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Human Genetic Disorders

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CHROMOSOMAL DISORDERS

Chromosomal Aneuploidy

Trisomy 21 (Down Syndrome)

Chromosome and Gene Location

- Additional chromosome 21
- Critical region at 21q22

Inheritance

- 95% meiotic nondisjunction (47 chromosomes present)
  - 80–90% maternal, increases with maternal age
  - 10–20% paternal
- 3–4% unbalanced translocation (46 chromosomes with an extra chromosome 21 fused to another acrocentric chromosome)
  - 66% sporadic (not inherited)
  - 33% balanced translocation in one parent
- 1–2% mosaicism (at least two different cell lines)
  - Results from postzygotic nondisjunction or loss of the extra 21 in one cell line

Incidence

- 1/800 live births

Clinical Manifestations

- Flat facial profile, thick nuchal fold, upward slanting palpebral fissures, depressed nasal bridge, epicanthal folds, Brushfield spots of iris (Fig. 13.1A), single transverse palmar crease (Fig. 13.1B), gap between the first and second toes (Fig. 13.1C), and low-set c-shaped ears
- Developmental delay, learning disabled (IQ = 40–80), poor Moro reflex, infantile hypotonia, joint hyperflexibility, and increased risk for Alzheimer disease
- Congenital heart defects (endocardial cushion defects including atrioventricular canal defect and ventricular septal defects), increased risk for childhood acute leukemia, hypothyroidism, obesity, short stature, increased incidence of pulmonary hypoplasia, and duodenal atresia
- Ultrasound findings may include increased nuchal translucency, thickened nuchal fold, congenital heart defects, duodenal atresia, short humerus and femur, short middle phalanx of fifth finger, and echogenic bowel
- Seventy-five percent spontaneously abort in first trimester. Of those live born, 80% survival at age 30

Laboratory

- Chromosome analysis identifies extra chromosome 21
- Prenatal diagnosis through chromosome analysis of chorionic villi or amniocentesis
- An increased risk could be indicated by altered prenatal maternal serum markers or non-invasive prenatal screening (NIPS) using cell-free fetal nucleic acids

Treatment

- Not curable, supportive/symptomatic

Trisomy 13 (Patau Syndrome)

Chromosome and Gene Location

- Additional chromosome 13

Inheritance

- 80% meiotic nondisjunction (47 chromosomes present)
  - 80–90% maternal, increases with maternal age
  - 10–20% paternal
- 20% unbalanced translocation (46 chromosomes with an extra chromosome 13 fused to another acrocentric chromosome)

Incidence

- 1/10,000 births

Clinical Manifestations

- Midline abnormalities ranging from simple ocular hypotelorism to cyclopia to complete absence of eyes, prominent occiput, microcephaly, malformed low-set ears, cleft lip and palate, polydactyly, and transverse palmar crease (Fig. 13.2)
- Complete or incomplete holoprosencephaly, severe intellectual disability, seizures, deafness, hypotonia, and apneic spells

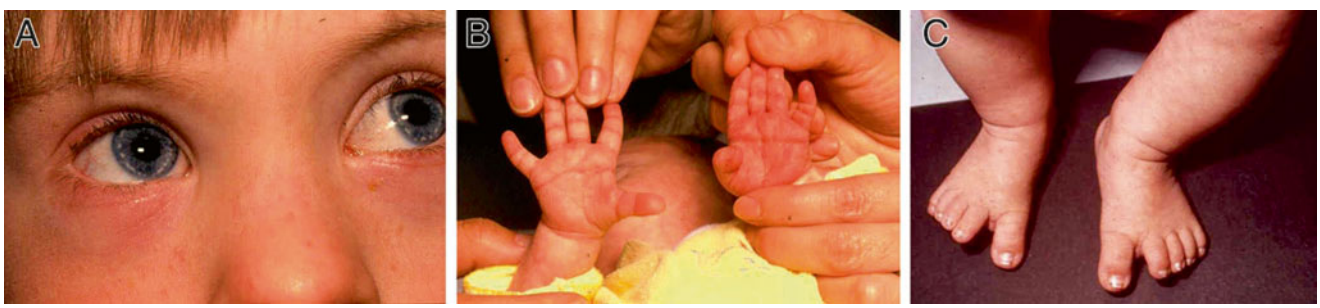

Fig. 13.1. Down syndrome – brushfield spots on irides (**A**). Single transverse palmar creases and fifth finger clinodactyly (**B**). Gap between first and second toe (**C**).

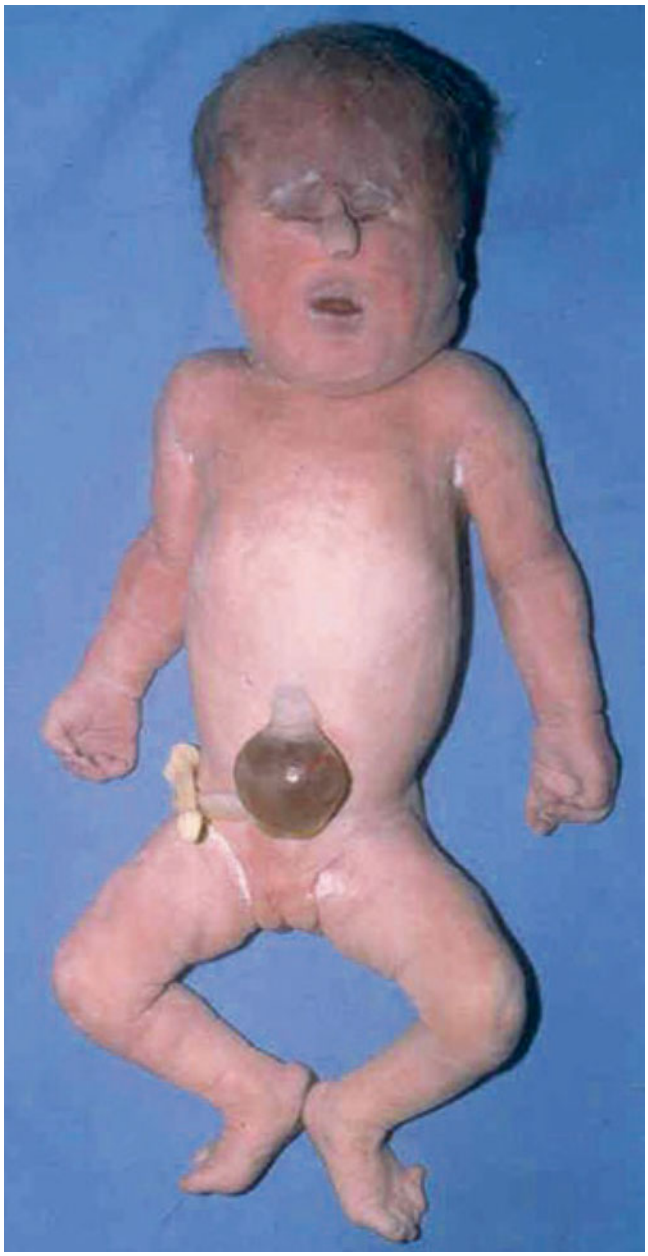

Fig. 13.2. Trisomy 13 – showing hypertelorism and tubelike nasal structure. Polydactyly on foot.

- Congenital heart defects (hypoplastic left heart and ventricular septal defects), urogenital defects, cryptorchidism, bicornuate uterus and hypoplastic ovaries, polycystic kidneys, umbilical hernia, and omphalocele
- Ultrasound findings may include holoprosencephaly, cleft lip and palate, cystic hygroma, polydactyly, congenital heart defects, cystic kidneys, and omphalocele
- 95% spontaneously abort. Of those live born, 90% die within first year of life

Laboratory

- Chromosome analysis identifies extra chromosome 13
- Prenatal diagnosis through chromosome analysis of chorionic villi or amniocentesis
- An increased risk could be indicated by altered prenatal maternal serum markers or non-invasive prenatal screening (NIPS) using cell-free fetal nucleic acids

Treatment

- Not curable, supportive/symptomatic

Trisomy 18 (Edward Syndrome)

Chromosome and Gene Location

- Additional chromosome 18

Inheritance

- Meiotic nondisjunction
  - 95% maternal, increases with maternal age
  - 5% paternal

Incidence

- 1/5,000–1/10,000 births

Clinical Manifestations

- Microcephaly with prominent occiput, micrognathia, malformed ears, clenched hands, second and fifth digits overlapping third and fourth (Fig. 13.3), rocker bottom feet, single transverse palmar crease, and hypoplastic nails
- Severe intellectual disability, seizures, and hypertonia
- Severe intrauterine growth retardation, congenital heart defects (ventricular septal defects), urogenital defects, cryptorchidism, horseshoe kidney, diaphragmatic hernia, and omphalocele
- Ultrasound findings may include clenched hands, club and rocker bottom feet, micrognathia, congenital heart defects, omphalocele, diaphragmatic hernia, neural tube defects, choroid plexus cysts, and cystic hygroma

Life Expectancy

- 95% spontaneously abort. Of those live born, 90% die within first year of life

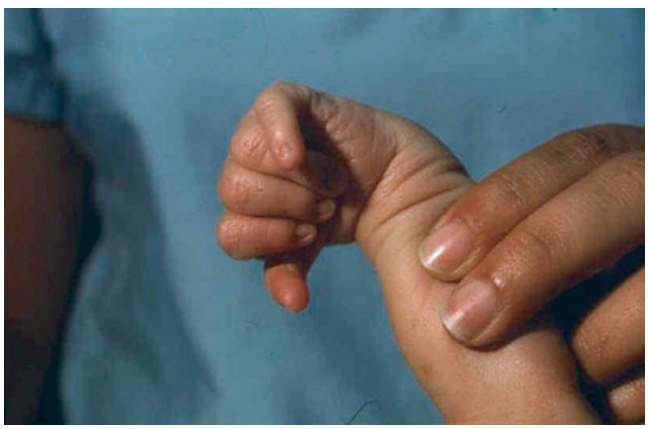

Fig. 13.3. Trisomy 18 – clenched hand and overlapping fingers.

