Most Sturge–Weber children have focal motor, complex partial, or other seizures that are often refractory to AEDs. Seizures in the first year of life portend mental retardation. Whether or not they have seizures, Sturge–Weber children tend to have learning disabilities and behavioral disturbances. Depending on the lesion site, they also have focal, lateralized neurologic deficits, such as homonymous hemianopsia and spastic hemiparesis. When present, these deficits arise contralateral to the port-wine stain.

In Sturge–Weber syndrome, as in other neurocutaneous disorders, physical and cognitive deficits often worsen. Neurologists usually attribute the deterioration to increasing sclerosis surrounding the cerebral lesions.

Ataxia-Telangiectasia

The cutaneous component of ataxia-telangiectasia consists of aggregations of small, dilated vessels (telangiectasia) on the conjunctiva, bridge of the nose, and cheeks. Neurologic manifestations become evident in children aged 3–5 years when degeneration of the cerebellar vermis – the neurologic component – causes a progressively severe gait ataxia. Subsequently, patients develop cognitive impairment.

Unlike most other neurocutaneous disorders, ataxia-telangiectasia is inherited in a recessive pattern. It is attributable to a genetic abnormality on chromosome 11 that interferes with DNA repair.

Another, almost unique feature of ataxia-telangiectasia is its consistent association with immunodeficiency. Children with ataxia-telangiectasia have both cellular immunity impairment and complete or nearly complete deficiency of immunoglobulin, IgA or IgE. Their immunodeficiency leads to severe sinus and respiratory tract infections, which may represent their first symptoms. It also allows the development of lymphomas and other neoplasms. (The same association of immunodeficiency with lymphoma also occurs in acquired immunodeficiency syndrome [AIDS] and immunosuppression for organ transplantation.)

OTHER GENETIC NEUROLOGIC DISORDERS

Neurologists routinely encounter children with cognitive and behavioral disturbances. Often combinations of cognitive impairments that sometimes reach profound levels, distinctive physical signs, and peculiar behavior allow neurologists to propose a diagnosis of one of the following genetically based neurologic syndromes.

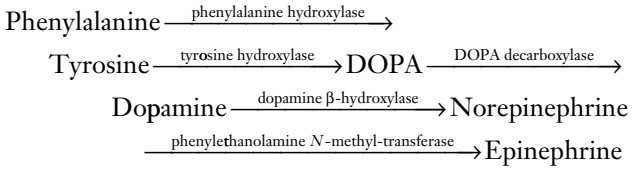
Autosomal Chromosomal Disorders

Phenylketonuria (PKU) (Chromosome 12)

An autosomal recessive inherited deficiency in the catabolic enzyme, *hepatic* phenylalanine hydroxylase, produces PKU. In a triumph of medicine, near-universal testing and implementation of effective, simple dietary treatment have either eliminated PKU or, if it occurs, markedly reduced its consequences.

A deficiency of phenylalanine hydroxylase, which normally converts phenylalanine to tyrosine, would ordinarily lead to a triad of major biochemical ramifications:

1. The deficiency would prevent the normal metabolism of phenylalanine to tyrosine. Thus, affected untreated individuals have elevated plasma concentrations of phenylalanine and little or no tyrosine.
2. The deficiency would also prevent the normal synthesis of "downstream" neurotransmitters, including dopamine, norepinephrine, and melatonin (see Chapter 21).



3. A deficiency of phenylalanine hydroxylase would divert phenylalanine metabolism to secondary metabolic pathways. Those pathways yield phenylpyruvic acid and eventually phenylketones, which would be excreted in the urine. Untreated affected individuals thus characteristically have PKU.

Before the introduction of effective treatment, affected infants, after appearing normal from birth through their next several months, would fall behind in all areas of growth. In addition, because of reduced melatonin, most of these infants lacked pigment, which bestowed on them blond hair, blue eyes, and a fair complexion, but also eczema. Phenylketones in their urine turned it particularly malodorous.

In untreated children, cognitive delays appeared as early as 8 months of age and language development lagged. Almost all of them were eventually left mentally retarded, and two-thirds of them profoundly so. Although occasional children and adults with PKU had little or no mental retardation, evaluations found that many of them had nonspecific, poorly defined "psychiatric illness."

A mutation on chromosome 12 transmits PKU in a classic autosomal recessive pattern. Its incidence varies widely between countries, being highest in Turkey and lowest in Japan. In the United States, hospitals routinely test all newborns for PKU with screening procedures that detect elevated concentrations of plasma phenylalanine, such as the Guthrie test. One note of caution: These tests may be invalid immediately after birth when residual maternal enzyme might still be metabolizing phenylalanine.

A phenylalanine-free diet usually prevents neurologic damage, especially mental retardation. Noncompliance with the diet, as particularly occurs with PKU adolescents, produces neuropsychologic aberrations. If pregnant women with PKU do not strictly adhere to their phenylalanine-free diet, they accumulate toxic levels of phenylalanine and its metabolic products, which easily pass through the placenta. In this case, the fetus, even

though likely to be only heterozygous for the PKU gene, is vulnerable to the toxins and liable to develop mental retardation. A new synthetic tetrahydrobiopterin (a cofactor of PAH), sapropterin (Kuvan), may speed the metabolism of phenylalanine.

Physicians should be aware that subsisting exclusively on phenylalanine-free foods is difficult and expensive. The diet, which is devoid of artificial sweeteners, leads to short stature, anemia, and hypoglycemia.

Homocystinuria (Chromosome 21)

Cystathionine beta-synthase, along with vitamin B_6, converts homocysteine to cystathionine (see Fig. 5-8). A deficiency of this enzyme leads to accumulation not only of homocysteine but also its precursor, methionine. The genetic disorder, homocystinuria, is attributable to a mutation on chromosome 21. Other conditions that lead to accumulation of homocysteine and possibly some of the same clinical manifestations include vitamin B_{12} deficiency, exposure to nitrous oxide, and use of certain AEDs (such as carbamazepine and phenytoin).

Homocystinuria leads primarily to vascular thrombotic events, particularly strokes in young and middle-aged adults, and mental retardation. The relationship between homocystinuria and strokes is so strong that an elevated serum homocysteine level is a risk factor for stroke (see Chapter 11). The other features of homocystinuria, which reflect malformation of multiple organs, include dislocation of the ocular lens, pectus excavatum or carinatum, and a tall, Marfan-like stature. In addition to mental retardation, which is almost universal, homocystinuria patients often have behavioral disturbances, obsessive-compulsive symptoms, and personality disorders.

Treatment in the presymptomatic stage reduces the likelihood of patients developing the illness' major complications, including mental retardation. Administering vitamin B_6, the most common strategy, facilitates the metabolism of homocysteine and reduces levels of methionine and homocysteine in approximately 50% of patients. However, administering folate and B_6 has not as yet proven to reduce the stroke risk, despite reducing serum homocysteine levels, in adults with elevated levels of homocysteine.

Prader–Willi and Angelman Syndromes (Chromosome 15)

Approximately 75% of Prader–Willi syndrome cases are paternally inherited – the rest are sporadic. Children with this disorder have mental retardation and behavior problems, but their identifying symptoms consist of hyperphagia and resultant obesity. However, to say that children with Prader–Willi syndrome have hyperphagia understates their behavior. They eat relentlessly and sometimes aggressively, with no regard for their bodily needs. They eat barely edible food. They grab meals from family members' plates, break refrigerator locks, and rummage through garbage cans. Whether or not the incessant eating represents a compulsion, obsessive-compulsive symptoms are a manifestation of the illness.

