.
- List the advantages and limitations of using phenotype to diagnose WS.
- List three genetic conditions that may easily be mistaken for WS.
- Explain the relevance of family history and pedigree to diagnosing WS.
- Define the role of an audiologist in diagnosing WS.
- Describe the advantages and limitations of genotyping in diagnosing WS.
- Define the role of a genetic counselor in diagnosing WS.
- Define the role of a craniofacial team in the diagnostic process.
- Define the role of a speech-language pathologist in diagnosing WS.

RECOGNIZING GENETIC PROBLEMS

A problem must be recognized before it can be diagnosed. Visual and auditory evidence of genetic problems is all around us. We can see it in our patients' faces, hear it in coworkers' speech and voices, observe it in the behavior of strangers on the street, and sometimes see it reflected in a mirror. The first step in diagnosing WS is to train ourselves to observe syndromic implications, even if the evidence is subtle, or, in the case of hearing loss, invisible. It might seem that anyone would immediately notice the phenotypic signs of WS, because for the most part they are visually striking. Hearing loss, when present, is often severe and affects the patient's communicative ability in a variety of ways. However, my experience in working with families of patients with WS contradicts the assumption that individuals with WS know they have a genetic syndrome. The following statement by the mother of a child with WS type 3 summarizes the effect of a definitive diagnosis on the patient's perception of her facial anomalies and hearing loss.

When my son was one year old, an audiologist suspected that my son and I had WS due to our facial features and hearing loss. We underwent genetic counseling to verify that we did have WS Type 3. Based on pictures of my father, it was suspected that he also had WS. Receiving this diagnosis somehow helped me to deal with our differences. Until then, I never knew what caused my facial anomalies and hearing loss. Knowing the cause of our differences has helped me to accept them.

In this family's case, knowledge of a genetic syndrome ultimately led to understanding, treatment, and acceptance of the effects of WS. The suggestion that a genetic syndrome is present and is the cause of the individual's complaint (usually hearing loss) is not always received so favorably. Disbelief, denial, and anger are also common reactions to unwanted information. I believe there are several reasons for this. Some reasons apply to syndromes in general, but some are specific to the diagnosis of WS.

The first, and probably most compelling, reason patients deny the presence of a genetic syndrome results from the power of the word "syndrome." To most people, "syndrome" invariably means the presence of mental retardation, developmental delay, or cognition problems in general. Although mental retardation is not characteristic of WS, the word "syndrome" alone is enough to generate fear and to prevent the patient from accepting a syndrome-based diagnosis.

Another cause of disbelief results from family familiarity with and acceptance of the phenotypic features of WS. The family may "know" that family members have experienced profound unilateral deafness for four generations, but they also "know" that the deafness was caused by "normal" aging, or exposure to noise, or to measles in infancy. They "know" that blue eyes and prematurely gray hair run in their family, but they regard these anomalies as

desirable family traits. Family members may be proud that they have “dad’s blue eyes” or “aunt Sallie’s white hair streak.” They do not yet understand the relationship of these anomalies to the less desirable anomaly of hearing loss. No one has pointed out this relationship, and they do not have the scientific background to make that connection for themselves. As one parent put it, “I’d never heard of Waardenburg syndrome until my son was born. My parents were deaf and I grew up with facial differences and a severe hearing loss in my right ear. I never realized that I could pass deafness onto my children and I did not know that my hearing loss and facial anomalies had any sort of genetic cause.”

In addition, individuals may ignore the phenotypic signs of WS because many of those features are regarded as attractive, even beautiful. Bright blue eyes, for example are considered very socially desirable facial features. The idea that beautiful features can indicate a syndrome is surprising to most individuals.

The opposite attitude is also possible. Perhaps the family phenotype is more unusual than attractive. Perhaps the presence of heterochromia, partial albinism, or prematurely gray hair subjected family members to peer ridicule. Perhaps family members feel shame at their “unique” appearance. In such cases, individuals may resort to hair dye, contact lenses, and makeup to conceal evidence of a genetic phenotype. The problem with this approach is that concealing the syndromic evidence makes it difficult to identify the cause of the patient’s hearing loss. If the individual is unaware of the diagnostic significance of his or her physical appearance, he or she may be unable to provide health care professionals with important diagnostic information, and the health care professional may not be trained to ask for this information. In such cases, the relationship of syndrome to hearing loss may remain undiagnosed.

Finally, the words “genetic syndrome” imply that someone is at fault for the presence of the problem, in this case hearing loss. Although family members may logically know that the parents did not deliberately choose to have a child with WS, and although WS may arise in any child as a new mutation, there is still an element of blame attached to the parent whose genetic makeup caused the condition. The family may experience denial, guilt, shame, anger, or other emotions regarding the birth of a child with a genetic disorder. Helping family members cope with these emotions is challenging, and is often best done by someone with special skills in counseling. Chapter 6 details options for counseling individuals with WS and their family members.

Although as health care professionals, we may be unable to alter the attitudes of individuals toward their genetic makeup, we can alter *our* attitudes. The first step is to become aware of genetic problems through initial observations and then to subject these initial observations to formal diagnostic testing procedures.

Sometimes it is not the patient, but the health care professional, who hinders the diagnosis of a genetic problem. We may mistakenly believe that, unless we are physicians, geneticists, or genetic counselors, we have no business preparing family pedigrees or discussing genetic issues with family members.

It is true that issues such as blood typing, DNA testing, and other specific genetic treatment options are best left to experts with extensive training in genetics and genetic counseling. On the other hand, as medical care providers, we are all obligated to reveal our findings to patients, convey our concern and our reasons for concern, and to suggest short- and long-term plans of care for our patients. We are, in fact, legally liable for what we *do not* tell patients. Audiologists, for example, have been subjected to litigation for *not* informing the parents of children with genetically induced hearing losses that the probable cause of their children's hearing loss was genetic. If genetic problems appear to exist, the affected individual, as well as immediate family members, have a right to know that genetics may be the cause of their physical problems.