Laboratory

- Chromosome analysis identifies extra chromosome 18
- Prenatal diagnosis through chromosome analysis of chorionic villi or amniocentesis
- An increased risk could be indicated by altered prenatal maternal serum markers or non-invasive prenatal screening (NIPS) using cell-free fetal nucleic acids

Treatment

- Not curable, supportive/symptomatic

Klinefelter Syndrome (XXY)

Chromosome and Gene Location

- Extra X chromosome in a male

Inheritance

- Meiotic nondisjunction
  - 55% maternal nondisjunction
  - 45% paternal nondisjunction
- Also may be mosaic XY/XXY or rarely XX/XXY

Incidence

- 1/800 males

Clinical Manifestations

- Tall habitus, undervirilized, small testes, gynecomastia, and poor musculature
- Mild delay, behavioral immaturity, shyness, learning disabilities (reading) speech delay
- Infertility
- Normal life expectancy

Laboratory

- Chromosome analysis identifies XXY
- Prenatal diagnosis through chromosome analysis of chorionic villi or amniocentesis
- Maternal serum screening and ultrasound findings are not useful
- An increased risk could be indicated by non-invasive prenatal screening (NIPS) using cell-free fetal nucleic acids

Treatment

- Testosterone supplementation for the development of secondary sexual characteristics

Turner Syndrome (45, X)

Chromosome and Gene Location

- Missing or structurally abnormal X chromosome

Inheritance

- 55% 45,X
  - 80% loss of paternal X chromosome
  - 20% loss of maternal X (no maternal age effect)
- 25% 46,XX
  - Structural alteration in one X chromosome
- 15% mosaic
  - 45,X with 46,XX, 46,XY, or others

Incidence

- 1/2,000–1/5,000 female births
- Most common chromosome finding in spontaneous abortions

Clinical Manifestations

- Short stature, webbed neck (Fig. 13.4), lymphedema of hands and feet, high arched palate, cystic hygroma, low posterior hairline, and hypoplastic widely spaced nipples
- Normal or near normal intelligence; may have delay in speech, neuromotor skills, and learning abilities
- Gonadal dysgenesis (infertility, primary amenorrhea), renal malformations (horseshoe kidney), cardiovascular malformations (coarctation of aorta, hypoplastic left heart), and increased risk for gonadoblastoma if mosaic for some Y chromatin

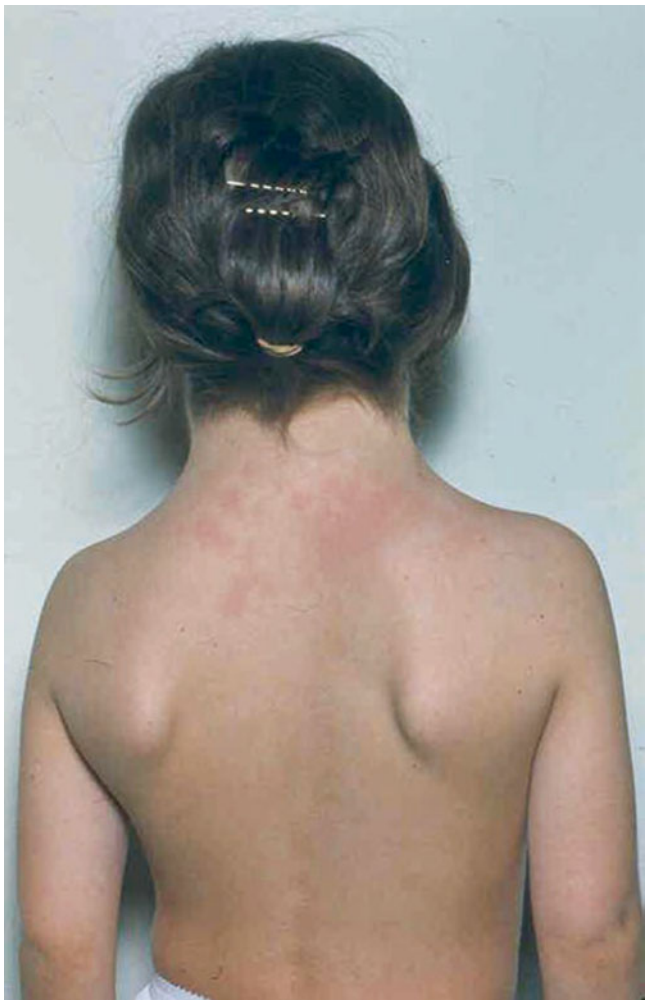

Fig. 13.4. Turner syndrome – webbing of the neck and low posterior hairline.

- Ultrasound findings include cystic hygroma (detectable after 10 weeks), lymph collections (ascites, pleural effusion), congenital heart disease, and renal anomalies
- 99% spontaneously abort; those who survive infancy usually reach adulthood

Laboratory

- Chromosome analysis indicates monosomy X or other variants
- Prenatal diagnosis through chromosome analysis of chorionic villi or amniocentesis
- An increased risk could be indicated by altered prenatal maternal serum markers or non-invasive prenatal screening (NIPS) using cell-free fetal nucleic acids

Treatment

- Estrogen, thyroid, and growth hormone replacement therapy for development of secondary sexual characteristics and growth

Microdeletion Syndromes

- See Table 13.1

Angelman Syndrome

Chromosome and Gene Location

- 15q11.2

Inheritance

- Angelman syndrome results from the loss of the maternally imprinted region at chromosome 15q11.2. Loss can occur via numerous mechanisms. Recurrence is dependent on mechanism of loss
  - 60–70% deletion of maternal 15q11.2
  - 5% paternal uniparental disomy (UPD) (two copies of the paternal chromosome)
  - 3% imprinting defect
  - 11% ubiquitin-protein ligase E3A (*UBE3A*) mutation
  - 11% unknown

Incidence

- 1/20,000

Clinical Manifestations

- Prominent mandible, open-mouthed expression, hyperreflexia, microcephaly, brachycephaly, and optic atrophy
- Ataxia, severe intellectual disability, seizures, and gross motor developmental delay
- Absent speech, inappropriate laughter, arm flapping, and feeding difficulties
- Most survive into adulthood

Laboratory

- First-tier testing
  - Molecular methylation analysis identifies missing maternal allele
  - Methylation-sensitive multiple ligation-dependent probe amplification (MLPA) detects missing maternal allele or deletion
- Second-tier testing
  - Fluorescent in situ hybridization (FISH) or chromosomal microarray (CMA) identifies deletion
  - Molecular UPD studies identify two copies of paternal allele
  - Sequence analysis identifies mutations in *UBE3A* gene
  - Mutation analysis of imprinting center

Treatment

- Not curable, supportive/symptomatic

Table 13.1. **Microdeletion Syndromes**

Syndrome	*Features*	*Location*
Angelman	Ataxia, seizures, happy demeanor, severe intellectual disability	15q11–q13
Chromosome 1p36 deletion	Intellectual disability, dysmorphic, hypotonia, seizures	1p36
Chromosome 22q11.2 deletion (DiGeorge, velocardiofacial)	Cleft palate, heart defect, developmental delay, thymic and parathyroid hypoplasia	22q11.2
Cri du chat	"Cat-like" cry as newborn, microcephaly, intellectual disability	5p15.2
Miller–Dieker	Lissencephaly, intellectual disability	17p13.3
Prader–Willi	Hyperphagia, obesity, intellectual disability, hypogonadism, small hands and feet	15q11–q13
Smith–Magenis	Sleep disturbances, self-injurious behaviors, intellectual disability	17p11.2
Williams	Supravalvular aortic stenosis, intellectual disability, hypercalcemia, social personality	7q11.2
Wolf–Hirschhorn	High, broad nasal bridge, microcephaly, growth deficiency, clefting, hypertelorism, intellectual disability	4p16

Prader–Willi Syndrome

Chromosome and Gene Location

- 15q11.2

Inheritance

- Prader–Willi syndrome results from the loss of the paternally imprinted region at chromosome 15q11.2. Loss can occur via numerous mechanisms. Recurrence is dependent on mechanism of loss
  - 75% deletion of paternal 15q11.2
  - 20–25% maternal UPD (two copies of maternal chromosome 15)
  - Remainder is thought to be due to imprinting defects

Incidence

- 1/10,000–1/25,000

Clinical Manifestations

- Hypotonia, hypogonadism, obesity, small hands and feet, almond-shaped eyes, and short stature
- Mild to moderate intellectual disability
- Failure to thrive and hyperphagia
- Most survive into adulthood

Laboratory

- First-tier testing
  - Molecular methylation analysis identifies missing paternal allele
  - Methylation-sensitive MLPA detects missing paternal allele or deletion
- Second-tier testing
  - FISH and/or CMA identifies deletion
  - Molecular UPD studies identify two copies of maternal allele if either first-tier test is abnormal
  - Mutation analysis of imprinting center

Treatment

- Not curable, supportive/symptomatic

1p36 Microdeletion Syndrome

Chromosome and Gene Location

- 1p36

Inheritance

- 90–95% sporadic
- 5–10% familial translocations

Incidence

- 1/5,000–10,000

Clinical Manifestations

- Microcephaly, deep-set eyes, flat nasal bridge, cardiac malformations, and hypotonia
- Intellectual disability and seizures
- Growth retardation
- Most survive into adulthood

Laboratory

- Deletion may or may not be detected on chromosome analysis depending upon resolution of the study and size of the deletion
- FISH and/or CMA identifies deletion

Treatment

- Not curable, supportive/symptomatic

Cri Du Chat Syndrome

Chromosome and Gene Location

- 5p15

Inheritance

- 85–90% sporadic (85% deletion, 4% mosaics, 3% ring chromosomes, 4% translocations)
- 10–15% familial translocations, inversions, and parental mosaicism

Incidence

- 1/50,000

Clinical Manifestations

- "Cat-like" cry, microcephaly, hypertelorism, micrognathia, transverse palmar crease, and hypotonia
- Intellectual disability
- 50% no speech, growth failure
- Most survive into adulthood

Laboratory

- Deletion may or may not be detected on chromosome analysis depending upon resolution of the study and size of the deletion
- FISH and/or CMA identifies deletion

Treatment

- Not curable, supportive/symptomatic

22q Deletion Syndrome (DiGeorge/Velocardiofacial Syndrome)

Chromosome and Gene Location

- 22q11.2

Inheritance

- 90% are deletions involving multiple genes
- Approximately 10–15% are familial (autosomal dominant)

Incidence

- 1/4,000

Clinical Manifestations

- The disturbance of neural crest migration of pharyngeal pouches is thought to cause clinical features
- Interpatient variability may be dependent on extent of deletion

- Hypertelorism, down-slanting eyes, high arched palate, micrognathia, low-set ears, bulbous nose, square nasal tip, cleft palate (velocardiofacial (VCF)), small open mouth, retrognathia, microcephaly, and slender hands and digits
- Cardiac manifestations include tetralogy of Fallot, outflow tract defect, right-sided aortic arch, interrupted aortic arch, and ventricular septal defect
- Mild-moderate learning difficulties, seizures, tetany, and emotional and behavioral problems
- Hypoparathyroidism, neonatal hypocalcemia (DiGeorge (DGS)), immune/T-cell deficit (DGS), hypernasal speech, hypospadius, and short stature
- Most reach adulthood if cardiac lesion is not life threatening

Laboratory

- Hypocalcemia, decreased T cells
- Deletion of 22q11 is usually not visible on chromosome analysis
- FISH and/or CMA identifies deletion