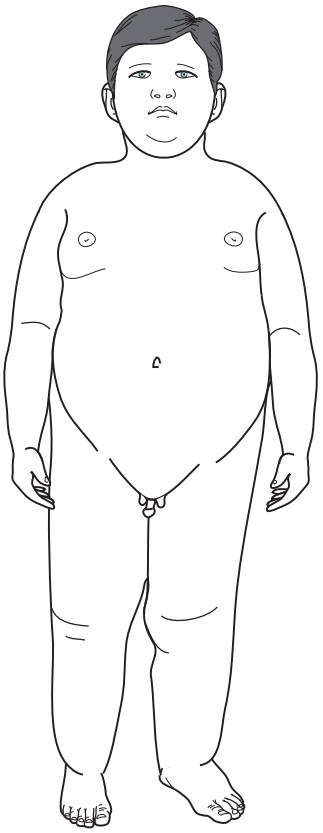


FIGURE 13-14 ■ An 8-year-old boy with Prader–Willi syndrome shows the distinctive obesity, which can reach grotesque proportions, small penis and testicles, short stature, small hands, and short feet. Girls with the syndrome, who also have obesity and hypogonadism, usually have small labia majora and no labia minora. Because both boys and girls with Prader–Willi syndrome also have intellectual disabilities, neurologists remember the manifestations of the illness as the "three Hs": hyperphagia, hypomentia, and hypogonadism.

Beyond their striking obesity and other physical anomalies (Fig. 13-14), Prader–Willi children have low normal to below normal IQ. They comprise about 1% of children with mental retardation. They also tend toward affective disorders that may, after adolescence, be accompanied by psychotic features. The severity of the obesity does not correlate with either the nature or severity of the neuropsychiatric disturbances, but, like obesity in general, it carries the comorbidities of hypoventilation, hypersomnia, hypertension, diabetes, stroke, and osteoporosis.

The immediate cause of the morbid obesity, hyperphagia, does not respond to medicines or behavioral therapy. Currently available bariatric surgical procedures have produced little benefit. However, some studies found that recombinant growth hormone injections increase height and muscle mass, and noninvasive ventilation reduces hypoventilation.

In contrast to Prader–Willi children, those carrying a very closely related microdeletion on the same chromosome show a completely different phenotype – Angelman syndrome. This disorder, which is usually inherited from

FIGURE 13-15 ■ Children with Down syndrome are short with low-set ears that have small lobes. Their eyes' epicanthal folds are widened and the lids appear to slant upward – thus the outdated term "mongolism." The bridge of the nose is depressed. The tongue, characteristically large, tends to protrude over a slack jaw. Children's palms are broad with a single midline crease, and their fingers are short and stubby.

FIGURE 13-16 ■ This 10-year-old girl shows the characteristic elfin (elf-like) appearance of Williams syndrome. She is short. Her forehead is broad and her cheeks are prominent. Her nose has a flat bridge, and its nostrils are full and turned slightly upward. Her teeth are hypoplastic and widely spaced.

the mother, comprises severe mental retardation with prominent deficiency of language skills; epilepsy; microcephaly; *stereotypies* (involuntary repetitive, patterned, and purposeless movements); jerky-ataxic voluntary movements and ataxic gait; a smiling face; and paroxysms of unprovoked laughter. The jerky movements and superficially happy appearance have given rise to the term "happy puppet syndrome." Affected adults generally continue to display the same laughter, require assistance with their daily activities, and suffer from refractory epilepsy.

Until genetic testing is completed, girls with Angelman syndrome may appear to have Rett syndrome because of their mental retardation, language impairment, microcephaly, and involuntary movements (see later). They may also appear to have idiopathic autism because of their language impairment, inappropriate behavior and stereotypies; however, their preserved social skills weigh against that diagnosis.

Down Syndrome (Trisomy 21)

At 1 in 600 births, Down syndrome is the most frequently occurring disorder in this group. Affected children have distinctive physical features (Fig. 13-15) and mild to moderate mental retardation, with a median IQ of 40–50. They are also plagued by hearing loss, congenital cardiac anomalies, and gastrointestinal disease, and, as adults, the development of hypothyroidism and leukemia.

Another, almost uniform complication is that, by age 50 years, Down syndrome leads to an Alzheimer-like dementia (see Chapter 7). In fact, one theory holds that both Down syndrome and Alzheimer disease result from a common genetic abnormality on chromosome 21.

Down syndrome children retain social skills that partly compensate for their mental retardation. Although they do not have psychotic or autistic behavior, they occasionally have behavior that fulfills criteria for ADHD. Beginning when they are young adults, depression becomes comorbid. Curiously, severely affected children may have orofacial dyskinesias unrelated to neuroleptic exposure.

The cause in most children is chromosome 21 trisomy, but a translocation of that chromosome causes some cases. Nevertheless, because all these patients share the same phenotype, clinicians still call the translocation variety "trisomy 21."

The incidence of Down syndrome correlates with increasing maternal age (especially after 40 years), but babies born to very young mothers also have an increased incidence of the disorder. Its incidence also increases, but not to the same degree, with increasing paternal age. Because a chromosome analysis of amniotic fluid cells can identify a fetus with Down syndrome, obstetricians urge women older than 40 years to undergo amniocentesis. Even though it is obviously genetic, neurologists do not classify Down syndrome as an *inherited* disorder of mental retardation because it is not transmitted from generation to generation. (This distinction allows neurologists to state that fragile X syndrome [see later] is the most common form of inherited mental retardation.)

Williams Syndrome (Chromosome 7)

Lifelong neuropsychologic oddities and a distinctive, "elfin" facial appearance (Fig. 13-16) characterize Williams syndrome. Children with this disorder are slow to acquire motor milestones, have strikingly poor sense of visuospatial relationships, and cannot perform construction or copying tasks. The majority have ADHD, phobias, or both. In general, they perform in the mild to

moderate intellectual disability range on testing, with an average IQ of approximately 65 points. As adults, Williams syndrome individuals rarely find steady employment and develop memory impairment at a greater rate than controls.

On the other hand, they have no gross physical neurologic abnormalities, such as microcephaly, stereotypies, or epilepsy. However, the disorder leads to defects in the elastic qualities of the skin and congenital abnormalities at the root of the aorta, which cause supravalular aortic stenosis.

Most strikingly, the disorder paradoxically seems to enhance certain neuropsychologic functions. For example, remarkably, and so far inexplicably, affected individuals frequently possess unusual talents in music, many showing perfect pitch. Their conversations, although lacking substance and often one-sided, are garrulous and bubbly. Neurologists often call their personal interactions "hypersocial."

Although some Williams syndrome cases have followed an autosomal dominant inheritance pattern, spontaneous mutations have led to most cases. The genetic abnormality consists of a microdeletion in chromosome 7.

Velocardiofacial (VCF) Syndrome (Chromosome 22)

Neurologists and psychiatrists have come to recognize VCF, along with Prader–Willi, and Williams, and Lesch–Nyhan, as genetic disorders with distinctive, relatively consistent neuropsychiatric manifestations. As its name implies, VCF consists primarily of abnormalities, in various combinations and degrees of severity, of the soft palate (*v*elum palatinum [Latin, *velum*, veil]), *c*ardiac system, and *f*ace.

A cleft palate or velopharyngeal dysfunction is the most obvious characteristic. The deformity causes palate insufficiency that gives the child's voice a nasal tone. Hearing the nasality, physicians may further suspect the diagnosis by inspection of the palate at rest and during voluntary retraction. In addition, VCF children may have external ear malformations that cause hearing impairment and worsen the speech impediment. The facial appearance of children with VCF has several characteristic, if not pathognomonic, features (Fig. 13-17).

Children's cardiac anomalies, which are congenital, include ventricular septal defects and abnormalities in the pulmonary artery and aorta. They often necessitate open-heart surgery.

Although VCF's primary components are physical, its neuropsychiatric comorbidities are more likely to determine the child's life course. Many VCF patients are severely retarded. They score in the borderline to mildly impaired range on IQ testing, e.g., in the 70s. Most importantly, schizophrenia and major depression emerge as many VCF children mature. For example, major depression occurs in up to approximately 40% and psychotic symptoms, which are usually indistinguishable from schizophrenia, occur in up to approximately 30% of adult VCF patients.