Patients initially consult health care providers for diagnosis of a problem. Perhaps they want to know how well they see or hear. Perhaps they or their children are having learning problems or difficulty achieving scholastically. What should we do when we suspect those problems have a genetic cause, but have no proof of this? For example, suppose a parent brings a child to your facility for hearing testing. In preliminary observations you notice that the child has bright blue eyes and a central white streak of hair in her forehead. The child's pure tone audiogram indicates a moderate bilateral sensorineural hearing loss. You notice that the child's parent has unusual facial features consistent with WS1. What should you do next? Here are general guidelines for resolving such issues:

- Ask for more information. Be specific to the issues that concern you. For example, you might ask, "Who else in your family has eyes like Beverly's? Does hearing loss run in your family?"
- Be prepared to tell the parents or the individual why you are asking these questions. Although you may understand the relationship between hair and eye color and hearing loss, they may see no relationship between the two and consider your questions irrelevant and intrusive. You might say, "People with gray hair, blue eyes, and hearing loss often have an inherited form of hearing problem called 'Waardenburg syndrome.' I am concerned that Beverly's hearing loss may be caused by a genetic problem. That's why I am asking for information about her physical appearance."
- Conduct or recommend additional appropriate testing to confirm your findings. For example, the presence of a WS1 phenotype coupled with the indication of sensorineural hearing loss on Beverly's audiogram justifies recommending speech audiometry testing and otoacoustic emissions testing. Recommend additional testing if it will help lead to a diagnosis of a genetic problem and/or if it will help you plan a solution to the patient's problems.

- Approach the possibility of a genetic problem directly. Say something like, “I am concerned that Beverly may have an inherited form of hearing loss (or whatever problem you are examining Beverly for). The reasons I believe this are that Beverly has blue eyes, a white streak in her hair, and a sensorineural hearing loss. This combination of problems often occurs in individuals with a syndrome called ‘Waardenburg syndrome.’ If Beverly does have this syndrome, other members of your family may be at risk for hearing loss. I would like to talk with you and your family about this. We may need to test your entire family for hearing loss. You may have questions about genetics that I am not able to answer. That’s why I would like you to consider talking with a genetic counselor. Let’s plan another meeting to talk about what we can do for Beverly’s hearing loss, and how we can prevent hearing loss in your family.” We are assuming of course, that the family wants to prevent hearing loss. Some families who belong to the Deaf community may consider hearing loss to be normal and desirable. Even if this is the case, the family is entitled to learn all the options for dealing with genetic syndromes.
- Document your findings in writing, and back them up with photographs of the patient. This is good clinical practice and provides you with visual support for your recommendations and your written reports to parents and/or affected individuals. Photographs are especially useful in determining family phenotype, as discussed below. If you believe a genetic problem is the cause of your patient’s symptoms, begin by observing the patient’s phenotype.

DIAGNOSING WS PHENOTYPE

Previous chapters discussed the major and minor phenotypic manifestations of all four types of WS in detail. Suppose a patient in your caseload appears to have a phenotype consistent with WS. What should you do to confirm that the problem really is WS and not a genetic syndrome with similar phenotypic features? The simplest and most cost-effective method is to conduct a thorough physical observation of the patient’s face, take a careful case history, and develop a family pedigree. This approach has several advantages: it can be completed in a timely and cost-effective manner; is usually nonthreatening to the patient; is noninvasive; and can be conducted without using expensive specialized diagnostic equipment. The disadvantages are that this method provides physical evidence suggesting presence of WS, but cannot reliably diagnose the specific type. Sometimes this method provides evidence of

pigment-disorder syndromes that are similar to WS. At best, this method provides the evidence needed to make appropriate referrals for genetic counseling, and genetic testing. It is also a good starting point for planning for specific therapies including speech therapy and aural rehabilitation. I recommend beginning observations with an overall observation of the patient's facial features.

Facial Observations

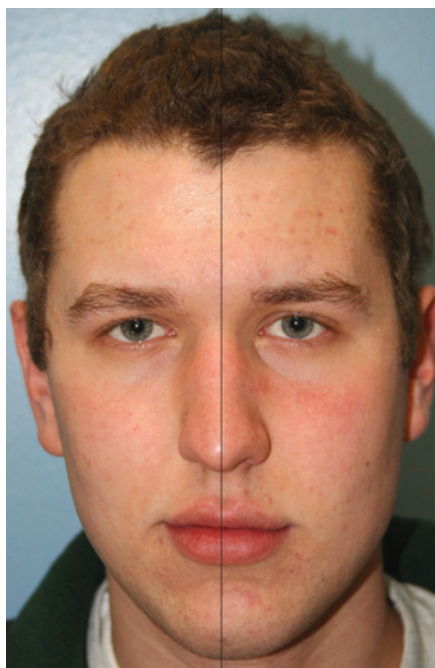
I find it most helpful to observe the patient's face from several vantage points: full face, both profiles, back of the head and neck, and top of the head. I also photograph the patient from these vantage points so that I have a visual record of my observations to supplement my written observations. I begin by examining the patient from a full-face perspective.

Full-Face Observation

From a full-face perspective one can determine facial *proportions*, facial *size*, and facial *symmetry*. Figure 4-1A shows normal adult facial proportions.



A.



B.

FIGURE 4-1. Normal facial proportions for adults.

Normally proportioned adult faces can be divided into three equal sections, as demonstrated in Figure 4-1A. These proportions are consistent for gender and race, but not for age. The faces of babies and small children are still growing, and their facial structures have not yet achieved their final relationships. Older adults may experience bone loss related to long-term use of dentures, and their faces may have undergone skeletal changes that affect their facial proportions. Individuals with WS 1 may also fail to meet these proportional guidelines because of the presence of dystopia canthorum and because facial asymmetry is common in individuals with WS. Facial *symmetry* means that both the right and left sides of the face are approximately the same size and shape. Many normal individuals, as well as individuals with WS of any type, may have noticeable facial asymmetry. The man in Figure 4-1B has noticeable facial asymmetry. The human nose is often asymmetric as a result of trauma. Full-face observations also allow observation of eye position, eye color, eye-brow appearance, structure of the nasal bridge, and hair color.