Treatment

- Cardiac surgery, calcium supplements, and supportive care

Smith–Magenis Syndrome

Chromosome and Gene Location

- 17p11.2

Inheritance

- Most are sporadic interstitial deletions
- A few cases of pericentric inversions with breakpoints in 17p11

Incidence

- 1/50,000

Clinical Manifestations

- Brachycephaly, flat, broad midface, and prominent forehead
- Seizures and intellectual disability
- Hyperactivity, sleep disturbances, behavioral problems including screaming outbursts and self-mutilation behaviors, and speech delay
- Most survive into adulthood

Laboratory

- Chromosome analysis detects deletion in most cases
- FISH and/or CMA identifies deletion

Treatment

- Not curable, supportive/symptomatic

Miller–Dieker Syndrome

Chromosome and Gene Location

- 17p13.3

Inheritance

- 90% are sporadic deletions
- Approximately 10–15% are familial

Incidence

- 1/100,000

Clinical Manifestations

- Lissencephaly, microcephaly, anteverted nostrils, carp mouth, and agenesis of corpus callosum
- Seizures and intellectual disability
- Failure to thrive and absent speech
- Life expectancy is variable, but most die in childhood

Laboratory

- Deletion may or may not be detected on chromosome analysis depending upon resolution of the study and size of the deletion
- FISH and/or CMA identifies deletion

Treatment

- Not curable, supportive/symptomatic

Williams Syndrome

Chromosome and Gene Location

- 7q11.23

Inheritance

- Mostly sporadic
- Few cases of autosomal dominant inheritance have been reported

Incidence

- 1/20,000 live births

Clinical Manifestations

- Broad forehead, bitemporal narrowness, periorbital fullness, wide mouth, broad nasal tip, long philtrum, micrognathia, growth retardation, and small widely spaced teeth
- Cardiac manifestations include supravalvular aortic stenosis and peripheral pulmonary stenosis
- Intellectual disability
- Gregarious personality, joint limitations, and hypercalcemia
- Most survive into adulthood

Laboratory

- Elevated serum calcium
- Deletion is usually not visible on chromosome analysis
- FISH and/or CMA identifies deletion

Treatment

- Not curable, supportive/symptomatic
- Elimination of vitamin D and calcium from the diet

Wolf–Hirschhorn Syndrome

Chromosome and Gene Location

- 4p16.3

Inheritance

- 85–90% sporadic
- 10–15% familial translocations

Incidence

- 1/50,000

Clinical Manifestations

- Microcephaly, hypertelorism, micrognathia, and hypotonia
- Seizures and intellectual disability
- Congenital heart defects, renal malformations, and genital malformations
- Most survive into adulthood

Laboratory

- Deletion may or may not be detected on chromosome analysis depending upon resolution of the study and size of the deletion
- FISH and/or CMA identifies deletion

Treatment

- Not curable, supportive/symptomatic

Chromosome Breakage Syndromes

Fanconi Anemia

Chromosome and Gene Location

- Genetically heterogeneous (multiple gene loci involved)

Inheritance

- Autosomal recessive

Incidence

- 1/22,000

Clinical Manifestations

- Short stature, absent or hypoplastic radii and thumbs, brown skin pigmentation, cryptorchidism, and renal anomalies
- Pancytopenia, anemia, increased incidence of leukemia, and solid tumors

Molecular Basis of Disease

- Multiple complementation groups have been identified and appear to be involved in the formation of a protein complex that participates in a DNA damage response pathway. The exact molecular mechanism that leads to impaired genomic stability has not been elucidated

Laboratory

- Increased chromosomal breakage, gaps, and rearrangements after exposure to diepoxybutane or mitomycin C (DNA alkylating agents)
- Mutation analysis is available for specific mutations

Treatment

- Transfusions and bone marrow transplantation
- Not curable, supportive/symptomatic

Bloom Syndrome

Chromosome and Gene Location

- 15q26.1

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical Manifestations

- Short stature
- Facial erythema
- Increased susceptibility to infections
- Increase incidence of leukemia
- High pitched voice

Molecular Basis of Disease

- Decreased activity of DNA ligase I leads to genomic instability and multisystem anomalies

Laboratory

- Increased sister chromatid exchange (12× normal)
- Quadrilateral formation is increased as are random breaks and translocations between nonhomologous chromosomes

Treatment

- Not curable, supportive/symptomatic
- Minimize exposure to radiation/mutagenic agents

Ataxia Telangiectasia

Chromosome and Gene Location

- 11q22–q23, *ATM* gene

Inheritance

- Autosomal recessive

Incidence

- 1/40,000–1/100,000

Clinical Manifestations

- Cerebellar ataxia, conjunctival telangiectasia, and IgA deficiency
- Predisposition to malignancy
- Increased infections
- Growth failure, onset first 2 years of life

Molecular Basis of Disease

- Defect in DNA repair mechanisms leading to chromosomal breakage, increased intrachromosomal recombination, sensitivity to ionizing radiation (IR), and abnormal resistance to inhibition of DNA synthesis by IR

Laboratory

- Increased chromosomal breakage and X-radiation sensitivity; especially with breakpoints at sites of immunoglobulin genes or receptors
- 7;14 chromosomal translocation is identified in 5–15% of cells
- Molecular analysis of *ATM* gene identifies mutation in approximately 95% of patients

Treatment

- Not curable, supportive/symptomatic
- Treatment of infections and neoplasms and avoidance of radiation

Xeroderma Pigmentosum

Chromosome and Gene Location

- Multiple loci

Inheritance

- Autosomal recessive

Incidence

- 1/250,000

Clinical Manifestations

- Sensitivity to sunlight (blistering and freckling with little exposure, beginning in childhood)
- Predisposition to malignancy (especially skin cancer)
- Mental deterioration in some

Molecular Basis of Disease

- Defect in ultraviolet-induced DNA repair mechanisms
- Skin cells unable to repair sunlight-induced DNA damage

Laboratory

- Diagnosis is based on clinical criteria; no routine clinical laboratory abnormality is observed in patients with XP
- Cytogenetic analysis can identify clones of cells with chromosome abnormalities, increased ultraviolet-induced chromosome breaks, and sister chromatin exchanges
- Fibroblasts show UV hypersensitivity and abnormal unscheduled DNA synthesis

Treatment

- Not curable, supportive/symptomatic
- Avoidance of ultraviolet light

TRINUCLEOTIDE REPEAT DISORDERS

- A growing number of inherited disease syndromes (primarily neurologic) are known to be caused by the abnormal presence of an expanded tract of trinucleotide repeats within disease-specific genes (Table 13.2)
- Typically, the clinical hallmark of these trinucleotide repeat diseases is anticipation. Anticipation is defined as the clinical observance of an earlier age of onset and increased rate of disease progression due to amplification in the number of expanded repeats in successive generations
- The diagnosis is made by determining the number of trinucleotide repeats within a specific disease-causing expandable allele (within the proper clinical context). The normal allele will have a "normal range" of trinucleotide repeats, whereas the disease-associated (expanded) allele will contain an increased number of repeats (in the hundreds and thousands, for some diseases)

Fragile X Syndrome

Chromosome and Gene Location

- Xq27.3

Inheritance

- X-linked dominant

Incidence

- 1/5,000 males (accounts for up to 5% of male intellectual disability)
- 1/2,500 females

Clinical Manifestations

- Intellectual disability
- Large narrow face, prominent forehead and jaw, with moderately increased head circumference, and large ears
- Macroorchidism (80%)

Molecular Basis of Disease

- Expanded CGG repetitive element within *FMR1* gene
  - 5–44 normal
  - 45–54 intermediate (minimal expansion due to meiotic instability in a small percentage of cases), no associated phenotype
  - 55–200 premutation (meiotic instability with potential to expand to full mutation), fragile X-associated tremor/ataxia syndrome (FXTAS) characterized by cerebellar ataxia with the observation of white matter lesions on MRI and intentional tremor is observed in both males and females with almost half of all male premutation carriers affected by age 79; other clinical manifestations of FXTAS include memory loss, cognitive deficit, parkinsonism, and neuropathy; premature ovarian failure (POF) is also observed in an average 21% of female premutation carriers; however, penetrance is inversely correlated with the number of repeats in the intermediate and premutation carrier ranges

Table 13.2. **Trinucleotide Repeat Disorders**

Disease	*Gene*	*Gene location*	*Repeat sequence*	*Repeat location, type of region*	*Normal allele size (no. of repeats)*	*Expanded mutant allele (fully penetrant)*
Fragile X syndrome	*FMR1*	Xq	CGG	Noncoding region of Exon 1, 5′ untranslated region	5–44	>200
Myotonic dystrophy type 1	*DMPK*	19q	CTG	3′ untranslated region	5–34	50 to >2,000
Myotonic dystrophy type 2	*CNBP/ ZNF9*	3q	CCTG	Intron 1	11–26	75–11,000
Friedreich ataxia	*FXN*	9q	GAA	Intron 1	5–33	66–1,700
Huntington disease	*HTT*	4p	CAG	Exon 1, polyglutamine coding	10–26	>40
Spinocerebellar ataxia type 1	*ATXN1*	6p	CAG	Exon 8, polyglutamine coding	19–38	>38
Spinocerebellar ataxia type 2	*ATXN2*	12q	CAG	Exon 1, polyglutamine coding	14–31	>32
Spinocerebellar ataxia type 3	*ATXN3*	14q	CAG	Exon 10, polyglutamine coding	<44	52–86
Spinocerebellar ataxia type 6	*CACNA1A*	19p	CAG	3′ End of gene, polyglutamine coding	4–18	20–33
Spinocerebellar ataxia type 7	*ATXN7*	3p	CAG	Exon 1, polyglutamine coding	4–19	>36
Spinal and bulbar muscular atrophy	*AR*	Xq	CAG	Exon 1, polyglutamine coding	11–34	>37

  - >200 full mutation, leads to abnormal methylation and transcriptional suppression of *FMR1* gene and absence of FMRP (RNA binding protein)
  - CGG repeat expansion is through female germ line (males transmit premutation repeat without much change)
- Sherman paradox
  - Describes apparent deviation from traditional Mendelian inheritance and varies according to whether the causative gene is transmitted through a male or female
  - In fragile X, this is the result of expansion from premutation to full mutation through the female germ line only

Laboratory

- Molecular analysis (PCR and Southern blot with methylation analysis) detects expanded CGG repeat and is the recommended first-tier molecular test, as expanded CGG repeats account for ~99% of disease-causing mutations
- Molecular analysis by sequencing and dosage analysis detect the remaining 1% of *FMR1* mutations
- Chromosomal fragile site may be apparent by standard chromosome analysis when cultured in folate-deficient/thymidine inhibiting media