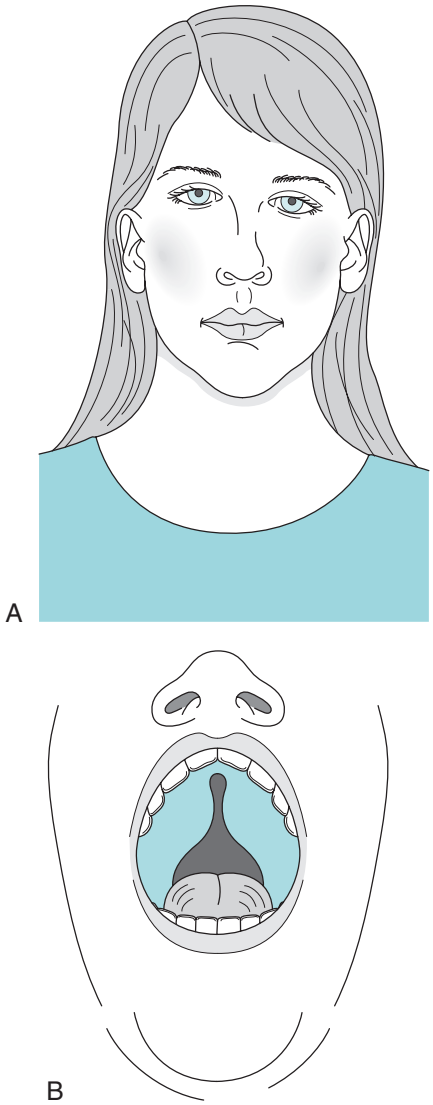


FIGURE 13-17 *A,* The face of children with velocardiofacial syndrome typically appears long, tapering to a small lower jaw (micrognathia). A tubular nose with a broad tip and small nasal alae, and deformed ears are also typical. *B,* The cleft palate, another hallmark of the disorder, may not be as overt as in this figure.

VCF, which occurs in 1/3000 children, is an autosomal dominant genetic disorder that stems from microdeletion in chromosome 22. However, with 75% or more cases occurring sporadically, VCF is inherited in only a minority of cases.

Its neuropsychiatric components offer clues to the genetic basis of schizophrenia. The VCF mutation and several others associated with schizophrenia localize to the same region on chromosome 22. Of all of them, the VCF mutation is the statistically most powerful genetic risk factor for schizophrenia. Moreover, unlike many of the other mutations associated with schizophrenia, the VCF mutation is not confined to a single ethnic population.

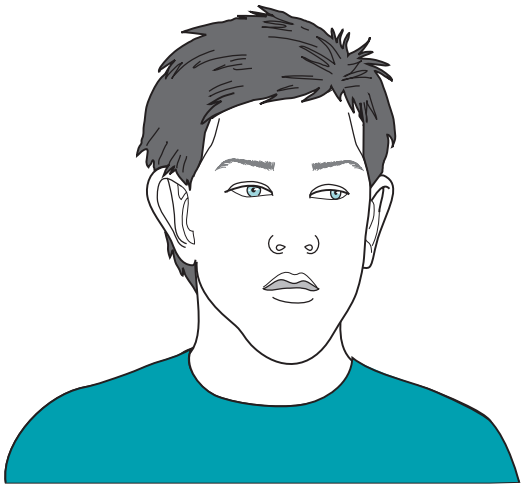


FIGURE 13-18 This fragile X syndrome boy, with the full mutation resulting in an IQ of 65, has the syndrome's typical features. He has a prominent forehead and jaw; long, thin face; and large, low-set, "seashell-shaped" ears. Although his penis will remain normal in size for his age, his testicles will grow during puberty to a remarkably large size – two- to threefold greater in volume than normal. This *macro-orchidism* occurs in almost all fragile X syndrome boys and represents the single most consistent physical anomaly.

Sex-Linked Chromosomal Disorders

Fragile X Syndrome

The *fragile X syndrome*, like many other genetic disorders, consists of mental retardation, behavioral disturbances, and distinctive nonneurologic physical stigmata (Fig. 13-18). About 70% of boys who inherit the entire or "full" mutation have moderate to severe mental retardation. In contrast, most females carrying the full mutation – typically the mother and sisters of affected boys – show none of the syndrome's physical stigmata. However, about one-third of them have borderline IQs and one-quarter have IQs of 70 or less.

Fragile X syndrome boys display strikingly abnormal behavior, including stereotypies, particularly flapping or wringing of their hands. Many bite their fingers or hands and engage in other self-injurious behavior. Mostly because of these behaviors, fragile X is the single most common monogenetic cause of autistic spectrum disorders. About 15–30% of fragile X boys have autism. They may have ADHD, anxiety, and other psychiatric disorders, but the mental retardation usually overwhelms those manifestations.

The mutation (FMR1) consists of excessive repetitions of the CGG trinucleotide in the X chromosome.*

Genetic testing can easily detect the mutation in the blood and, during prenatal screening, in amniotic fluid cells. Some neurologists have stated that all children with autism spectrum disorders and mental retardation should undergo genetic testing for fragile X. As with other excessive trinucleotide repeat disorders, the mutation tends to increase in size and its symptoms emerge at an earlier age (anticipation) and are more pronounced in successive generations.

Compared to the normal complement of 5–44 CGG repeats, boys with the full mutation typically have 200 or more repeats. In other words, boys with fragile X syndrome have 200 or more CGG repeats. Those with only 55–200 have the *premutation*, which leads to a muted version of the disorder.

Occurring in about 1 in 1200 males and half as frequently in females, and responsible for as many as 10% of all cases of mental retardation, fragile X syndrome ranks as the most common cause of inherited mental retardation. Unlike the inheritance in Down syndrome, fragile X syndrome parents regularly and predictably transmit the mutation to one or more of their children. Thus, neurologists often find that the child presenting for fragile X evaluation has a male relative with mild, if not overt, mental retardation.

Unlike boys with the full mutation, those with the *premutation* (55–200 CGG repeats) lack overt intellectual impairment and physical stigmata. Nevertheless, the premutation has several ramifications. The number of repeats in ova may expand from premutation levels to greater than 200. Thus, an asymptomatic mother who carries the premutation may have children with the syndrome. However, sperm can carry only the premutation. Thus, fathers can transmit only the premutation to their daughters. The premutation also induces developmental problems, including ADHD, depression, and features of autism spectrum disorders. Sometimes the premutation may produce manifestations only after individuals reach 40 years of age. For example, women with the premutation undergo premature ovarian failure and menopause. Also, men with the premutation may develop cerebellar dysfunction (gait ataxia and intention tremor), cognitive impairment, mood disorders, and a wide variety of other psychiatric conditions.

Rett Syndrome

Generally restricted to girls, *Rett syndrome* symptoms emerge 6–18 months after an initial normal birth and development. Then girls with Rett syndrome regress in virtually all phases of psychomotor development. Over the next several years, they lose their language skills, ability to walk, other learned motor activities, and intellectual abilities. They often deteriorate to a state of profound mental retardation. Moreover, 60–90% of them develop epilepsy, beginning on average at the age of 3 years.

Rett syndrome girls display two striking neurologic abnormalities: stereotypies and acquired microcephaly (Fig. 13-19). Their stereotypies consist of incessant hand movements, particularly hand wringing, hair pulling, clapping, or flapping. As these stereotypies progress, Rett children often lose hand function. In addition, most of them also have stereotypies that do not involve the hands, such as bruxism, mouthing, and body twisting.

*Excessive trinucleotide repeats in other genes produce Friedreich ataxia and other spinocerebellar degenerations, myotonic dystrophy, and Huntington disease (see Chapters 2, 6, and 18, respectively, and Appendix 3D). Neurologists refer to illnesses caused by excessive trinucleotide DNA repeats as polyglutamine illnesses.