Eye Measurements

Physicians, geneticists, and genetic counselors often measure *eye position* to determine if the patient's eyes are at a normal distance from one another. The "normal" distance between eyes is approximately the distance of the length of one eye measured from corner to corner. Epicanthal folds can make normal eyes appear to be farther apart than normal. Geneticists and genetic counselors usually perform the W index and other biometric indexes to determine presence of dystopia canthorum. If you are not confident in your ability to accurately make biometric measurements, you can recommend that this be done by another medical professional if your initial visual examination indicates that such measurements are necessary.

Eye Color

Bright blue eyes are common in persons with WS. They are also common in normal individuals, so this feature alone is not compelling enough to render an accurate diagnosis. Nevertheless, blue eyes are often associated with syndromes in general and deserve a second look. Observe the eyes for heterochromia iridis, strabismus, and size and location of pupils. In some patients with WS, eye color may have changed from solid blue to patchy blue-brown during adolescence. Question the patient about eye color changes and ask if vision problems or cataracts are present. The eye problems associated with WS are usually structural, not functional, although there are reports of anophthalmia, strabismus, and amblyopia in specific populations of individuals. Remember that eye color can be concealed or changed if the patient is wearing contact lenses. Ask the patient to remove contacts while eye observation takes place.

Nasal Bridge Appearance

Individuals with WS 1 usually have a broad, flattened nasal bridge, sometimes with eyebrows meeting at midline. Epicanthal folds are often present because the flattened nasal bridge allows overlying skin to drape down over the inner corners of the eye. Because this condition is often more pronounced in infancy and childhood, I often ask adult patients to bring photographs of themselves as infants or children.

Hair

Observe the individual's head and facial hair for signs of prematurely gray or white areas. The classic position for white hair is just above the forehead. However, depigmented hair may be found in eyebrows, eyelashes, beards, sideburns, and in any place on the head. Even if the hair appears uniformly colored, ask the patient if he or she changed hair color with dye. Ask the person if his or her hair turned gray prematurely (before the age of 30) or if prematurely gray hair "runs in the family."

Profiles

Profile observation supplies information about the patient's ears, mandibular structure, dental relationship, and hair color and placement. In WS, pigmentary anomalies and retrognathic mandible are common. Facial profiles may be orthognathic (perfect), retrognathic (receding chin), slightly retrognathic (normal for most Caucasians), or prognathic (protuberant chin). Figure 4-2 shows the profile of a young man with WS. His mandible is slightly retrognathic, and he has a profound unilateral hearing loss. Retrognathic profiles are common in individuals with WS of any type.

Observe the appearance of the outer ears. Look for the presence of preauricular pits or tags. Notice the placement of the auricles relative to the rest of the head and neck. Individuals with very retrognathic profiles sometimes have auricles that are rotated downward and backward toward the back of the neck.

Back of the Head

A posterior observation point allows for observation of a patient's skin, neck, and hair. Because skin and hair contain pigment, this location often reveals pigmentary anomalies associated with WS. Persons with WS may also have vascular anomalies such as port-wine stain (Figure 4-3), sometimes called strawberry nevus, located at the base of the neck. Observe the back of the



FIGURE 4–2. A young man with retrognathic profile and profound unilateral hearing loss. Notice that this individual also has numerous nevi on his jaw and neck.



FIGURE 4–3. Port-wine stain is a vascular anomaly often located on the back of the neck. This individual has a port-wine stain extending from the base of the neck, well into the skin of the scalp. Port-wine stains often fade or diminish in size over time.

neck for port-wine stains, freckles, moles, or depigmented areas of skin in otherwise normally pigmented skin. Observe the patient's hair for white or silver hair in otherwise dark hair, or for uniformly silver or very white hair.

Top of the Head

Observing the top of the patient's head is a good way to observe hair placement and color. It also provides a way to observe skull shape and symmetry. Observe the patient's hair for signs of WS as described above.

The presence of physical features of WS may strongly suggest the presence of a syndrome, but do not provide enough evidence for an accurate diagnosis, because several conditions have very similar phenotypes to that of WS. Differential diagnosis is sometimes required to separate these conditions from that of WS.

DIFFERENTIAL DIAGNOSIS OF WS

As observers, we must be careful not to reach inaccurate conclusions based on limited phenotypic assessment. Accurate syndrome identification depends on the presence of a *pattern* of anomalies, not on isolated unusual facial features. Several medical conditions have phenotypes similar to those of WS, and can be confused with it. These conditions usually involve pigmentary anomalies of hair, skin, and/or eyes. The following are brief descriptions of the most common conditions that can be mistaken for WS.

Conditions Causing Albinism or Partial Albinism

Albinism means lack of pigment in skin, hair, or eyes. A number of physical problems cause albinism, but not all of these problems result from genetic syndromes.

Nevus Anemicus

Nevus anemicus is a congenital deficiency of terminal blood vessels. The skin and tissue that should be supplied by these vessels may look pale and lighter colored than surrounding skin. This is a medical condition, not a syndrome, and it is not associated with pigmentary anomalies of the eyes or hair. Hearing loss is not present, nor are unusual facial features characteristic of this condition.

Hypomelanosis of Ito (Ito Syndrome)

This genetic condition occurs sporadically and produces symmetric depigmented streaks, patches, swirls, or sprays on the skin of affected individuals. These problems are present at birth and are sometimes accompanied by wide-set eyes and anomalous auricles. Skeletal anomalies have been reported in some cases. This is a comparatively rare disorder, with only 180 cases being reported as of 1992 (Wiedemann & Kunze, 1997). Hearing loss is not present in patients who have this disorder. The condition has been linked to an X/autosome translocation involving Xp11 (Hodgson et al., 1985).