Treatment

- Not curable
- Supportive/symptomatic

Myotonic Dystrophy Type 1

Chromosome and Gene Location

- 19q13.2

Inheritance

- Autosomal dominant

Incidence

- 1/8,000 (DM1 and DM2, together, represent the most common muscular dystrophy in adults)

Clinical Manifestations

- Myotonia (sustained muscle contraction), muscle wasting, and facial weakness
- Cataracts
- Hypogonadism
- Frontal balding
- Cardiac conduction disturbances

- Diabetes mellitus (5%)
- Swallowing and speech disability
- Respiratory failure
- Neonatal hypotonia
- Delayed motor development
- Wide phenotypic range and age of onset from severely affected infants (congenital DM1) to classically affected adults (classic DM1) to minimally symptomatic elderly individuals (mild DM1) with mildly affected adults having myotonia and cataracts vs congenital DM1 which is characterized by severe weakness and often fatal respiratory insufficiency

Molecular Basis of Disease

- Expansion of a trinucleotide CTG repeat in the myotonic dystrophy protein kinase (*DMPK*) gene
  - 5–34 normal allele size
  - 35–49 mutable normal (premutation) allele; not associated with disease
  - >50 full penetrance allele; severity of phenotype increases as repeat size increases (mild DM1: 50–150 repeats; classic DM1: 100–1,000 repeats)
  - >1,000 full penetrance allele, severely affected (congenital form)
  - Expansion occurs preferentially through maternal transmission but can also occur through paternal transmission

Laboratory

- Molecular analysis identifies expanded repeat in nearly 100% of cases
- Electromyogram demonstrates characteristic electrical myotonic discharges
- Muscle biopsy may show marked proliferation of fibers within the central nuclei, sacroplasmic masses, and type 1 muscle fiber atrophy

Treatment

- Not curable, supportive/symptomatic
- Monitor and treat for cataracts, cardiac conduction disturbances, diabetes, sleep apnea, hypogonadism, and other endocrine problems

Myotonic Dystrophy Type 2 (Proximal Myotonic Myopathy)

Chromosome and Gene Location

- 3q21.3

Inheritance

- Autosomal dominant

Incidence

- 1/8,000 (DM1 and DM2; together, the most common muscular dystrophy in adults)

Clinical Manifestations

- Myotonia (sustained muscle contraction), proximal weakness primarily in the thighs, and muscle pain
- Cataracts
- Cardiac conduction disturbances
- Insulin insensitivity predisposing to hyperglycemia and diabetes mellitus
- Hypogonadism
- Onset typically occurs in the third decade of life
- Myotonic dystrophy type 2 includes DM2 and proximal myotonic myopathy (PROMM)

Molecular Basis of Disease

- Expansion of a trinucleotide CCTG repeat in intron 1 of the *CNBP/ZNF9* gene
  - Reported allele sizes usually include the total number of repeats/base pairs in the $(TG)_n(TCTG)_n(CCTG)_n$ repeat tract all present at the DM2 locus
  - Tetranucleotides (TCTG or GCTG) commonly interrupt the CCTG repeats in the normal range; however, these sequence interruptions are not found in fully expanded pathogenic alleles
  - 11–26 CCTG repeats (104–176 bp total allele length) normal allele
  - 27–74 CCTG repeats (177–372 bp total allele length) intermediate normal (intermediate/borderline alleles of unclear significance) allele; never been reported
  - 75–11,000 CCTG repeats (372–44,000 bp total allele length) full penetrance allele
  - CCGT repeat size typically contracts through either maternal or paternal transmissions and somatic instability causes CCGT repeat sizes to increase as the affected individual ages
  - Phenotype and age of onset cannot be predicted by CCGT repeat size as there is no correlation between repeat size and severity of disease

Laboratory

- Molecular analysis identifies expanded repeat in 99% of cases
- Electromyogram demonstrates characteristic electrical myotonic changes
- Muscle biopsy may show marked proliferation of fibers within the central nuclei and type 2 muscle fiber atrophy

Treatment

- Not curable, supportive/symptomatic
- Monitor and treat for cataracts, cardiac conduction disturbances, diabetes, and hypogonadism

Friedreich Ataxia

Chromosome and Gene Location

- 9q21.11

Inheritance

- Autosomal recessive

Incidence

- 1/25,000–1/50,000

Clinical Manifestations

- Progressive ataxia, muscle weakness, dysarthria, and dysphagia
- Absent deep tendon reflexes and decreased vibration and/or joint-position sense
- Optic nerve atrophy (25%)
- Deafness (13%)
- Scoliosis
- Hypertrophic cardiomyopathy (66%)
- Bladder dysfunction (urinary frequency and urgency)
- Hammer toes, pes cavus (foot deformity marked by high arch), and restless leg syndrome
- Diabetes (30%) or glucose intolerance (50%)
- Obstructive sleep apnea (20%)
- Age of onset is approximately 10–15 years for classic Friedreich ataxia (FRDA); however, ~15% of cases are associated with delayed onset (late-onset FRDA, LOFA, and very late-onset FRDA, VLOFA), and ~12% are associated with delayed-onset and intact tendon reflexes (FRDA with retained reflexes, FARR)

Molecular Basis of Disease

- Expansion of a trinucleotide GAA repeat in intron 1 of the frataxin *(FXN)* gene
  - 5–33 normal allele
  - 34–65 premutation (meiotic instability with potential to expand to full penetrance allele) allele. (Note: the term borderline alleles, defined as 44–66, is sometimes used because the shortest repeat length associated with disease has not yet been clearly determined)
  - 66–1,700 full penetrance allele
  - Carriers of permutation alleles are very rare; therefore, expansion of alleles from one generation to the next is typically not observed, and anticipation is not a hallmark characteristic of this disease
  - Statistically significant correlations have been observed between the size of the smaller of the two expanded alleles and age of onset (i.e., LOFA and VLOFA), presence of leg muscle weakness, duration of wheelchair use, and presence of other clinical manifestations

Laboratory

- Molecular analysis identifies two expanded repeat sizes in 90–94% of cases
- Molecular analysis by sequencing and dosage analysis detects the remaining *FXN* mutations
- Nerve conduction studies generally show slow or absent sensory nerve conduction velocities but normal motor nerve conduction

Treatment

- Not curable, supportive/symptomatic
- Monitor for hypertrophic cardiomyopathy (by echocardiography and electrocardiogram), diabetes, and deafness
- Treat with assistive devices for weakness, antispasmodic agents for bladder dysfunction, and speech therapy to maximize communication

Huntington Disease

Chromosome and Gene Location

- 4p16.3

Inheritance

- Autosomal dominant

Incidence

- 3/100,000–7/100,000 (Western European ancestry)
- 0.1/100,000–15/100,000 (range, all ethnicities)

Clinical Manifestations

- Slowly progressive fatal disorder with onset of neurologic or psychiatric changes usually in mid-life (35–44 years)
- Life expectancy is approximately 50–60 years or about 15–18 years after initial onset of disease
- Early (preclinical)
  - Behavioral/mood changes and personality changes (72%)
  - Depression
  - Anxiety
  - Delusions and hallucinations
  - Abnormal eye movements
  - Minor changes in coordination and movement
- Middle (clinical)
  - Chorea (90%)
  - Involuntary movements
  - Difficulty with voluntary movements (slow, difficult to initiate or control, impaired reaction time, trouble with balance and walking)
  - Weakness
  - Dysarthria and dysphagia
  - Cognitive decline
- Late
  - Inability to walk and speak
  - Incontinence
  - Rigidity and dystonia
  - Total dependence on others
- Juvenile Huntington disease (onset prior to age 20 years) is characterized by motor, cognitive, and psychiatric changes; however, the clinical presentation differs and is much more severe than in adults; epileptic seizures are also common

Molecular Basis of Disease

- Disease results from an expansion of a trinucleotide CAG repeat in exon 1 of the *HTT* gene
  - 10–26 normal allele
  - 27–35 intermediate allele (meiotic instability, expansion to full penetrance allele may occur with transmission); not associated with disease
  - 36–39 reduced penetrance allele (at risk but not certain to develop symptoms of disease)
  - >40 full penetrance allele
  - >60 full penetrance allele is associated with juvenile onset Huntington disease
  - Expansion can occur through both maternal and paternal transmission; however, large expansions are more frequently observed through paternal transmission
  - Inverse correlation between number of CAG repeats and age of onset

Laboratory

- Molecular analysis identifies expanded repeat in 100% of cases
- Imaging studies such as magnetic resonance imaging (MRI) identifies atrophy of the caudate nucleus and putamen

Treatment

- Not curable, supportive/symptomatic

Autosomal Dominant Cerebellar Ataxias

Chromosome and Gene Location

- Numerous loci have been identified, and more than 30 subtypes have been delineated (commonly referred to as spinocerebellar ataxias, SCAs are numbered by subtype with the exception of DRPLA; dentatorubropallidoluysian atrophy)

Inheritance

- Autosomal dominant

Incidence

- 1–5/100,000

Clinical Manifestations

- Clinical manifestations vary by subtype; however, the most common features include adult-onset gait ataxia, dysarthria, ataxia (NOS), visual disturbance and diplopia, and dizziness
- Peripheral neuropathy
- Death usually occurs 10–20 years following age of onset

Molecular Basis of Disease

- Many subtypes of spinocerebellar ataxia (SCA) result from expansion of trinucleotide CAG repeat, although some (e.g., SCA5) result from nonrepeat mutations
- SCA3 (also known as Machado–Joseph disease) is the most common subtype followed by SCA 1, 2, 6, and 7 (represented in Table 13.2)

Laboratory

- Molecular analysis identifies expanded trinucleotide repeat in most subtypes
- Neuroimaging may be necessary to distinguish hereditary forms of ataxia from acquired forms

Treatment

- Not curable, supportive/symptomatic

Spinal and Bulbar Muscular Atrophy (Kennedy Disease)

Chromosome and Gene Location

- Xq12

Inheritance

- X-linked recessive

Incidence

- 1/50,000 males

Clinical Manifestations

- Teen to adult onset, usually in the third to fifth decades of life
- Slowly progressive proximal muscle weakness, muscle atrophy, and fasciculations with bulbar involvement, dysarthria, and dysphagia
- Androgen insensitivity (gynecomastia, reduced fertility, testicular atrophy)
- Normal life expectancy

Molecular Basis of Disease

- Expansion of trinucleotide CAG repeat in the human androgen receptor (AR) gene
  - 11–34 normal allele size
  - 35 unknown clinical significance
  - 36–37 reduced penetrance allele (at risk but not certain to develop symptoms of disease)
  - >37 full penetrance allele
  - The larger the expansion, the earlier the age at onset of disease and the more rapid the disease progression

Laboratory

- Molecular analysis identifies expanded repeat in 100% of cases

Treatment

- Not curable, supportive/symptomatic
- Hormone replacement as needed
- Monitor with annual strength testing and pulmonary function