FIGURE 13-19 ■ A 6-year-old girl with Rett syndrome, displaying stereotypies, incessantly moves her hands as though she were washing or clapping. In addition she pulls her hair and has bruxism. In another hallmark of the disease, her head circumference is only 48 cm, which would be normal for a 3-year-old girl, but 2 standard deviations below the mean for her age (51 cm). Because her head circumference had been normal during her first 2–3 years, neurologists determined that she had developed *acquired microcephaly*. She has also progressively lost her language ability and now cannot speak in a meaningful manner. When her symptoms first appeared, her pediatrician understandably suggested the erroneous diagnosis of autism.

Stereotypies usually first appear at about 18 months of age. Although different stereotypies emerge, the first one that appears persists through life.

Head growth follows a normal trajectory from birth to about 6 months, but then it decelerates while relatively normal body growth continues. When the head's size becomes relatively small for the body, neurologists diagnose *acquired microcephaly*. It contrasts with congenital microcephaly, as found in congenital rubella infections, where the head is small at birth.

Rett syndrome is attributable in about 85% of cases to a mutation in a gene – MECP2 – on the X chromosome. The mutation is presumably lethal to a male fetus, but a male fetus will rarely inherit an attenuated variant of the mutation and survive with a *forme fruste* of the disorder.

In typical Rett syndrome cases, loss of language, prevalence of epilepsy, and stereotypies mimic autism and Angelman syndrome; however, Rett syndrome children, for practical purposes, are only girls, have microcephaly, and regress in their motor skills. Also, in contrast to children with the common storage diseases, Rett syndrome children do not have either organomegaly or retinal abnormalities.

Lesch–Nyhan Syndrome

Another mutation carried on the X chromosome causes the infamous Lesch–Nyhan syndrome, which consists of mental retardation, a distinctive behavioral phenotype of self-mutilation, and dystonia. This disorder is transmitted in a recessive sex-linked pattern and therefore appears only in boys. Because the dystonia is the most salient feature, this book includes Lesch–Nyhan syndrome among the involuntary movement disorders (see Chapter 18).

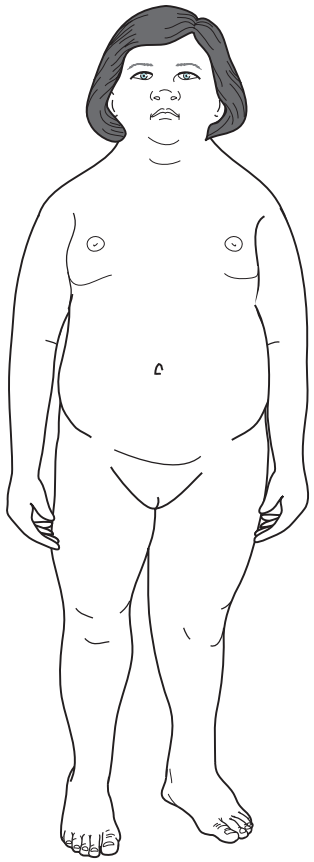


FIGURE 13-20 ■ This 16-year-old girl with Turner syndrome (XO) has mental retardation and the distinctive short stature and webbed neck. As with several other genetic disorders, her ears are low-set (but hidden by a low hairline), her nose is flat, and its bridge spreads into broad epicanthal folds. Because she characteristically failed to undergo puberty, she lacks breast development and other secondary sexual characteristics. Also, her elbows' carrying angles are relatively straight, which is the male pattern.

Turner Syndrome (XO)

Individuals with Turner syndrome have a mutation in or, more usually, absence of one of their sex chromosomes. With a complement of only 45 fully functioning chromosomes, these individuals are usually described as having an "XO" chromosome pattern. From infancy, they are outwardly phenotypically female, but with readily identifiable dysmorphic features (Fig. 13-20). In addition, they do not undergo puberty.

A minority (10–20%) of Turner syndrome girls have mild to moderate mental retardation, but the majority – up to 70% – have learning difficulties. In general, they have learning disabilities, attention deficit, and greater

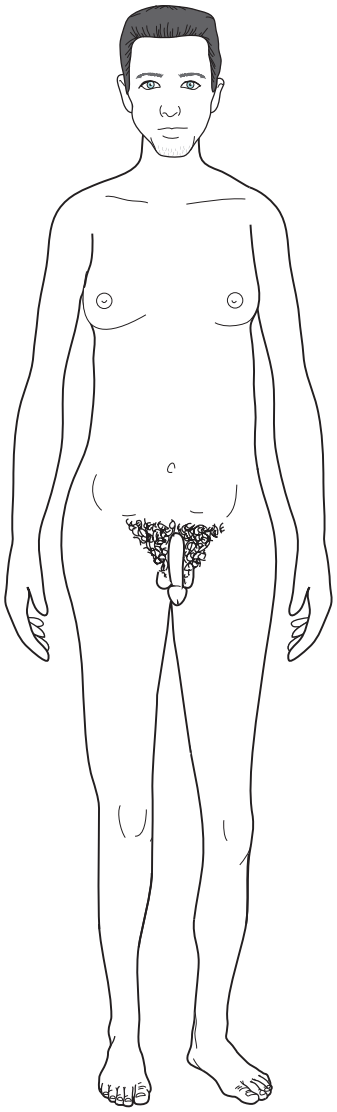


FIGURE 13-21 ■ After a delayed and then incomplete puberty, this 30-year-old man with Klinefelter syndrome (XXY) has grown taller than 6.5 feet (198 cm), largely due to his disproportionately long legs. His body has assumed a eunuchoid habitus with gynecomastia, sparse facial hair, female pattern of pubic hair, and small testicles. In addition to the XXY syndrome, conditions characterized by excessive height include the XYY and Marfan syndromes and homocystinuria.

impairment on performance than verbal IQ testing. Turner syndrome may be another example – along with Williams syndrome – of preserved verbal ability despite cognitive impairment.

Klinefelter Syndrome (XXY)

With an additional X chromosome, Klinefelter syndrome boys are tall but eunuchoid (Fig. 13-21). As young men, their unusual height and lack of secondary sexual characteristics may draw medical attention, but physicians most often diagnose Klinefelter syndrome only after the boys fail to go through puberty. In fact, physicians sometimes first discover the disorder when an infertility evaluation shows that the man has testicular dysgenesis and lacks sperm.

Klinefelter syndrome boys have a below average IQ, typically between 80 and 90. However, only about 25% have any degree of intellectual disability and, when present, it is usually mild. While in school, Klinefelter syndrome boys tend to have dyslexia and other learning disabilities. According to some reports, they have a passive personality and decreased libido.

XYY Syndrome

Men who carry an extra Y chromosome are tall, averaging 6′3″ (1.9 m), with a normal male habitus, including normal secondary male sexual characteristics, and prominent acne in adolescence. They appear quite different than those with Klinefelter syndrome. Moreover, they father children and those children have a normal chromosome complement.

The original studies of the XYY syndrome, which were performed in prisons, suggested that the disorder expressed itself as deviant, violent, and aggressive behavior. With their size and behavior, affected men were labeled "super-males." In retrospect, the population base for those studies tainted those results.

Modern studies have rejected a causal relationship between a XYY karyotype and aggression. They found that XYY men often, but not necessarily, have delays in acquiring speech and other neurodevelopmental milestones. They frequently show learning disabilities, and their IQ is 10–20 points lower than that of their siblings. Their muscles are weaker rather than stronger than controls and they have poor fine motor control. As adults, they have characterologic problems, but no increased risk of schizophrenia or bipolar disorder. If they commit a crime, it is typically not violent; however, because of their intelligence and neurodevelopmental delays, they are likely to be apprehended.

Heavy Metal Exposure

Aside from industrial accidents (such as occurred in Japan's Minamata Bay), environmental gases and eating certain fish cause most mercury toxicity in neonates and infants. Large sea fish, such as swordfish, shark, king mackerel, and tuna, and certain fresh-water ones, such as pike and bass, have relatively high mercury concentrations. Pregnant women should avoid eating all of them.