Piebaldism

Piebaldism is an autosomal-dominant condition that has been traced to a mutation of gene 4q12-13. The phenotype of this condition is very similar to that of WS. Areas of depigmented skin frequently occur on the head and trunk, as well as in the eyebrows, eyelids, eyelashes, and forelock. Heterochromia iridis may be present. Deafness is not a characteristic of this syndrome,

nor is broad nasal root or dystopia canthorum. Piebaldism is often found in patients of African ancestry. It is impossible to differentiate piebaldism from WS on phenotypic appearance alone. Case history information about family occurrence of hearing loss may be helpful in making the distinction, but genetic analysis is the only certain way of distinguishing between the two conditions (Baraitser & Winter, 1996; Wiedemann & Kunze, 1997).

Oculocutaneous Albinism/Ocular Albinism

Oculocutaneous albinism produces total absence of pigment in all of the individual's skin, hair, and eyes. If pigment is lacking only in the eyes the condition is called ocular albinism. The patient often experiences photophobia, strabismus, and low vision. Some patients have nystagmus (involuntary oscillation of the eyeballs). For most patients, ocular albinism is an X-linked type called Nettleship-Falls ocular albinism. This means that the gene that causes ocular albinism is located on the X chromosome and is passed from mother to son. A less common, autosomal recessive form of ocular albinism results from a mutation of genes 11q14-q21, and affects males and females equally.

Oculocutaneous albinism Type 2 has similar phenotypic features, except that skin and hair have a generalized decreased pigmentation and are pale, rather than white. Type 2 originates from a problem with the 15q11-q13 gene locus. Oculocutaneous albinism may be present in WS2, but genetic testing is needed for accurate differential diagnosis, because oculocutaneous albinism occurs in several other syndromes.

The National Organization of Albinism and Hypopigmentation (NOAH) provides information and support to individuals who have pigmentary conditions. The Web site also contains photographs of individuals with albinism, as well as information on annual conventions and educational presentations. For more information on albinism, see <http://www.albinism.org> or write the organization at: P.O. Box 959, East Hampstead, NH 03826-0959.

Vitiligo

Vitiligo is an autoimmune disorder that has been associated with mutations on chromosomes 1, 7, 8, and 4. Depigmented patches of skin are common on the face, hands, feet, elbows, knees, and chest. Hair may lose pigment, and the depigmented areas of skin may increase in size. Hearing loss and craniofacial anomalies do not accompany this problem. Some cases of vitiligo appear to be hereditary; others are associated with trauma, hyperthyroidism, diabetes, and adrenal problems. The main problems associated with vitiligo are cosmetic, especially when the condition occurs in individuals with very dark skin. Sometimes this condition resolves spontaneously (Simon & Janner, 1998). The following resources can provide support services and information about vitiligo.

American Vitiligo Research Foundation

P.O. Box 7540
Clearwater, FL 33758
Phone: 727-461-3899
Fax: 727-461-4796
E-mail: vitiligo@avrf.org
Web site: <http://www.avrf.org>

National Vitiligo Foundation

611 S. Fleishel Ave
Tyler, TX 75701
Phone: 903-531-0074
Fax: 903-525-1234
E-mail: vitiligo@billistic.com
Web site: <http://www.vitiligofoundation.org>

Conditions Producing Heterochromia Iridis

Heterochromia iridis occurs as an occasional anomaly in a number of syndromes, including Horner's syndrome and piebaldism (discussed above). The condition may also be associated with disease and trauma.

Horner Syndrome

Horner's is not a genetic syndrome, but rather a collection of symptoms that may be caused by a variety of etiologies. If the problems causing Horner's syndrome are congenital, the child may be born with heterochromia iridis, as well as one or more of the following symptoms: absence of sweating on the same side as the brain injury, paralysis of sympathetic nerve supply to the eyelid producing lid ptosis (drooping), and unequal pupil size. Horner's syndrome is symptomatic of a variety of neurologic problems including Arnold-Chiari malformation, brain tumors, meningitis, spinal cord injury, and Hodgkin's disease. It is not associated with hearing loss or additional pigmentation anomalies.

Eye Trauma

Eye trauma may destroy the pigment layer of the iris and lead to formation of scar tissue. Figure 4-4 shows the eye of a man who experienced eye trauma as a child when someone snapped a suspender fastener in his eye. He is legally blind in this eye. A close look at the injured eye (right eye in the photograph) shows bands of scar tissue across the underlying blue pigment that remains in the iris. This man's uninjured eye is brown and has normal vision. This is an example of heterochromia iridis resulting from trauma. Sometimes



FIGURE 4–4. Eye trauma can sometimes approximate the appearance of heterochromia iridis. The eye on the left has lost brown pigment because of a traumatic accident in this man's childhood. His normal eye is brown.

this condition causes eye pain when the eye is exposed to strong sunlight. Corrective surgery or protective contact lenses may be needed to treat the problem. Patients remember eye trauma. Always ask the patient about the cause of an anomaly before assuming that it is genetic.

References for Differential Diagnosis

These textbooks are especially useful in making a differential diagnosis. The books are expensive, but are worth the expense if you work with patients who have genetic problems. For occasional use, interlibrary loan is an affordable option.