NEUROMUSCULAR DISORDERS

Duchenne/Becker Muscular Dystrophy

Chromosome and Gene Location

- Xp21.2

Inheritance

- X-linked recessive

Incidence

- 1/3,500 (male) 1/1,500 (female carriers)
  - 30% of cases are new mutations
  - 5–15% of sporadic cases are result of gonadal mosaicism (mother carries a subpopulation of oocytes with the mutation)

Clinical Manifestations

- Duchenne muscular dystrophy
  - Proximal muscle weakness leading to difficulties involving gait, jumping, and climbing stairs
  - Positive for Gower sign (use of arms to push oneself into standing position by moving hands up one's thighs, indicative of hip weakness)
  - Pseudohypertrophy of the calf muscles and proximal muscle weakness
  - Rapidly progressive with loss of ability to walk before age 13
  - Dilated cardiomyopathy (100% after by age 18)
  - Intellectual disability (25–35%)
  - Death usually occurs by the third decade in most
- Becker muscular dystrophy
  - Milder course of muscle involvement with later-onset skeletal muscle weakness
  - Slower progression, wheelchair dependent after age 16
  - Survival into the 30–40 s, with dilated cardiomyopathy being the most common cause of death
  - Cognitive problems are rare
- Female carriers of Duchenne/Becker muscular dystrophy (DMD or BMD)
  - Muscle weakness (19% DMD carriers, 14% BMD carriers)
  - Myalgia cramps (5%)
  - Left ventricle dilation (19% DMD carriers, 16% BMD carriers)
  - Dilated cardiomyopathy (8% of DMD carriers)

Molecular Basis of Disease

- Dystrophin is a protein found in the sarcolemma of normal muscle. It is thought to be involved in the anchoring of the cytoskeleton of the muscle cell to extracellular proteins
- DMD and BMD result from alterations within the dystrophin (*DMD*) gene
- Deletions in 50–70% of DMD and BMD
  - Deletions that disrupt the reading frame of the triplet code (frameshift mutations) lead to DMD
  - Deletions that do not disrupt the reading frame of the triplet code (in-frame mutations) most often lead to BMD
- Duplications in 5–10% of DMD and BMD
- Point mutations in 20–35% of DMD and 10–20% of BMD

Laboratory

- Pathology
  - Variability in size of muscle fibers, degeneration, atrophy of individual fibers, and proliferation of endomysial and perimysial connective tissue
- Antidystrophin antibodies detect
  - <5% of normal dystrophin in DMD
  - 5–20% in mild DMD or severe BMD
  - >20% normal dystrophin correlates with BMD
- Serum creatinine phosphokinase (CK) concentration
  - >5–10× the normal range (100% of affected individuals)
  - 50% of DMD carriers and 33% of BMD carriers have elevated CK levels (2–10× normal)
  - Caution must be used as CK levels vary with age, pregnancy, and activity
- Genetics
  - Deletions and duplications detected directly by molecular analysis
  - Linkage analysis is available when deletion/duplication analysis negative

Treatment

- Not curable, supportive/symptomatic
- Treatment of dilated cardiomyopathy with medication and transplantation in rare cases
- Corticosteroid therapy (prednisone) in affected individuals to improve strength and function

Spinal Muscular Atrophy, Types I–IV

Chromosome and Gene Location

- 5q13.1

Inheritance

- Autosomal recessive

Incidence

- 1/25,000

Clinical Manifestations

- See Table 13.3

Molecular Basis of Disease

- Survival motor neuron *(SMN1)* gene is homozygously deleted in nearly all of types I and II and about 80% of type III spinal muscular atrophy (SMA)
- 2–5% of type I SMA is caused by compound heterozygosity for an *SMN1* deletion and point mutation
- The presence of three or more copies of *SMN2*, a gene just adjacent to *SMN1*, is associated with a milder SMA phenotype in individuals with two *SMN1* deletions and/or point mutations

Laboratory

- The primary test used to diagnose individuals with SMA is molecular analysis for deletions in exon 7 and/or exon 8 of *SMN1* gene
- Muscle biopsy reveals group atrophy of type 1 and type 2 muscle fibers

Treatment

- Not curable, supportive/symptomatic

Charcot–Marie–Tooth Disease

Chromosome and Gene Location

- Numerous loci have been identified

Inheritance

- Autosomal dominant, recessive and X-linked forms (see Table 13.4)

Incidence

- 1/3,300 (the most common genetic cause of neuropathy)

Clinical Manifestations

- Hereditary neuropathy resulting in progressive distal muscular atrophy and weakness of arms and legs (presenting in first to third decade)
- Pes cavus
- CMT1 – Charcot–Marie–Tooth type 1 (50%)
  - Demyelinating peripheral neuropathy
  - Distal muscle weakness and atrophy
  - Decreased nerve conduction velocities
  - Absent deep tendon reflexes
  - Onset 5–25 years
  - Six subtypes (CMT1A–CMT1F) are distinguishable only by molecular analysis
  - Autosomal dominant inheritance
- CMT2 – Charcot–Marie–Tooth type 2 (20–40%)
  - Axonal (non-demyelinating) neuropathy
  - Distal muscle weakness and atrophy
  - Normal or slightly decreased nerve conduction velocities
  - Deep tendon reflexes are preserved
  - Milder phenotype than CMT1
  - 15 subtypes distinguishable by molecular analysis
  - Autosomal dominant inheritance
- Autosomal dominant intermediate CMT
  - Demyelinating and axonal neuropathy

Table 13.3. **Spinal Muscular Atrophy (SMA) Subtypes**

Type I (Werdnig–Hoffmann)	*Type II (Dubowitz disease)*	*Type III (Kugelberg–Welander)*	*Type IV*
Onset 0–6 months	Onset after 6 months	Onset after 10 months	Onset second or third decade of life
Reduced fetal movements	Mild/arrested type 1	Ambulation feasible	Muscle weakness
General muscle weakness	Low muscle tone	Waddling gait	Independent ambulation
Low muscle tone	Non-ambulatory	Muscle weakness	
Respiratory muscle weakness	Finger trembling	Fasciculations	
Arthrogryposis	Absent tendon reflexes	Contractures	
Tongue fasciculations	Increased life span when respiratory function preserved		
Contractures			
Lack of motor development			
Absence of tendon reflexes			
Death often by 1 year			

Table 13.4. **Charcot–Marie–Tooth (CMT) Subtypes**

Disorder (% of CMT)	*CMT1 (50 %)*		*CMT2*	*CMT4*	*X-linked CMT*
	CMT1A (70–80 %)	*CMT1B (5–10 %)*	*(20–40 %)*	*(rare)*	*(10–20 %)*
Gene location	17p	1q	Multiple loci	Multiple loci	X
Gene name	*PMP22*	*MPZ*	Multiple genes	Multiple genes	*GJB1* (*90 %*), *PRPS1*, other unknown genes
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive	X-linked dominant
Molecular genetics	1.5 kb duplication of *PMP22*, point mutations in *PMP22*	Point mutations in *MPZ*	Point mutation in *NFL* and *HSPB1*	Point mutations in *GDAP1*, *EGR2*, or *PDX*	Point mutations in *GJB1*

  - Decreased nerve conduction velocities
- CMT4 – Charcot–Marie–Tooth type 4
  - Demyelinating or axonal neuropathy
  - Distal muscle weakness and atrophy
  - Pes cavus
  - Autosomal recessive inheritance
- CMTX – X-linked Charcot–Marie–Tooth (10–15%)
  - Axonal neuropathy in males, intellectual disability, deafness, and spasticity
  - Five subtypes

Molecular Basis of Disease

- Multiple genes at different loci are involved (see Table 13.4). Molecular analysis is available for many subtypes. Some subtypes are clinically indistinguishable and are designated solely on molecular findings

Laboratory

- Molecular testing is available for many of the CMT subtypes
- Electrophysiological studies and nerve biopsy may be helpful in distinguishing it from other acquired and hereditary forms of peripheral neuropathy and in establishing a diagnosis of CMT

Treatment

- Not curable, supportive/symptomatic

Hereditary Neuropathy with Liability to Pressure Palsies

Chromosome and Gene Location

- 17p11.2

Inheritance

- Autosomal dominant

Incidence

- Unknown

Clinical Manifestations

- Recurrent transient palsies (i.e., carpel tunnel syndrome and foot drop)
- Sensory dysfunction (result of compression to peripheral nerve)
- Pes cavus (20%)
- Absent ankle reflexes (50–80%) and reduced tendon reflexes (15–30%)
- Scoliosis

Molecular Basis of Disease

- Deletion at 17p11.2 involving the peripheral myelin protein 22 *(PMP22)* gene (80%) or point mutations in the *PMP22* gene (20%)
- Unequal crossing over between misaligned repetitive elements leads to the hereditary neuropathy with liability to pressure palsies (HNPP) deletion and the CMT1A duplication syndromes
- De novo mutations are most often paternally derived

Laboratory

- Cytogenetics using FISH or molecular genetics analysis identifies deletion at 17p11.2 involving the *PMP22* gene or a point mutation
- Nerve biopsy reveals sausage-shaped swellings of myelin sheath
- Increase in distal motor latency of the median nerve at the wrist in both symptomatic and asymptomatic individuals
- Reduced motor and sensory nerve conduction velocity

Treatment

- Not curable, supportive/symptomatic

SKELETAL DISORDERS

Craniosynostosis

Apert Syndrome

Chromosome and Gene Location

- 10q24 (*FGFR2*)

Inheritance

- Autosomal dominant, vast majority due to new mutation

Incidence

- 1/65,000–1/100,000

Clinical Manifestations

- Brachycephaly due to coronal craniosynostosis
- Hypoplasia of midface and hypertelorism
- "Mitten hand" deformity; symmetric and severe osseous or cutaneous syndactyly affecting hands and feet, and broad thumbs and great toes
- Fused cervical vertebrae, typically C5–C6
- Genitourinary anomalies in 10%
- Cardiac anomalies in 10%
- Intellectual disability

Molecular Basis of Disease

- Mutation in fibroblast growth factor receptor 2 (*FGFR2*), tyrosine kinase receptor involved in regulation of osteogenesis
- Two common gain-of-function mutations account for >98% of cases

Laboratory

- Targeted molecular testing for common mutations, whole-gene sequencing, and deletion/duplication studies of *FGFR2* are all available

Treatment

- Not curable, supportive/symptomatic and surgical management
- Early surgical consultation and correction are important to reduce the risk of intracranial pressure

Crouzon Syndrome

Chromosome and Gene Location

- 10q24 (*FGFR2*)

Inheritance

- Autosomal dominant with variable expressivity

Incidence

- 1/25,000

Clinical Manifestations

- Coronal, lambdoid, or sagittal craniosynostosis
- Hypoplasia of midface
- Hypertelorism
- Proptosis
- Beaked nose
- Normal intelligence