Usually consumed in an organic form (methylmercury [CH_3Hg^+]), a pregnant woman's gastrointestinal tract absorbs ingested mercury. It readily crosses the placenta and tends to accumulate in fetal brain tissue. Over time, mercury intoxication causes brain damage and eventually cognitive impairment.

On the other hand, the mercury in old-style dental fillings dissolves at such a slow rate that it carries no significant risk. Even dentists who prepared the fillings on a daily basis had no propensity to develop mercury-related illnesses. Removing mercury-containing dental fillings offers no benefits.

Several researchers and many parents proposed an ominous association between autism and the measles, mumps, and rubella (MMR) vaccination because it contained an ethylmercury ($C_2H_5Hg^+$) preservative, thimerosal. Because the vaccination may have led to a brief but significant mercury exposure in infants, several studies suggested that it caused autism and other disorders. Although vaccine manufacturers stopped adding mercury preservatives during the 1990s, the incidence of autism continued to climb. That epidemiologic data and many other studies have exonerated both the current and older MMR vaccinations as a cause of autism and other neuropsychologic impairments.

Lead intoxication in infants and children, depending on its intensity, causes mental retardation, learning disabilities, and other signs of cerebral impairment. This intoxication originates in infants and children ingesting lead-based paint chips and environmental pollution. Although acute intoxication causes seizures, the more common low-level exposure leads to subtle cognitive impairment.

REFERENCES

Adzick NS, Thom EA, Spong CY, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med 2011;364: 993–1004.

Ashwal S, Russman BS, Blaso PA, et al. Practice parameter: Diagnostic assessment of the child with cerebral palsy. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2004;62:851–63.

Bailey DB, Raspa M, Holiday D, et al. Functional skills of individuals with fragile X syndrome: A lifespan cross-sectional analysis. Am J Intellect Dev Disabil 2009;114:289–303.

Barkovich AJ, Moore KR, Grant E, et al. Diagnostic Imaging: Pediatric Neuroradiology. Philadelphia: Elsevier; 2007.

Belzeaux R, Lacon C. Neurofibromatosis type 1. Psychiatric disorders and quality of life impairment. Presse Med 2006;35:277–80.

Ben Zeev Ghidoni B. Rett syndrome. Child Adolesc Psychiatric Clin North Am 2007;16:723–43.

Bourgeois JA, Coffey SM, Rivera SM, et al. A review of fragile X premutation disorders: Expanding the psychiatric perspective. J Clin Psychiatry 2009;6:852–62.

Canfield RL, Henderson CR, Cory-Slechta DA, et al. Intellectual impairment in children with blood lead concentrations below 10 μg per deciliter. N Engl J Med 2003;348:1517–26.

Capone G, Goyal P, Ares W, et al. Neurobehavioral disorders in children, adolescents, and young adults with Down syndrome. Am J Med Genet C Semin Med Genet 2006;142C:158–72.

Cassidy SB, Driscoll DJ. Prader–Willi syndrome. Eur J Hum Genet 2009;17:3–13.

Coffey DE, Brumback RA. Pediatric Neuropsychiatry. Philadelphia: Lippincott Williams & Wilkins; 2006.

Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006;355:1345–56.

Detrait ER, George TM, Etchevers HC, et al. Human neural tube defects: Developmental biology, epidemiology, and genetics. Neurotoxicol Teratol 2005;27:515–24.

Elison S, Stinton C, Howlin P. Health and social outcomes in adults with Williams syndrome. Res Dev Disabil 2010;31:587–99.

Feinstein C, Chahal L. Psychiatric phenotypes associated with neurogenetic disorders. Psychiatr Clin North Am 2009;32:15–37.

Green T, Gothelf D, Glaser B, et al. Psychiatric disorders and intellectual functioning throughout development in velocardiofacial (22q11.2 deletion) syndrome. J Am Acad Child Adolesc Psychiatry 2009;48:1060–8.

Hadders-Algra M. The Neurological Examination of the Child with Minor Neurological Dysfunction. 3rd ed. London: Mac Keith Press; 2010.

Hagerman RJ, Berry-Kravis E, Kaufman W, et al. Advances in the treatment of fragile X syndrome. Pediatrics 2008;123:378–90.

Hankins GD, Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. Obstet Gynecol 2003;102:628–36.

Hiraiwa R, Maegaki Y, Oka A, et al. Behavioral and psychiatric disorders in Prader–Willi syndrome. Brain Dev 2007;29:535–42.

Howlin P, Udwin O. Outcome in adult life for people with Williams syndrome – results from a survey of 239 families. J Intellect Disabil Res 2006;50:151–60.

Jacquemont S, Hagerman RJ, Hagerman PJ, et al: Fragile-X syndrome and fragile X-associated tremor/ataxia syndrome: two faces of FMR1. Lancet Neurol 2007;6:45–55.

Jones KL. Smith's Recognizable Patterns of Human Malformation. 6th ed. Philadelphia: Elsevier; 2006.

Kobrynski LJ, Sullivan KE. Velocardiofacial syndrome, DiGeorge syndrome: The chromosome 22q11.2 deletion syndromes. Lancet 2007;370:1443–52.

Krakovsky G, Huth MM, Lin L, et al. Functional changes in children, adolescents, and young adults with cerebral palsy. Res Dev Disabil 2007;28:331–40.

Leyfer OT, Woodruff-Borden J, Klein-Tasman B. et al. Prevalence of psychiatric disorders in 4 to 16-year-olds with Williams syndrome. Am J Med Genet 2006;141B:615–22.

McCarthy J. Behavioral problems and adults with Down syndrome: Childhood risk factors. J Intellect Disabil Res 2008; 52:877–82.

Muzykewicz DA, Newberry P, Danforth N, et al. Psychiatric comorbid conditions in a clinic population of 241 patients with tuberous sclerosis. Epilepsy Behav 2007;11:506–13.

Neul JL, Kaufman WE, Glaze DG, et al. Rett syndrome: Revised diagnostic criteria and nomenclature. Ann Neurol 2010;68:944–50.

Pelc K, Cheron G, Dan B.Behavior and neuropsychiatric manifestations in Angelman syndrome. Neuropsychiatric Dis Treat 2008;4:577–84.

Scheimann AO, Butler MG, Gourash L, et al. Critical analysis of bariatric procedures in Prader–Willi syndrome. J Pediatr Gastroenterol Nutr 2008:46;80–3.

Siegel MS, Smith WE. Psychiatric features in children with genetic syndromes: Toward functional phenotypes. Child Adolesc Psychiatr Clin North Am 2010;19:229–61.

Stinton C, Elison S, Howlin P. Mental health problems in adults with Williams syndrome. Am J Intellect Dev Disabil 2010;115:3–18.

Temudo T, Ramos E, Dias K, et al. Movement disorders in Rett syndrome: An analysis of 60 patients with detected MECP2 mutation and correlation with mutation type. Mov Disord 2008;23:1384–90.

Urv TK, Zigman WB, Silverman W. Psychiatric symptoms in adults with Down syndrome and Alzheimer's disease. Am J Intellect Dev Disabil 2010;115:265–76.

Vignoli A, LaBriola F, Canevini MP. Evolution of stereotypies in adolescents and women with Rett syndrome. Mov Disord 2009;24: 1379–83.

Walker A, Kaufman DM, Solomon G, et al. Child and Adolescent Neurology for Psychiatrists. Philadelphia: Lippincott Williams & Wilkins; 2008.

Wiedemann HR, Kunze J. Clinical Syndromes. 3rd ed. London: Times Mirror International Publishers; 1997.

Willimas CA. The behavioral phenotypes of the Angelman syndrome. Am J Med Genet C Semin Med Genet 2010;154C:432–7.

Winterkorn EB, Pulsifer MB, Thiele EA. Cognitive prognosis of patients with tuberous sclerosis. Neurology 2007;68:62–4.