- Baraitser, M., & Winter, R. M. (1996) *Color atlas of congenital malformation syndromes*. London: Mosby-Wolfe. This atlas provides color photos of most major genetic syndromes, but does not provide extensive information about natural history or treatment of the problems caused by the syndromes.
- Jones, K. L. (1997) *Smith's recognizable patterns of human malformation*. Philadelphia: W.B. Saunders Co. This text is my personal favorite for comparing syndromes. In addition to descriptions and black and white photographs of major syndromes, the text contains comprehensive comparative charts of embryonic development and black and white line drawings of chromosomal anomalies. The book includes chapters on problem solving, morphogenesis and dysmorphogenesis, and minor anomalies. Normal growth charts are included, as well as a very useful appendix listing syndromes based on location of problem. For example, there are lists of

syndromes with heart anomalies, syndromes with broad nasal bridge, microglossia, and the like. The size of this book is easy to handle, and it is not heavy, except in the intellectual sense.

- Roy, F. H. (1997). *Ocular differential diagnosis*. Baltimore: Williams and Wilkins. Although this is a very specialized text for diagnosing eye anomalies it has excellent descriptions and comparative charts. However, it has no photographs, is diagnostic only, and contains no material regarding treatment or outcome of the problem. It is available in paperback.
- Schneider, V., & Cabrere-Meza, G. (1998). *Rudolph's brief atlas of the newborn*. London: B. C. Decker Inc. Color photographs enhance written descriptions of most major problems of the newborn infant. The atlas includes topics such as deformations, chromosomal disorders, neonatal dermatology, and endocrine and metabolic disorders. Tips for differential diagnosis are included, along with probable outcome. This is an excellent all-round resource guide to the problems of newborn infants.
- Simon, C., & Janner, M. (1998). *Color atlas of pediatric diseases with differential diagnosis*. New York: International Thompson Publishing. Like the preceding atlas, this one includes differential diagnosis of diseases throughout childhood. The color photographs are excellent, although the book is rather large and unwieldy to handle.
- Wiedemann, H. R., & Kunze, J. (1997). *Clinical syndromes*. London: Mosby-Wolfe. This atlas weighs about 5 pounds, but is packed with black and white photographs of most major syndromes, including some European syndromes that are uncommon in North America. It contains comments about main and supplementary signs, etiology, prognosis, differential diagnosis, and treatment.
- Zatoureff, M. (1996). *Diagnosis in color. Physical signs in general medicine* (2nd ed.). London: Mosby-Wolfe. The color photographs and descriptions in this text are organized by body part, with the section on the head being particularly useful. Most descriptions are of adult patients. The atlas has ethnically diverse descriptions and photographs. It is lightweight, and small enough to be easily portable.

FAMILY CASE HISTORY AND FAMILY PEDIGREE

Physical observations can be enhanced by careful discussions with family members, and by compiling a family pedigree.

Taking a Case History

If initial visual observations indicate a syndromic phenotype, I prefer to schedule a second interview with the family to discuss family history in depth. I begin by telling the patient or the family *why* I want additional family information. Although I understand the relationships between hair and eye color and hearing loss, the family may see no relationship and may consider such questions irrelevant. For example, I might say, “People with gray hair, blue eyes, and hearing loss often have an inherited form of hearing problem called ‘Waardenburg syndrome.’ I am concerned that your hearing loss may be caused by a genetic problem. That is why I am asking for more information about your family’s physical appearance.” I also give the patient a list of questions that I am likely to ask, so that he or she can discuss the questions with other family members or get the answer from family records. Scheduling a second interview has several advantages: it allows the patient time to adjust to the idea that a syndrome might be present in his or her family, it lets the patient gather materials and photographs that will be useful during the interview, and it allows the family members time to discuss family appearance among themselves.

I ask that patients bring photos of themselves as an infant and as a child; photos of family members that demonstrate signs of WS; as well as dates of birth, causes of death, and unusual facts about family members. I ask the patient to “draw a family tree” indicating birth anomalies, stillbirths, and marriages with close family members, and I ask that they identify the ethnic background of family members. I ask them to bring their family tree with them to the interview. This saves time during the interview itself, and opens the door for discussion during the interview.

Examples of genetic case history forms can be found in numerous textbooks. Some very useful examples include those provided by Milunksy (2001), Jorde, Carey, and White (1995), Peterson-Falzone, Hardin-Jones, and Karnell (2001), and Shprintzen (1997). A family history for someone suspected of having a genetically based disorder consists of basically two parts: general information that might indicate a genetic component and specific information that might indicate the specific problem under consideration—in this case WS.

General Information

General information, in this instance, does not refer to identifying material such as name, age, and birthplace. Rather, it refers to questions whose answers might lead to the likelihood that a genetic problem is present. I usually combine the

interview with the taking of a pedigree (discussed below). Sometimes the patient has already constructed a pedigree. In that case, I combine the interview with discussions, and possible corrections, of the pedigree. Table 4-1 lists general questions that may produce answers indicating a genetic risk factor.

Taking a Pedigree

In the past, genetic counselors and geneticists were the professionals who constructed pedigrees. They still do this, but other professionals have begun using pedigrees to make initial diagnostic decisions as well. Speech pathologists and audiologists in particular are beginning to use pedigrees more frequently for the purposes of obtaining genetic information, and also to help make decisions as to appropriate patient referral. Figure 4-5 shows basic symbols used to construct a pedigree. Other symbols may be devised to represent conditions not portrayed by this basic code. I usually interview the proband and construct the pedigree from most recent to most distant generations.