Molecular Basis of Disease

- Mutation in *FGFR2*, tyrosine kinase receptor involved in regulation of osteogenesis

Laboratory

- Targeted molecular testing for common mutations, sequencing of select exons or the entire FGFR2 gene, and deletion/duplication studies of *FGFR2* are all available

Treatment

- Not curable, supportive/symptomatic and surgical management

Pfeiffer Syndrome (Types I–III)

Chromosome and Gene Location

- 8p11.2 (*FGFR1*) type I
- 10q24 (*FGFR2*) types I–III

Inheritance

- Autosomal dominant with variable expressivity

Incidence

- 1/100,000

Clinical Manifestations

- See Table 13.5

Molecular Basis of Disease

- Type I: mutation in fibroblast growth factor receptor (*FGFR*) 1 (5% of cases) or 2 (95% of cases), tyrosine kinase receptors involved in regulation of osteogenesis
- Type II or III: mutation in *FGFR2*, tyrosine kinase receptor involved in regulation of osteogenesis

Laboratory

- Targeted molecular testing for common mutations, sequencing of select exons or the entire *FGFR1*/*FGFR2* genes, and deletion/duplication studies of *FGFR1*/*FGFR2* are all available

Treatment

- Not curable, supportive/symptomatic and surgical management
- Types II and III are typically more severe and have an increased risk for early death, but early and aggressive surgical and medical treatment may increase the possibility of a positive outcome

Table 13.5. **Clinical Findings of Pfeiffer Syndrome**

	Craniofacial	*Extremities*	*Intellect*	*Other*
Type I	Brachycephaly (premature synostosis of coronal and often sagittal sutures)	Broad, medially deviated thumbs and great toes, variable syndactyly	Typically normal	Hearing loss, hydrocephalus occasionally
Type II	Cloverleaf skull (premature synostosis of all but metopic and squamosal sutures), extreme proptosis	Broad, medially deviated thumbs and great toes, elbow ankylosis/synostosis	Developmental delay/ intellectual disability commonly	Choanal stenosis/atresia, laryngotracheal anomalies, hydrocephalus, seizures
Type III	Turribrachycephaly (premature synostosis of bicoronal, sagittal, and metopic sutures), extreme proptosis	Broad, medially deviated thumbs and great toes	Developmental delay/ intellectual disability commonly	Choanal stenosis/atresia, laryngotracheal anomalies, hydrocephalus, seizures

Adapted from Robin et al. NH, Falk MJ, Haldeman-Englert CR. (Updated [09/27/2007]). FGFR-Related Craniosynostosis Syndromes. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997–2009. Available at http://www.genetests.org. Accessed [04/09/2009]

Saethre–Chotzen Syndrome

Chromosome and Gene Location

- 7p21.1 (*TWIST1*)

Inheritance

- Autosomal dominant

Incidence

- 1/25,000–1/50,000

Clinical Manifestations

- Brachycephaly due to coronal craniosynostosis
- Ptosis
- Maxillary hypoplasia
- Small ears with prominent crus
- Cutaneous syndactyly
- Normal intelligence typically
- Patients with microdeletions may have intellectual disability

Molecular Basis of Disease

- Typically caused by loss of function of the *TWIST* gene, which negatively regulates FGFR and osteogenic transcription factors. Loss-of-function mutations, exonic or whole-gene deletions, and translocations/inversions involving 7p21 have all been reported

Laboratory

- Targeted molecular testing for common mutations, sequencing of select exons or the entire gene, and deletion/duplication studies of *TWIST1* are all available

Treatment

- Not curable, supportive/symptomatic and surgical management

Muenke Syndrome

Chromosome and Gene Location

- 4p16.3 (*FGFR3*)

Inheritance

- Autosomal dominant

Incidence

- 1/30,000

Clinical Manifestations

- Brachycephaly due to bilateral coronal craniosynostosis or anterior plagiocephaly due to unilateral coronal craniosynostosis
- Intellectual disabilities
- Strabismus
- Hearing loss
- Carpal bone and/or tarsal bone fusions
- Broad toes and/or thumbs
- High-arched palate or cleft lip and/or palate

Molecular Basis of Disease

- Specific pathogenic mutation p.Pro250Arg in *FGFR3* which accelerates bone differentiation

Laboratory

- Targeted molecular testing for the common mutation, sequencing of select exons or the entire gene, and deletion/duplication studies of *FGFR3* are all available

Treatment

- Not curable, supportive/symtomatic

Achondroplasia

Chromosome and Gene Location

- 4p16.3 (*FGFR3*)

Inheritance

- Autosomal dominant; 80% result from a new mutation

Incidence

- 1/25,000

Clinical Manifestations

- Short stature, proximal shortening of long bones, disproportionate shortening of limbs, and genu varum
- Large head, frontal bossing, and hypoplasia of midface
- Infantile hypotonia
- Gross motor developmental delay
- Normal intelligence
- Normal life expectancy
- Also at risk for cord compression due to odontoid hypoplasia

Molecular Basis of Disease

- Mutation in transmembrane domain of fibroblast growth factor transmembrane receptor (*FGFR3*)
- >99% caused by same mutation

Laboratory

- X-ray implicates skeletal involvement
- Targeted mutation testing for the common mutations in *FGFR3* that account for >99% of cases is available. Sequencing of select exons or the entire *FGFR3* gene is also available

Treatment

- Not curable, supportive/symptomatic

Osteogenesis Imperfecta (Types I–VII)

Chromosome and Gene Location

- See Table 13.6

Inheritance

- See Table 13.6

Incidence

- 1/20,000–30,000

Clinical Manifestations

- See Table 13.6
- A genetic consultation is recommended given clinical and molecular genetic diagnosis of one of the many types may be quite complex

Molecular Basis of Disease

- Collagen is the major protein of the white fibers of connective tissue, cartilage, and bone
- There have been numerous types of collagen identified

Table 13.6. **Clinical Findings of Osteogenesis Imperfecta**

	Inheritance	*Clinical findings*	*Gene*	*Abnormal collagen chains*
Type I	Autosomal dominant	Bone fragility, blue sclera, hearing loss	*COL1A1*	Pro-α1(I)
Type II	Autosomal dominant, but usually new germ line mutation, 6–7% recurrence risk due to parental gonadal mosaicism	Perinatal lethal, calvarial under-mineralization, beaded ribs, compressed long bones, dark blue sclera	*COL1A1* *COL1A2*	Pro-a1(I) Pro-α2(I)
Type III	Autosomal dominant Autosomal recessive (rarely)	Multiple prenatal bone fractures, limb shortening, limb deformities, deafness, blue sclera	*COL1A1* *COL1A2*	Pro-a1(I) Pro-α2(I)
Type IV	Autosomal dominant	Mild short stature, mild deformity, dentinogenesis imperfecta, normal/gray sclera	*COL1A1* *COL1A2*	Pro-a1(I) Pro-α2(I)
Type V	Autosomal dominant	Variable stature, multiple fractures, moderate bone deformities, normal sclera	Unknown	
Type VI	Uncertain	Mild short stature, multiple fractures, rhizomelic shortening, normal sclera	Unknown	
Type VII	Autosomal recessive	Mild short stature, multiple fractures, bone deformity, normal sclera	*CRTAP*	

Adapted from: Steiner RD, Adsit J, Basel D. COL1A1/2-Related Osteogenesis Imperfecta. 2005 Jan 28 [Updated 2013 Feb 14]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2014. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1295/. Accessed [11/21/2014].

- Mutations in the procollagen genes, whose products make up the triple helix of type 1 collagen, lead to the various types of osteogenesis imperfecta
- Clinical presentation is dependent on the extent to which the mutation alters the protein product

Laboratory

- X-ray implicates skeletal involvement
- Molecular genetic testing of the procollagen and some of the other disease-causing genes is available
- Collagen testing on cultured fibroblasts available

Treatment

- Not curable, supportive/symptomatic
- Surgical intervention when indicated

CONNECTIVE TISSUE DISORDERS

Marfan Syndrome

Chromosome and Gene Location

- 15q21.1 (*FBN1*)

Inheritance

- Autosomal dominant
- 15–30% result from a new mutation

Incidence

- 1 in 5,000–10,000

Clinical Manifestations

- Diagnosis based on clinical criteria
- Tall, thin habitus, long extremities, and arachnodactyly (Fig. 13.5A)
- Pectus deformities (Fig. 13.5B) and scoliosis
- Ectopia lentis and retinal detachment
- Mitral valve prolapse, aortic dilation (Fig. 13.5C), and aortic aneurysm
- Without treatment, life expectancy is reduced to about two-thirds normal life span. With proper management of cardiovascular manifestations, life expectancy approximates that of the general population

Molecular Basis of Disease

- *FBN1* codes for fibrillin, a structural protein, which is the major constituent of microfibrils

Laboratory

- Sanger sequencing and deletion/duplication testing via array comparative genomic hybridization (aCGH) or multiplex ligation-dependent probe amplification (MLPA) is available for the *FBN1* gene
- *FBN1* analysis is also available as a part of several clinically available multigene panels which utilize next-generation sequencing

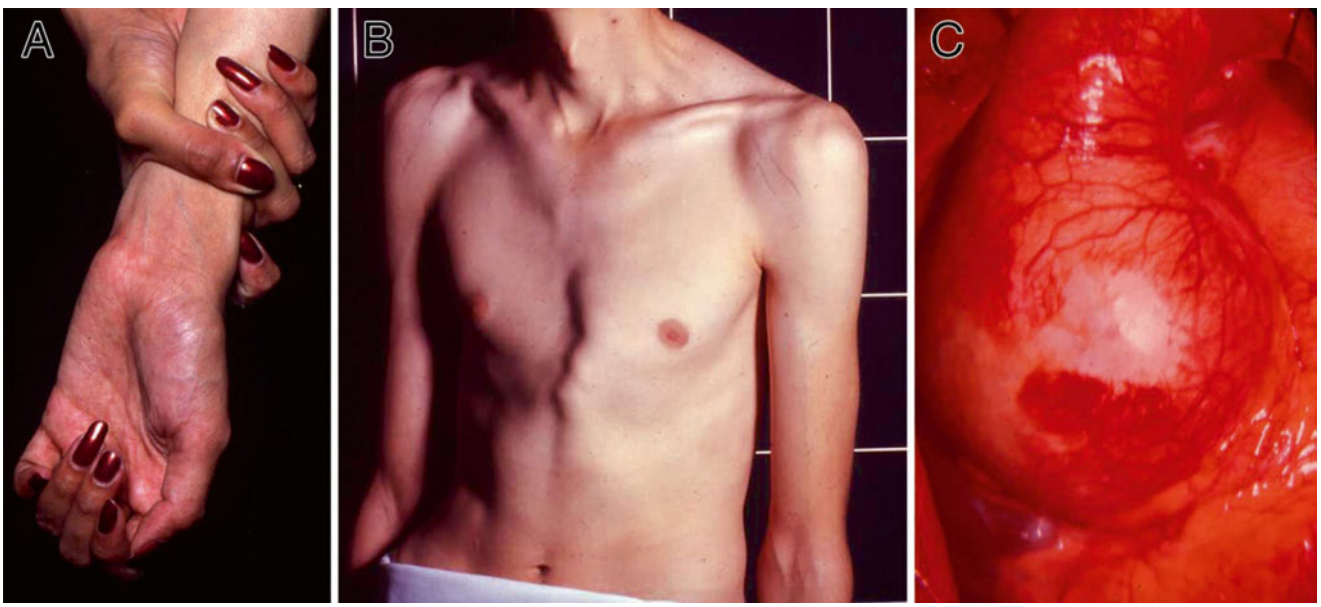

Fig. 13.5. Marfan syndrome – arachnodactyly, wrist sign (**A**). Pectus deformity and striae on shoulders (**B**). Intraoperative view of dilated aortic root (**C**).