CHAPTER 13

Questions and Answers

1–11. Match the neurocutaneous disorders (a–d) with their primary manifestation (1–11).

a. Tuberous sclerosis
b. Neurofibromatosis type 1 (NF1)
c. Sturge–Weber syndrome
d. Neurofibromatosis type 2 (NF2)

1. Acoustic neuroma
2. Facial lesions vaguely resembling rhinophyma
3. Progressive dementia
4. Neurofibromas
5. Angiofibromas (adenoma sebaceum)
6. Hypopigmented macules (ash leaf spots)
7. Intractable epilepsy
8. Café-au-lait spots
9. Facial angioma
10. Optic glioma
11. Shagreen patches

Answers: 1-d; 2-a; 3-a; 4-b; 5-a; 6-a; 7-a; 8-b; 9-c; 10-b; 11-a.

12–17. Which of the following disorders cause episodic inattention or changes in mood in children? (True/False)

12. Migraine
13. Complex partial seizures
14. Antihistamines
15. Cerebral palsy
16. Sedative medications
17. Absence seizures

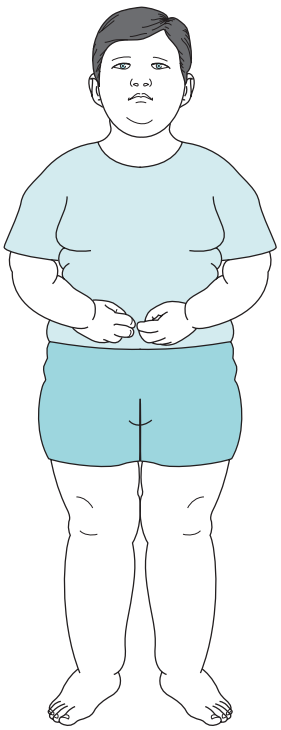
Answers: 12-True; 13-True; 14-True; 15-False; 16-True; 17-True.

18. Which genetic illness causes short stature?

a. XXY
b. XYY
c. XO
d. Marfan syndrome

Answer: c. Turner (XO), trisomy 21, XXX, and numerous metabolic syndromes cause a short stature. Klinefelter (XXY), "supermale" (XYY), and Marfan syndromes all cause a tall stature.

19. An 8-year-old boy, a son of college professors, has slowly and incompletely acquired milestones. Unlike his parents and sibs, he has suffered childhood obesity. His pediatrician recently found that he developed diabetes. He eats incessantly and disregards any limits that his parents place on his calorie consumption. After he broke away from his classmates on a school trip to the children's zoo and stole food from the rabbit cage, his teachers sent him for a psychiatric evaluation. Which abnormality explains his appearance and behavior?



a. Attention deficit hyperactivity
b. Fragile X syndrome
c. Valproate
d. A DNA deletion
e. A hypothalamic tumor

Answer: d. He has Prader–Willi syndrome. This disorder, which results from a deletion in chromosome 15, has several important aspects. It accounts for a small but significant segment of the childhood obesity epidemic. It may hold clues to the mechanism of satiety because children within this disorder lack negative feedback (stop eating) when either their blood sugar rises or their stomach is distended. Also, their compulsive behavior has an obvious but unexplained genetic basis. None of various bariatric surgical procedures has alleviated the obesity. Surprisingly, although obesity and neuropsychiatric

disturbances characterize Prader–Willi syndrome, the presence and severity of these two stigmata do not correlate in individual cases. Valproate leads to weight gain but not of this magnitude or with the compulsive eating. Hypothalamic tumors may cause obesity, but it develops over several months and is usually accompanied by headache, visual impairment, and sleep disorders.

20. A 40-year-old man with Down syndrome, his older brother states, has had a decline in his functional ability, the development of apathy, and loss of his social ability. Which of the following conditions should the physician consider?
a. Depression
b. Dementia
c. Leukemia
d. Hypothyroidism
e. All of the above

Answer: e. During and after their teenage years, Down syndrome individuals are prone to comorbid depression. They are also vulnerable to hypothyroidism and acute leukemia. Frequently occurring hearing loss, which was not listed, may cause or compound their communication and social ability. Most importantly, because they harbor three copies of chromosome 21, they tend to develop Alzheimer disease – with all its pathologic features – routinely and at a young age.

21. Which of the following conditions is the most common manifestation of NF1?
a. Mental retardation
b. Learning disabilities
c. Autistic behavior
d. Psychosis

Answer: b. Depending on the criteria, learning disabilities and hyperactivity commonly complicate NF1. Although mental retardation affects 4–8% of NF1, its prevalence is only slightly elevated compared to the general population (3%). Autistic behavior and psychosis are no more prevalent in NF1 individuals than in the general population.

22. Which two of the following characteristics distinguish Rett syndrome from autism?
a. Only girls affected
b. Stereotyped behavior
c. Loss of language skills
d. Seizures
e. Acquired microcephaly

Answer: a, e. Stereotyped behavior and seizures are common to autism and Rett syndrome. In fact, about 30% of autistic children and 70–90% of those with Rett syndrome develop epilepsy by the time they are adults. Language deficiency is variable.

23. Which syndrome carries the lowest incidence of mental retardation?
a. Klinefelter syndrome
b. Trisomy 21
c. Angelman syndrome
d. Down syndrome
e. Fragile X
f. Prader–Willi syndrome

Answer: a. Moderate to severe mental retardation is an integral part of all these conditions except for Klinefelter syndrome (XXY). Only about 30% of Klinefelter syndrome individuals, who are phenotypically male, have mental retardation. In addition, when they have mental retardation, it is usually mild. Often Klinefelter syndrome remains undetected until they undergo an evaluation for infertility.

24. A 1-year-old boy has a stroke because of sickle cell disease. It results in mild right hemiparesis. Which three of the following conditions will probably be additional consequences?
a. Chorea
b. Aphasia
c. Seizures
d. Spastic cerebral palsy
e. Stunted growth (growth arrest) of right arm

Answer: c, d, e. He will probably not have aphasia because, after an insult to his left hemisphere, the right will emerge as dominant for language and fine motor function.

25–30. Match the disorder (a–d) with its cause (25–30).
25. Choreoathetosis
26. Spastic quadriplegia
27. Spastic hemiparesis
28. Deafness
29. Seizure disorder
30. Cortical blindness
a. Cervical cord injury
b. Kernicterus
c. Werdnig–Hoffmann disease
d. Stroke *in utero*

Answer: 25-b; 26-a; 27-d; 28-b; 29-d; 30-c.

31. Which chromosome carries the mutation that determines velocardiofacial (VCF) syndrome?
a. Chromosome 22
b. Chromosome 7
c. Chromosome 15
d. Chromosome 12

Answer: a. A microdeletion on chromosome 22 determines VCF. The mutation is autosomal dominant. Because it appears as a sporadic mutation in 75% of cases, neither parent usually has the disorder. This mutation is a major risk factor for schizophrenia that cuts across ethnic lines. Chromosome 7 determines Williams syndrome; chromosome 15, Prader–Willi and Angelman; chromosome 12, phenylketonuria (PKU).

32. Regarding PKU, which one of the following statements is false?

a. The disease is transmitted in an autosomal recessive pattern.
b. The blood phenylalanine is high and tyrosine is low in affected individuals.
c. When PKU women conceive, their fetus would most likely be heterozygote for the PKU gene, and would therefore be unaffected by the mother's diet.
d. Diet sweeteners and many other "foods" contain phenylalanine, which individuals with PKU should avoid.

Answer: c. Woman with PKU, who must be homozygous for the disorder, bear children who, with rare exceptions, are heterozygote. (If the father were heterozygote, which is statistically unlikely, each of their offspring is 50% likely to be homozygous. If the father had PKU and therefore was homozygote for the disorder, 100% of their offspring would be homozygous.) Assuming that a pregnant woman, who has PKU, strays from her diet and consumes foods with phenylalanine, such as diet soda: she will accumulate excessive concentrations of phenylalanine. The phenylalanine and metabolic products readily cross the placenta. Even though the fetus is heterozygous (or, in rare instances, homozygous), those phenylalanine-containing substances will overwhelm its immature enzyme system and cause brain damage. Pregnant women with PKU must adhere strictly to their phenylalanine-free diet. A synthetic tetrahydrobiopterin (a cofactor of PAH), sapropterin (Kuvan), offers some protection.