The person who is first diagnosed with a problem is called the proband. Unless the proband is a small child or is developmentally delayed, he or she is usually the person interviewed. Patients often ask me “how far back” they should go to obtain family history. The farther back, the better. As we learned in an earlier chapter, genetic counselors look for patterns of transmission that might indicate the type of inheritance pattern. Autosomal dominant transmission usually produces a vertical pattern of affected individuals, and the problem is usually present in every generation. Autosomal recessive problems often present with a horizontal pattern of transmission and appear in several

TABLE 4-1. General Information to Obtain from Patients Suspected of Having a Genetic Problem

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1. Birth date, gender, and familial relationships of all known family members.
This can be easily charted as a pedigree using standard pedigree symbols.
 2. Ethnic background of family members.
 3. Cause of death for deceased family members.
 4. Number and cause of stillbirths and miscarriages.
 5. Presence of family-related hearing loss.
 6. Indication of consanguinity (mating between blood relatives).
 7. Presence of diseases that “run in the family.”
 8. Presence of mental retardation, cognitive problems, or mental illness in members of the family.
 9. Presence of family members with known chromosomal anomalies.
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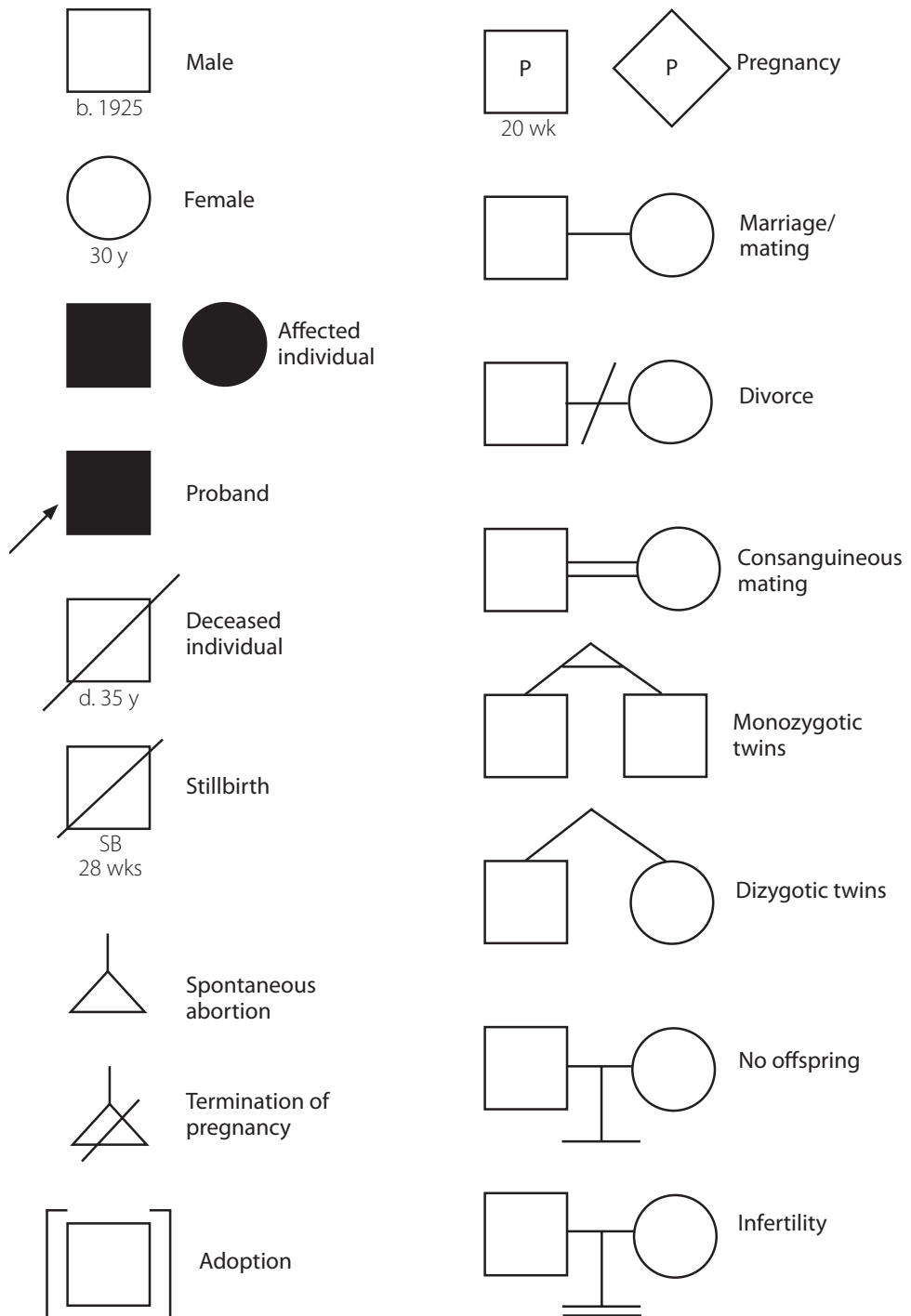


FIGURE 4-5. Symbols used to construct a family pedigree.

siblings within a family. Interviewing the family and constructing a pedigree is one way of discovering this pattern. As you talk with the proband or other family members, remind them that you want information about *all* family members, including those who have died before or at birth and those who have left the family through divorce or marital separation. Information about family members who have died stillborn or in infancy often provides some of the most valuable information when diagnosing genetic or chromosomal anomalies.

It is also helpful to ask family members about their racial and ethnic background. You can record this information above the entire family pedigree, or below the names and birthdates of specific individuals. Some syndromes are more common in some ethnic groups than others. WS, like many syndromes, is more common in consanguineous families than in others. Families who live, marry, and have children in small ethnic communities produce their children from a narrowed gene pool. The more closely the genetic relationships among individuals, the higher are the risks for individuals having genetic syndromes, including WS.

One of the disadvantages of taking a case history and constructing a pedigree is that the information you obtain may not be accurate or may have been sanitized by family members who want to conceal evidence of socially unacceptable behavior. Family members also vary in their observational powers and in their memory of pertinent facts. Discussing a family tree sometimes reveals startling or unwelcome information to the entire family. In one instance, I asked a student whom I suspected of having a genetic syndrome to construct a pedigree of her family. After interviewing family members, she told me that she had precipitated an argument among her aunts and uncles when she learned that one of her married uncles had not died of a heart attack as the family generally believed. Although he did die of a heart attack, he did so in bed with his 22-year-old secretary. Surviving family members were angered and scandalized when a grandparent revealed this information to the student. Other examples of information that can influence a family's accurate recollections of family history include instances of rape or incest, the (until now) unknown presence of illegitimate blood relatives in the extended family, the probability that a legal father is not actually the biological father, and adopted children who have never been told that they were not born to their adoptive parents. We depend on family members to provide truthful details about family relationships, but we cannot always be sure that the family will do so.