Treatment

- Surgical intervention when indicated
- Close monitoring of heart defects as they can lead to sudden death
- Use of beta-adrenergic blockade
- Clinical trials underway to assess the potential benefits of angiotensin II receptor antagonist drugs (losartan) on slowing aneurysm progression
- Referral to genetics for personal and family history evaluation, detailed medical exam, and appropriate health management

Loeys–Dietz Syndrome

Chromosome and Gene Location

- 9q22 (*TGFBR1*), 3p22 (*TGFBR2*), 15q22.33 (*SMAD3*), and 1q41 (*TGFB2*)

Inheritance

- Autosomal dominant
- ~75% result from new mutation

Incidence

- Unknown, no apparent enrichment in any ethnic group

Clinical Manifestations

- Minimal clinical diagnostic criteria not established
- Two clinical phenotypes described. LDS type I has vascular, skeletal, and craniofacial findings. LDS type II has vascular, skeletal, and cutaneous findings
- Dilatation or dissection of the aorta. Aortic dilatation presents in >95% of probands. Arterial aneurysms tend to be more aggressive and dissect at smaller aortic dimensions than in Marfan syndrome
- Other arterial aneurysms and tortuosity throughout the arterial tree
- Pectus excavatum or pectus carinatum and scoliosis
- Joint laxity
- Arachnodactyly
- Talipes equinovarus
- Ocular hypertelorism, bifid uvula/cleft palate, and craniosynostosis (most commonly sagittal, but also coronal and metopic) in LDS type I
- Translucent skin, easy bruising, and dystrophic scars in LDS type II

Molecular Basis of Disease

- Mutations in genes coding for a transforming growth factor ligand, cofactor, and two receptors, which regulate a variety of cellular processes, including proliferation, differentiation, cell cycle arrest, apoptosis, and formation of the extracellular matrix

Laboratory

- Sanger sequencing and deletion/duplication testing via array comparative genomic hybridization (aCGH) or multiplex ligation-dependent probe amplification (MLPA) is available for *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFB2*
- *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFB2* analysis is also available as a part of several clinically available multigene panels which utilize next-generation sequencing

Treatment

- Echocardiography at frequent intervals to monitor ascending aorta, MRA, or CT as indicated
- Early and aggressive surgical intervention
- Use of beta-adrenergic blockade
- Referral to genetics for personal and family history evaluation, detailed medical exam, and appropriate health management

Thoracic Aortic Aneurysm and Dissection

Chromosome and Gene Location

- Seven genes and two loci have been associated with thoracic aortic aneurysm and dissection (TAAD):
  - *TGFBR2* on 3p22
  - *TGFBR1* on 9q33–q34
  - *MYH11* on 16p13.13–p13, 12
  - *ACTA2* on 10q22–q24
  - *MYLK* on 3q21
  - *SMAD3* on 15q22.33
  - AAT2 (TAAD1) locus on 5q13–q14 (causative gene unknown)
  - AAT1 (FAA1) locus on 11q23.3–q24 (causative gene unknown)
  - Rare cases of *FBN1* mutations, 15q21.1, have been associated with isolated TAAD (incidence unknown)

Inheritance

- Autosomal dominant

Incidence

- Aortic aneurysms account for approximately 1–2% of deaths in industrialized society
- Approximately 20% of familial TAAD is accounted for by mutations in known genes. It is likely that other genes with variable penetrance have yet to be discovered

Clinical Manifestations

- Major diagnostic criteria for TAAD are the following:
- Presence of dilatation and/or dissection of the ascending thoracic aorta or dissection of the descending aorta just distal to the origin of the subclavian artery
- Exclusion of Marfan syndrome, Loeys–Dietz syndrome, and other connective tissue abnormalities
- Other occasional manifestations include inguinal hernia, scoliosis, aneurysms in other portions of the aorta, cerebral aneurysms, livedo reticularis (*ACTA2*), iris flocculi (*ACTA2*), bicuspid aortic valve (*ACTA2*), and patent ductus arteriosus (*MYH11*)

Molecular Basis of Disease

- *TGFBR1*, *TGFBR2*, and *SMAD3* code for proteins that regulate a variety of cellular processes, including proliferation, differentiation, cell cycle arrest, apoptosis, and formation of the extracellular matrix. Mutations in TAAD families are most often found in the kinase domain of these proteins, though rarely other mutations have been reported
- *MYH11* codes for smooth muscle heavy chain protein. Smooth muscle myosin is the major contractile protein of smooth muscle and is composed of a MYH11 dimer and two pairs of nonidentical light chains
- *ACTA2* codes for smooth muscle cell alpha-actin, a major contractile protein in smooth muscle cells
- *MYLK* codes for a phosphokinase which facilitates interactions between myosin and actin filaments, important in contractile activity

Laboratory

- Sanger sequencing and deletion/duplication testing via array comparative genomic hybridization (aCGH) or multiplex ligation-dependent probe amplification (MLPA) is available for *TGFBR1*, *TGFBR2*, *MYH11*, *ACTA2*, *FBN1*, and *SMAD3*
- Sanger sequencing is available for *MYLK*
- *TGFBR1*, *TGFBR2*, *MYH11*, *ACTA2*, *MYLK*, *FBN1*, and *SMAD3* analysis is also available as a part of several clinically available multigene panels which utilize next-generation sequencing

Treatment

- Echocardiography to monitor aortic root, consider imaging entire aorta and other vasculature
- Prophylactic surgical repair of the aorta (timing depends on rate of progression, causative gene, etc)
- Medications that reduce hemodynamic stress, such as beta-adrenergic blockade
- Aggressive treatment of hypertension
- Assessment and standard treatment for hernias and scoliosis
- Referral to genetics for personal and family history evaluation, detailed medical exam, and appropriate health management

Ehlers–Danlos Syndrome

Chromosome and Gene Location

- Classic type: 9q34 (*COL5A1*), and 2q31 (*COL5A2*)
- Vascular type: 2q31 (*COL3A1*)
- Others
  - Hypermobility type: causative gene is mostly unknown; there are some cases of *TNXB* mutations (6p21)
  - Kyphoscoliotic type: 1p36 (*PLOD1*)
  - Arthrochalasia type: 17q21–q22 (*COL1A1*), and 7q22 (*COL1A2*)
  - Spondylocheiro dysplastic form: 11p11.2 (*SLC39A13*)
  - Dermatosparactic type: 5q35.3 (*ADAMTS2*)
  - Musculocontractural type 1: 15q15.1 (*CHST14*)
  - Progressive kyphoscoliosis, myopathy, and hearing loss type: 7p15 (*FKBP14*)

Inheritance

- Classic type, arthrochalasia type, and vascular type are autosomal dominant
- Most rare forms of Ehlers–Danlos syndrome are autosomal recessive
- Mutations in TNXB can be inherited in an autosomal dominant or autosomal recessive manner

Incidence

- Classic type: estimated 1/20,000
- Vascular type: estimated 1/250,000

Clinical Manifestations

- Classic type
  - Skin hyperextensibility
  - Smooth, velvety skin
  - Widened atrophic scarring
  - Abnormal, delayed wound healing
  - Joint hypermobility
  - Joint dislocations
  - Easy bruising
  - Generalized tissue fragility
  - Less commonly, mitral and tricuspid valve prolapse, aortic root dilatation, and spontaneous rupture of large arteries
- Vascular type
  - Thin, translucent skin
  - Characteristic facial appearance (thin nose and lips, emaciated face with prominent cheekbones, eyes appear sunken or bulging, often with coloring around them and thin telangiectasia on the eyelids)
  - Easy bruising
  - Arterial, intestinal, and/or uterine fragility
  - Vascular rupture or dissection
  - GI perforation
  - Organ rupture

Molecular Basis of Disease

- Collagen is the major protein of the white fibers of connective tissue, cartilage, and bone
- Mutations in collagen genes lead to decreased synthesis, altered secretion, and instability of collagen
- The defect for some types is unknown

Laboratory

- Protein analysis is available for some subtypes
- Histological features are nondiagnostic
- Sanger sequencing and deletion/duplication testing via array comparative genomic hybridization (aCGH) or multiplex

ligation-dependent probe amplification (MLPA) is available for *COL5A1*, *COL5A2*, *COL3A1*, *COL1A1*, and *COL1A2*

- Sanger sequencing is available for *PLOD1*
- *ADAMTS2*, *CHST14*, *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, *FKBP14*, *PLOD1*, and *SLC39A13* analysis is also available as a part of several clinically available multigene panels which utilize next-generation sequencing

Treatment

- Not curable, supportive/symptomatic
- Referral to genetics for personal and family history evaluation, detailed medical exam, and appropriate health management

Stickler Syndrome

Chromosome and Gene Location

- 12q13 (*COL2A1*) and 1p21 (*COL11A1*) account for the majority of individuals with Stickler syndrome
- Also associated with 6p21.3 (*COL11A2*), 6q13 (*COL9A1*), 1p33–p32 (*COL9A2*), and 20q13.3 (*COL9A3*)

Inheritance

- Autosomal dominant for *COL2A1*, *COL11A1*, and *COL11A2*
- Autosomal recessive for *COL9A1*, *COL9A2*, and *COL9A3*

Incidence

- While the exact prevalence is unknown, estimations based on incidence of Pierre Robin sequence in newborns and the percent of these newborns who develop signs or symptoms of Stickler syndrome are approximately 1 in 7,500–9,000

Clinical Manifestations

- Progressive myopia, retinal detachment, and blindness
- Pierre Robin sequence (micrognathia and abnormal smallness of the tongue, often with cleft palate)
- Severe myopia, congenital glaucoma, retinal detachment, and cataracts
- Premature degenerative changes in various joints with abnormal epiphyseal development
- Mitral valve prolapse