33. When asked to assess a 9-year-old girl for poor social interactions, a psychiatrist learns that she had late acquisition of her developmental milestones. Her IQ is 88 and she has poor arithmetic and visual-spatial skills. Her handwriting is sloppy and she has impaired fine motor skills. On the other hand, she is articulate and verbal. In an entirely one-sided conversation, the child explained that she has learned two foreign languages, which she speaks with a natural accent, and plays two musical instruments. She has a cute upturned nose and her teeth are hypoplastic and wide-spaced. Which is the most likely disorder?
a. Rett syndrome
b. Turner syndrome
c. PKU
d. Angelman syndrome
e. Williams syndrome
f. Klinefelter syndrome

Answer: e. She has Williams syndrome, which the psychiatrists identified by the girl's elflike face, small and wide-spaced teeth, and neuropsychiatric disturbances. The underlying mutation causes mild to moderate intellectual disability with poor visual-spatial relationships resulting in constructional apraxia. In contrast, children and adults with Williams syndrome typically show outstanding verbal and musical abilities; however, their conversations remain notoriously one-sided and superficial.

34. Which other manifestations are likely to be present in the girl in Question 33?
a. Supravalvular aortic stenosis
b. Microcephaly
c. Stereotypies
d. Hepatosplenomegaly

Answer: a. Williams syndrome involves impaired formation of tissue elastin, which leads to supravalvular aortic stenosis. Although microcephaly does not appear in Williams syndrome, it is a manifestation of several other conditions, including Rett syndrome, Angelman syndrome, and congenital rubella infection. Stereotypies – repetitive, involuntary, meaningless movements, usually of the hands – are characteristic of several neurologic conditions, particularly Rett, Angelman, and fragile X syndromes. Stereotypies may also occur, although transiently, in complex partial and absence seizures.

35. Which one of the following statements concerning individuals with the XYY karyotype is true?
a. They live up to their appellation, "super-males".
b. They are usually taller than 6 feet and they tend to have facial acne.
c. They frequently have aggressive behavior and commit violent crimes.
d. Their karyotype is a valid defense against criminal prosecution.

Answer: b. Individuals with the XYY karyotype are phenotypic men and they can have children. They average 6 feet 3 inches and have acne, but they do not have pronounced muscle growth, unusually great strength, or athletic abilities. Their intellectual growth is slow and often does not reach average. They probably do not commit crimes more frequently or more violently than other individuals with mild intellectual impairment; however, they are less able to evade arrest than criminals with normal intellectual capacity. They remain cognizant of their activities and the legal system considers them culpable.

36. A 10-year-old boy with mental retardation has a tall stature, dislocated ocular lenses, and pectus carinatum. Which enzyme is probably deficient?
a. Cystathionine synthetase
b. Hypoxanthine-guanine transferase (HGPRT)
c. Phenylalanine hydroxylase
d. Tyrosine hydroxylase

Answer: a. Because of a deficiency in cystathionine synthetase, he has homocystinuria, which is caused by a mutation on chromosome 21. Its most prominent manifestations consist of mental retardation, dislocated lenses, tall stature, and skeletal abnormalities. Elevated serum homocysteine levels are a risk factor for stroke. HGPRT deficiency causes Lesch–Nyhan syndrome. Phenylalanine hydroxylase deficiency causes PKU. Tyrosine hydroxylase deficiency leads to parkinsonism.

37. Meningomyeloceles are not associated with which one of the following conditions?
a. Spastic paraparesis
b. Mental retardation
c. Incontinence

d. Meningitis
e. Flaccid quadriparesis

Answer: a. A meningomyelocele is a congenital neural tube closure defect. It causes flaccid, not spastic, paraparesis because of malformation of the junction of the lowest portion of the spinal cord and its emerging nerve roots. In addition, meningomyeloceles are often associated with comparable defects in the upper neural tube that often lead to hydrocephalus.

38. Which neurologic condition is associated with immunodeficiency?
a. Neurofibromatosis
b. Meningomyelocele
c. Sturge–Weber syndrome
d. Ataxia-telangiectasia

Answer: d. Ataxia-telangiectasia is associated with an IgA and IgE immunoglobulin deficiency as well as cellular immunity impairment. Lymphomas develop in ataxia-telangiectasia patients because of the immunodeficiency.

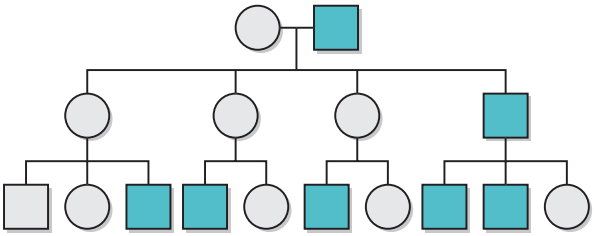
39. Match the condition (a–e) with its clinical feature (1–5).
a. Adrenoleukodystrophy
b. Rett syndrome
c. Fragile X syndrome
d. Down syndrome
e. Meningomyelocele
1. In only girls, autistic behavior, repetitive hand slapping, and acquired microcephaly
2. In only boys, progressive deterioration of mental and motor abilities
3. In boys and girls, short stature, prominent epicanthal folds, single crease, low-set ears, and mental retardation
4. In boys and girls with paraparesis, urinary incontinence, hydrocephalus, and mental retardation
5. In boys, but less commonly in girls, mental retardation and large ears; in boys, macro-orchidism

Answers: a-2; b-1; c-5; d-3; e-4.

40. Match the structures with their origin in the fetal ectoderm or mesoderm.
a. Brain
b. Scalp and face
c. Dura mater
d. Neural tube
e. Vertebrae
f. Spinal cord
g. Skull

Answer: Ectoderm: a, b, d, f. Central nervous system (CNS) fetal ectodermal structures include the neural tube and skin. Mesoderm: c, e, g. CNS-associated mesodermal structural elements include the skull, dura mater, and vertebrae.

41. With which of the following conditions is the following genotype most consistent?



a. Juvenile Huntington disease
b. Trisomy 21
c. Rett syndrome
d. Tuberous sclerosis
e. Fragile X
f. Tuberous sclerosis

Answer: e. The genotype illustrates a sex-linked recessive mutation carried by the Y chromosome. Fragile X inheritance fits, but this genotype is consistent with adrenoleukodystrophy, Duchenne dystrophy, Lesch–Nyhan syndrome, red–green color blindness, most cases of hemophilia, and even strains of male-patterned baldness. Tuberous sclerosis and Huntington disease, in its juvenile as well as its adult variant, are transmitted as an autosomal dominant. Trisomy 21 is rarely inherited. Although the Rett syndrome mutation (MECP2) is carried on the X chromosome, it is fatal in males and therefore appears only in girls.

42. Which of the following supplements reduces the incidence of meningomyelocele?
a. Thiamine
b. Vitamin A
c. Folic acid
d. Omega-3

Answer: c. Studies have found that 5 mg a day of folic acid before conception and during the first month of pregnancy reduces the incidence of neural tube defects by 85%.

43. Match the manifestations (1–10) with the genetically based disorder (a–d).
1. Stereotypies
2. Acquired microcephaly
3. Associated with trisomy 21
4. Mental retardation complicated by Alzheimer-like dementia
5. Nasal speech
6. A single palm crease
7. Large ears and large testes (macro-orchidism)
8. Autistic behavior
9. Cognitive deterioration arising in childhood
10. The full syndrome occurs almost exclusively in girls
a. Rett syndrome
b. Fragile X syndrome

c. Down syndrome
d. VCF syndrome

Answers: 1-a; 2-a; 3-c; 4-c; 5-d; 6-c; 7-b; 8-a, b; 9-a; 10-a.