Specific Information

In addition to the general questions mentioned above, specific questions can often provide information indicating the presence of WS or, on the other hand, indicate the presence of syndromes that have phenotypes similar to WS. Table 4-2 lists specific questions that can help the examiner determine if WS is likely to be present in the family and if the family would benefit from genetic testing.

TABLE 4–2. Specific Questions to Ask Patients Suspected of Having WS

Ask the following questions, and follow up with discussions or probing for more information if the answers to the questions are positive. Ask for photographic documentation of affirmative answers.

1. Who in your family has prematurely gray hair? Does anyone have very white or silver colored hair?
2. Who in your family has patches of white hair on their head, eyelashes, eyebrows, or beard?
3. Who in your family has hearing loss? When did the hearing loss occur? What do you believe caused this hearing loss? What kind of hearing loss is it? Is it in one, or in both ears? Was the hearing loss sudden, or did it come on gradually? Does hearing loss “run in your family”?
4. Who in your family has bright blue eyes?
5. Who in your family has eyes of two different colors? For example, one brown eye and one blue eye, or both eyes that are partly brown and partly patchy blue.
6. Did anyone in your family have eyes that changed color during puberty?
7. Who in your family has oriental looking eyes? Does anyone ever say that a family member looks oriental, or has “crossed” eyes? Skip this question if the person you are interviewing is Asian.
8. Who in your family has eyebrows that are bushy, slanted, or that meet above their nose?
9. Who in your family has lots of moles or freckles?
10. Does anyone in your family have a small lower jaw?
11. Who in your family has port-wine stains or strawberry birthmarks?
12. Who in your family has patches of pale or very white skin anywhere on their body?
13. Does anyone in your family have severe headaches of unknown cause, or “migraine” headaches?
14. Has anyone in your family been diagnosed with ALS, multiple sclerosis, or a severe neurologic condition of unknown cause?
15. Has anyone in your family ever been born with cleft lip and/or cleft palate?
16. Has anyone in your family ever been born with spina bifida (open spine), anencephaly (no head), or other spinal cord defects?
17. Has anyone in your family had a spontaneously aborted or stillborn baby? What was the cause of the early death of this child?
18. Has anyone in your family ever been diagnosed with hydrocephalus?
19. Has anyone in your family ever had difficulty digesting food, especially as an infant or small child?

continues

TABLE 4–2. *continued*

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20. Has anyone in your family ever been diagnosed with Hirschsprung's disease?
 21. Has anyone in your family had upper arm weakness or upper arm anomalies?
 22. Has anyone in your family been born with too many fingers or toes?
 23. Has anyone in your family been born with crooked fingers or toes?
 24. Has anyone in your family been born without eyes?
 25. Did anyone in your family marry a close blood relative? For example, marriage between first cousins.
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The most pertinent questions are those that help us identify family members who have genetic hearing loss. Again, there is room for inaccuracy because the family may have little information on the type, degree, or presence of hearing loss in family members of past generations. Even current family members with hearing loss may attribute their hearing loss to work-related causes or an illness in infancy, and not to a genetic cause, and they may in fact be correct in these assumptions. As you talk with the family, carefully observe the facial features of the family members. Remember that syndromes, including WS, sometimes arise as new mutations. The proband may be the first and only family member to have WS. Ask to see family photographs of previous generations of family members. Look for evidence of pigmentary anomalies in eyes, skin, and hair. If the photos are in black and white, ask questions about eye color and hair color. Observe photos of family members from both sides of the family because it is always possible, although unlikely, that members of both sides of the family carry the WS gene. This situation sometimes occurs in small populations where intermarriage from the same gene pool has occurred over generations. For this reason, I always ask the individuals what their ethnic background is. I have seen patients who are Turkish, patients who are of Northern Italian descent, and patients who are Welsh who have WS. In all instances the family were proud that they had maintained their ethnic identity by marrying only individuals from the same geographic location. In these cases, the family line remained ethnically "pure," but genetically flawed. Small gene pools allow for frequent transmission of undesirable genetic traits.

If time permits, photograph the proband and family members who are providing the family history. I document my findings in writing and add a summary to the written reports to the patient and to letters of referral. If what you see and learn from the family history and pedigree analysis leads

you to believe that a genetic problem exists, you will likely be referring the patient for genetic testing and genetic counseling. The more evidence you can provide in the letters of referral, the more quickly and accurately the problem can be diagnosed.

AUDIOLOGIC TESTING

Because hearing loss is invisible and can occur at any time in the life of a patient with WS, it is wise to recommend taking a baseline audiologic assessment of all family members suspected of having the WS gene. A general audiologic assessment for any patient usually includes pure tone air and bone conduction testing, otoscopy (physical observation of the ear canal and tympanic membrane), and impedance testing to determine the mobility of the tympanic membrane and middle ear function. These basic tests are generally performed on every individual who wants baseline measures of hearing performance and ear health. Ideally, family members having, or suspected of having, hearing loss, should receive the additional battery of advanced audiologic tests described in chapter 5. These include speech audiometry and otoacoustic emissions (OAE) testing. Information from these tests is useful in differential diagnosis of hearing loss. Craniofacial teams often have geneticists and genetic counselors as part of the diagnostic team, but such teams do not always have audiologists available to do on-site testing. Some teams have audiologists, but do not have equipment to do advanced examinations such as otoacoustic emissions (OAE) testing. If your facility has a full-service audiology program, it is best to do the hearing testing as part of the initial diagnostic workup. If you plan to refer your patient to a craniofacial team, or genetic counselor, the results of the audiologic test battery can save the patient time and money in the long run.