44. A 14-year-old girl is short, severely obese, and mildly mentally retarded. Her karyotype shows 23 chromosome pairs, including a normal XX, but 15q has a deletion. Which is the most likely syndrome?
a. Angelman
b. Turner
c. Fragile X
d. Prader–Willi
e. Down
f. Trisomy 21

Answer: d. All these disorders, including fragile X, can occur in girls and cause mental retardation. Of children with mental retardation, the obesity points suggests Prader–Willi syndrome, which is confirmed by the deletion in 15q. Angelman syndrome also results from the deletion in 15q, but its manifestations include severe mental retardation and hyperactivity. Turner syndrome (XO), which only occurs in girls, results from an absent sex chromosome, leaving only 22 full (autosomal) chromosome pairs with the single (X) chromosome.

45. Which is the most common neuropathology among premature infants who develop cerebral palsy?
a. Periventricular leukomalacia
b. Kernicterus
c. Microgyria
d. Porencephaly

Answer: a. In premature infants, periventricular leukomalacia, the destruction of the white matter surrounding the lateral ventricles, is closely associated with the subsequent development of cerebral palsy. Kernicterus, bilirubin staining of basal ganglia associated with the subsequent development of athetosis, is uncommon because of the prevention of hemolysis from Rhesus factor incompatibility and effective treatments of hyperbilirubinemia with exchange transfusion and phototherapy. Microgyria is small gyri of unknown cause throughout the entire cerebrum or in a limited area. Neurologists or neuropathologists sometimes find this condition in children with mental retardation. Porencephaly is essentially a hole in the brain that might have resulted from an *in utero* arterial occlusion or simply maldevelopment (see Fig. 20-4).

46. Which one of the following statements is true regarding fragile X syndrome?
a. Its symptoms occur exclusively in boys.
b. When trinucleotide repeats are abnormally long, but still within in the 55–200 range, affected boys and girls may remain completely or almost completely asymptomatic.
c. Fragile X syndrome is a rare cause of mental retardation.
d. When it causes mental retardation, the cognitive impairment is unaccompanied by behavioral changes.

Answer: b. Features of fragile X syndrome, such as learning disabilities and mild intellectual impairment, may occur in girls carrying the full mutation on one chromosome. Girls who inherit the mutation on both of their X chromosomes often show unequivocal disabilities. Boys with 55–200 trinucleotide repeats – the premutation – on their X chromosome generally have few symptoms, but those who have the full mutation typically have moderate to severe mental retardation. Overall, fragile X syndrome is the most common cause of *inherited* mental retardation.

47. Which of the following syndromes is least likely to include autism-like symptoms?
a. Fragile X
b. Rett
c. Klinefelter
d. Angelman
e. Tuberous sclerosis

Answer: c. Physicians often diagnose children with the other conditions as having autism, autism-like symptoms, or pervasive developmental disorder.

48. Which of the following diets or dietary supplements will best reduce elevated serum homocysteine levels?
a. Folic acid and vitamins B_6 and B_{12}
b. A methionine-free diet
c. Homocysteine
d. A phenylalanine-free diet

Answer: a. Although a methionine-free diet will lower serum homocysteine levels, the best strategy is to administer folic acid and vitamins B_6 and B_{12}. B_{12} deficiency, homocystinuria, and some antiepileptic drugs raise the serum homocysteine level.

49. Which of the following might expose a fetus to high levels of mercury?
a. Maternal dental fillings
b. The mother eating canned tuna every day
c. The mother eating fresh salmon every day
d. The mother eating trout every day

Answer: b. Large, predatory fish – shark, tuna, king mackerel, and swordfish – have relatively high concentrations of methylmercury, which readily crosses the placenta. Old-style mercury-containing dental amalgams cause an insignificant mercury exposure.

50. In the mid-1990s vaccine manufacturers stopped using ethylmercury (thimerosal), as a preservative in measles, mumps, and rubella (MMR) vaccinations. What effect did this change in policy have on the incidence of autism?
a. The incidence continued to rise with no change in rate

b. The incidence continued to rise but at a slower rate
c. The incidence began to fall
d. The incidence immediately fell to zero

Answer: a. The elimination of thimerosal from MMR vaccinations was not followed by a change in the steadily increasing rate of autism.

51. Asked to see a 19-year-old woman who is recovering from ventricular septal defect surgery, a psychiatrist learns from her parents that she has had depressive episodes at least since she was 16 years old and a cleft palate that required surgical repair in infancy. The psychiatrist finds that the woman has nasal speech, external ear deformities, and mild to moderate intellectual disability. Which of the following disorders or syndromes is most likely to underlie the woman's defects?
a. Prader–Willi
b. Turner
c. VCF
d. Williams

Answer: c. With anomalies of her heart, palate, and ears, and intellectual disability, this patient has the VCF syndrome. An important aspect of VCF is the prevalence of mood disorder and schizophrenic symptoms in adults with this syndrome. Congenital cardiac disease may complicate Turner and Williams syndromes as well as VCF.

52. A 6-year-old girl, born after a normal gestation and delivery to neurologically normal unrelated parents, began to lose her developmental milestones at age 3 years. Her language suffered the most, but then she stopped playing and simply clapped her hands for hours at a time. Looking back at her head circumference determinations, her pediatricians calculated that she had acquired microcephaly. Which mutation most likely explains her appearance, behavior, and development?

a. MECP2 mutation
b. Excessive trinucleotide repeats on the X chromosome
c. Microdeletion on chromosome 15
d. Excessive trinucleotide repeats on the short arm of chromosome 4

Answer: a. She has Rett syndrome, which is caused by a mutation in the gene MECP2 (methyl CpG-binding protein 2) in about 85% of cases. That gene governs the synthesis of methyl CpG-binding protein, which is critical to cell function because, in large part, it silences other genes.

53. In which trimester of pregnancy does cerebral myelination begin?
a. First
b. Second
c. Third
d. None of the above

Answer: c. Cerebral myelination begins only in the third trimester of pregnancy and is not complete until the second year of life.

54. What is the underlying cause of the following illnesses: Williams, Prader–Willi, and Angelman syndrome?
a. They result from excessive trinucleotide repeats.
b. They result from microdeletions.
c. They result from mitochondrial DNA mutations.
d. They are sex-linked disorders.

Answer: b. These disorders each result from minute deletions – microdeletions – in chromosomal DNA.

55. What is the incidence of epilepsy in Rett syndrome?
a. 10–20%
b. 33%
c. 50%
d. ≥60%

Answer: d. The incidence of seizures in Rett syndrome is 60–90%, but in autism approximately 33%. Because of these syndromes' stereotypies and intermittent loss of contact, children with these disorders seem to experience frequent seizures. On the other hand, physicians should not overlook seizures in these patients.

56. Testing shows that this 7-year-old boy, with lifelong slow development, has an IQ score of 60. He has no seizures, physical neurologic deficits, or general medical illness. His parents and two sisters have average intelligence. His X chromosomes tend to break in certain culture media. Which of the following is most likely to occur?

a. He is apt to suffer further decline in his IQ.
b. Some of his sisters' sons will have low IQ scores.
c. Some of his brothers' sons will have low IQ scores.
d. All his progeny will be unaffected.

Answer: b. In the context of his mental retardation, this boy's large, low-set ears indicate that he has fragile X syndrome. Once he reaches puberty, further examination will reveal another sign, *macro-orchidism* (large testicles). Children with the full fragile X syndrome, who are almost always male, additionally show symptoms of autism in 15–30% of cases. In fact, the fragile X mutation is the single most common monogenetic cause of autistic spectrum disorders. Because the mutation consists of a gene on the X chromosome containing excessive trinucleotide repeats, it tends to expand in successive generations. This expansion makes symptoms appear earlier and more profoundly (anticipation) in children and grandchildren. Fragile X syndrome causes mild to profound mental retardation.