Some programs, such as the Miami University Speech and Hearing Program, provide free hearing testing to WS patients as part of an ongoing research project. In other cases, patients may have to pay for audiologic testing out of pocket. Be sure to discuss this with patients before beginning costly and extensive audiologic testing.

GENETIC COUNSELING

If phenotypic observation, family history, and pedigree indicate the probability of WS (or of any other genetic syndrome), the family should be offered the opportunity to receive genetic counseling and genetic testing. Genetic counselors are specifically trained to compile family pedigrees, to make specific

recommendations about genetic testing, to explain the results of genetic testing, and to predict the likelihood that a particular genetic problem will be transmitted to members of a future generation. They also determine the transmission pattern of the genetic condition and help formulate long-term treatment plans.

GENETIC TESTING

If the family wants to know if the WS gene is in their family, the most accurate way of determining this is through genetic testing. Even genetic testing may have limited accuracy for the rarer types of WS. WS genetic testing is done by sending a blood sample from family members to a laboratory where genetic analysis takes place. Although costs vary from one facility to another, patients can expect to pay from \$1,500.00 to \$2,500.00 for a genetic analysis. The recommendation for a genetic analysis usually must come from a physician, genetic counselor, or craniofacial team. Insurance companies vary in their policies regarding financial reimbursement of genetic testing.

SPEECH-LANGUAGE PATHOLOGY

Speech-language pathologists (SLPs) are often among the first health care professionals to treat someone with WS. Sometimes the patient does not yet know he has WS and has consulted an SLP for speech therapy for communication problems secondary to hearing loss. In this case, if the SLP recognizes the condition, he or she is obligated to make the appropriate referrals after following the procedures described earlier in this chapter.

Persons with WS often have normal speech and language skills. When WS-related communication problems occur, they are most often related to presence of hearing loss. Although cleft palate sometimes accompanies WS, most cleft palate repairs are completed before speech problems arise. The majority of early cleft palate repairs are successful, and few of these children ultimately need speech therapy. Children with WS and cleft palate are ideal candidates for team treatment. SLPs often plan early intervention therapy sessions for the infant in order to prevent the child from acquiring compensatory articulation errors and to encourage normal language acquisition and development.

Congenital sensorineural hearing losses can also prevent children from hearing and acquiring normal speech and language. Children who are severely or profoundly deaf must be identified early and fitted with appropriate amplification systems. Some families prefer that the child communicate in sign language and remain or become part of the Deaf community. Other parents of children who are congenitally deaf because of WS choose to enroll their

children in programs or schools providing oral deaf education. Some children who are deaf are excellent candidates for cochlear implants. Remember that the type and extent of hearing loss must be determined before effective plans can be made to correct speech or language problems resulting from hearing loss. Parents, audiologists, and SLPs must work closely together to determine a long-term plan for treating both hearing loss and the communication problems resulting from the hearing loss.

All family members who have the WS gene should be identified, and all should at a minimum receive an audiologic assessment to establish a baseline hearing sample. Because WS hearing losses may theoretically occur at any time in the patient's life, and because congenital hearing losses due to WS may worsen at any time in the patient's life, hearing reassessments should be scheduled at least once a year. After WS-related problems have been identified, appropriate methods of treatment should be selected and implemented. Chapter 5 provides specific details on diagnosing and treating hearing loss in WS patients. Patients who have hearing loss plus additional physical problems, or patients who want to receive genetic testing and counseling as part of the treatment process, are often best treated by a craniofacial team.

CRANIOFACIAL TEAMS

Craniofacial teams are groups of health care professionals who specialize in treatment of anomalies of the head and face. Most large cities in the United States and Canada have craniofacial teams located in major hospitals. The American Cleft Palate Craniofacial Association publishes an annual ACPA Membership Team Directory. This directory lists team locations, specific contact information, and names and addresses of contact persons who are members of the ACPA. The ACPA also has a Web site for professionals and for individuals and families of individuals who have facial problems. Team treatment is an advantage for such persons because multiple problems can be evaluated and treated simultaneously in a central location. Other advantages to team treatment include demand for cost-effective health care services, interaction among health care specialists trained in different professions, and mandates of federal laws including Public Laws 93-112, 94-142, 99-457, 101-476, 101-336, and 105-14.

Craniofacial teams traditionally existed to manage the problems of children who were born with cleft lip and/or cleft palate. Recently, however, these teams have expanded their purpose and areas of specialization to treat children with multiple craniofacial anomalies, regardless of whether cleft palate is one of the anomalies. The professions represented on the team vary depending on the location of the team, the budget of the medical center where the team practices, the research interests or expertise of team members, and the availability of expert professionals to staff the team.

Teams may include any or all of the following professionals: oral-maxillo-facial surgeon, plastic and reconstructive surgeon, nurse, pediatrician, speech-language pathologist, pediatric dentist, orthodontist, prosthodontist, otolaryngologist, medical geneticist, clinical psychologist, social worker, genetic counselor, and, in some cases an audiologist. Most teams have a coordinator who interacts directly with the family by scheduling appointments, helping with financial concerns, counseling the family, and assisting family members with issues of transportation, follow-up, and initial interviews.

Team treatment is ideal for patients with WS who:

- Have cleft palate and WS
- Have multiple family members who are affected by WS
- Want to receive services in a central location
- Will benefit from multidisciplinary long-term treatment (as in WS 3 and 4)
- Require highly specialized surgery or medical treatment (cochlear implants, colon repair)
- Want plastic or reconstructive surgery to change their facial appearance
- Want to receive genetic counseling and family planning as part of their rehabilitation program.

In the above cases, craniofacial team treatment can save the patient time, money, and emotional stress by providing centrally located services from a team of highly trained professionals.

SUMMARY

This chapter has addressed the basic methods for differential diagnosis of WS. Chapter 5 will elaborate on diagnosis of hearing loss in individuals with WS.

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