Molecular Basis of Disease

- The *COL2A1* gene encodes the chains of type II collagen, a major structural component of cartilaginous tissues
- The *COL11A1* gene encodes the alpha 1 chain of type XI collagen, thought to play an important role in fibrillogenesis by controlling lateral growth of collagen II fibrils
- The *COL11A2* gene encodes the alpha 2 chain of type XI collagen expressed in cartilage but not in adult liver, skin, tendon, or vitreous
- The *COL9A1*, *COL9A2*, and *COL9A3* genes code for type IX collagen which, together, form a subunit of three alpha chains found in tissues containing type II collagen

Laboratory

- Skeletal X-rays show changes of a skeletal dysplasia
- Sanger sequencing and deletion/duplication testing via array comparative genomic hybridization (aCGH) or multiplex ligation-dependent probe amplification (MLPA) is available for *COL2A1*, *COL11A1*, *COL11A2*, *COL9A1*, *COL9A2*, and *COL9A3*
- *COL2A1*, *COL11A1*, *COL11A2*, *COL9A1*, *COL9A2*, and *COL9A3* analysis is also available as a part of several clinically available multigene panels which utilize next-generation sequencing

Treatment

- Not curable, supportive/symptomatic
- Referral to genetics for personal and family history evaluation, detailed medical exam, and appropriate health management

Alport Syndrome

Chromosome and Gene Location

- Xq22.3 (*COL4A5*), 2q36–q37 (*COL4A3*), and 2q35–q37 (*COL4A4*)

Inheritance

- *COL4A5* mutations are inherited in an X-linked pattern (80% total AS cases)
- *COL4A3* and *COL4A4* cases are inherited in both autosomal recessive (15% total AS cases) and autosomal dominant (5% total AS cases) patterns

Incidence

- Estimated to be 1 in 50,000 live births

Clinical Manifestations

- Renal failure
- Sensorineural deafness
- Lenticonus
- Macular changes

Molecular Basis of Disease

- Mutations in the type IV collagen genes result in abnormalities in expression of the collagen chains and absent or defective structure and function in the collagen networks of the basement membranes
- Molecular testing on clinical basis

Laboratory

- Microscopic hematuria
- Urinary red cell casts
- Proteinuria
- Leukocyturia
- Abnormal glomerular basement membrane on electron microscopy

Treatment

- Referral to genetics for personal and family history evaluation, detailed medical exam, and appropriate health management
- Not curable, supportive/symptomatic
- Kidney transplant as indicated

HEMATOLOGIC DISORDERS

Alpha Thalassemia

- Normal adult hemoglobin (Hb A) is a tetramer of two alpha and two beta globin chains. The alpha thalassemias are a group of inherited conditions characterized by decreased synthesis of alpha globin chains, resulting in an imbalance of globin chains in the formation of the hemoglobin (Hb) tetramer

Chromosome and Gene Location

- 16p13.3-pter (there are two alpha globin genes present at this locus on both copies of chromosome 16 for total normal complement of four alpha globin genes)

Inheritance

- Complex: individuals with alpha thalassemia may have alterations in two, three, or four alpha globin genes

Incidence

- Varies by population; most common in African-American, Southeast Asian, Mediterranean, and Indian populations
- Severe forms occur predominantly in Asians

Clinical Manifestations

- An individual with one altered alpha globin gene is a "silent" carrier and typically does not have any clinical symptoms (α^+-thalassemia)
- Individuals with two altered alpha globin genes, either of different chromosomes (i.e., in *trans*) or on the same chromosome (i.e., in *cis*), have alpha thalassemia trait (α^0-thalassemia), which manifests as minimal anemia with microcytosis
- Hemoglobin H (Hb H) disease results when three alpha globin genes are altered. Hb H is an abnormal tetramer of four beta chains and is unstable. Thus, Hb H disease is a form of hemolytic anemia. This is characterized by moderate anemia, enlarged liver and spleen, and erythroid hyperplasia in the bone marrow
- Bart hydrops fetalis results when all four alpha globin genes are not functional. Hb Bart is a tetramer of four gamma chains. The oxygen affinity of hemoglobin Bart is so high that it cannot release oxygen to the tissues. Onset is in the fetal period and includes severe hypochromic anemia, extramedullary erythropoiesis, generalized edema, pleural and pericardial effusions, hepatosplenomegaly, and hydrocephalus. This condition is not compatible with life; death occurs from anoxia in utero

Molecular Basis of Disease

- Alpha thalassemia results from mutations in the *HBA1* and *HBA2* genes that encode α_1-globin and α_2-globin, respectively. Mutations result in reduced production of the alpha globin chains. The clinical severity is determined by the degree of alpha globin chain deficiency relative to beta globin production. Numerous mutations have been found
- The most common types of mutations are deletions of one or both alpha globin genes, which results from the misalignment and subsequent recombination of the alpha globin genes during meiosis (i.e., nonhomologous crossover)

Laboratory

- Red blood cell indices reveal microcytic anemia in Hb H and α-thalassemia trait. Silent carriers generally have normal red blood cell indices. Hb Bart disease shows macrocytic red blood cells
- Peripheral blood smear demonstrates hypochromic red cells and anisopoikilocytosis in Hb Bart syndrome. In Hb H disease, microcytosis, hypochromia, anisocytosis, and poikilocytosis are apparent. Carriers have morphologic changes that are less severe than affected individuals and may also have reduced MCV and MCH
- Inclusion bodies can be shown in Hb H disease using supravital stain; carriers and those with alpha thalassemia trait can also show small amounts of inclusions
- Hemoglobin analysis (e.g., electrophoresis, HPLC, and isoelectric focusing) detects the presence of Hb H (the abnormal β-globin tetramer) in adults and Hb Bart (an abnormal ϒ-globin tetramer) in infants
- Molecular genetic analysis is clinically available

Treatment

- Hemolytic or aplastic crisis caused by Hb H disease can be treated with red blood cell transfusions
- Splenectomy may be performed in cases of massive splenomegaly
- Iron chelation therapy is used if chronic blood transfusions are necessary
- Surveillance includes hematologic evaluation and growth and development assessment. Iron overload should be monitored in individuals requiring transfusions

Beta Thalassemia

Chromosome and Gene Location

- 11p15.5

Inheritance

- Typically autosomal recessive

Incidence

- Most commonly found in Mediterranean and Southeast Asian populations but also in Middle Easterners, Africans, and African Americans

Clinical Manifestations

- The clinical presentation and classification of beta thalassemia is dependent on the extent to which beta chain production is decreased and the resulting imbalance of alpha globin chains to non-alpha globin chains

- Beta thalassemia becomes clinically evident as fetal hemoglobin production decreases after birth and adult hemoglobin fails to replace it (around 6 months of age)
- Beta thalassemia major results from the homozygous or compound heterozygous mutations that severely reduce beta chain production
  - Onset between 6 and 24 months
  - Characterized by microcytic anemia, failure to thrive, fever, diarrhea, liver and spleen enlargement, and progressive pallor
  - Complications from iron overload include growth retardation, failure of sexual maturation, dilated cardiomyopathy, pericarditis, liver fibrosis and cirrhosis, diabetes, and parathyroid, thyroid, and pituitary insufficiency
  - Death often occurs in second or third decade due to cardiac complications
  - Untreated individuals exhibit severe failure to thrive, jaundice, increased skin pigmentation, liver and spleen enlargement, poor musculature, "chipmunk face," skeletal deformities, and stunted growth and have a shortened life expectancy
- Beta thalassemia intermedia has milder phenotype and results from homozygosity or compound heterozygosity of alleles with reduced beta chain production; it may result from coinheritance of alpha and beta thalassemia
  - Variable presentation may include milder anemia, liver and spleen enlargement, moderate skeletal features, pallor, jaundice, cholelithiasis, osteopenia and osteoporosis, and extramedullary erythropoietic masses
  - There is an increased risk for iron overload due to increased absorption of iron in the intestine
  - Transfusions are performed as needed
- Beta thalassemia minor or thalassemia trait refers to a heterozygous carrier state. Carriers generally do not exhibit clinical symptoms other than possible mild anemia

Molecular Basis of Disease

- Beta thalassemia results from mutations in the *HBB* gene, which encodes for the beta hemoglobin subunits
- The clinical presentation of beta thalassemia is dependent on the extent to which the genetic alteration disrupts beta chain production ranging from complete absence of production (i.e., β^0 mutations) to "silent" or mild production disturbances (β^+ mutations) and subsequently imbalance in the alpha to non-alpha globin chain ratio
- Normally, both alpha and beta globin chains are produced in roughly equal amounts. When beta globin synthesis is decreased, there are more free alpha chains. Free alpha chains are very unstable and precipitate in the red cell. This results in ineffective erythropoiesis and anemia. Subsequently, there is a phenomenal increase in erythropoiesis with marrow expansion and persistence of erythropoiesis in the liver and spleen
- More than 200 genetic alterations have been described in the *HBB* gene, including:
  - Nucleotide substitutions
  - Deletions
  - Transcriptional mutations
  - RNA processing mutations
- Molecular analysis may be helpful in determining clinical phenotype and identifying at-risk relatives

Laboratory

- Red blood cell indices reveal microcytic anemia
- Peripheral blood smears show nucleated red blood cells, microcytosis, hypochromia, anisocytosis, and poikilocytosis
  - Carriers have reduced MCV and MCH, and RBC morphology is less severe than in affected individuals. Nucleated red blood cells are generally not seen in carriers
- Elevated iron
- Hyperplastic marrow with hyperplasia of red cell precursors
- Hemoglobin analysis shows reduced amounts of Hb A (normal adult hemoglobin) and increases in normal minor hemoglobins, such as Hb A2
- Molecular analysis is clinically available

Treatment

- Thalassemia major
  - Regular transfusions to correct anemia, suppress erythropoiesis, and inhibit gastrointestinal absorption of iron
  - Iron chelation to prevent iron overload
  - Bone marrow transplantation from HLA-identical sib or cord blood transplantation from related donor
  - Ongoing surveillance is necessary to monitor effectiveness of transfusion and chelation therapy
    - Regular physical exams including growth and development assessment
    - Liver function tests; serum ferritin
    - Ophthalmologic, audiologic, and cardiac exams
    - Endocrine function and liver ultrasound
    - In adults, bone densitometry, serum AFP, and gallbladder echography are also assessed
- Thalassemia intermedia
  - Symptomatic therapy
  - Splenectomy
  - Folic acid supplementation
  - Sporadic red cell transfusions
  - Radiotherapy, transfusions, and hydroxyurea for treatment of extramedullary erythropoietic masses
  - Chelation therapy if iron overload develops

Sickle Cell Anemia

Chromosome and Gene Location

- 11p15.5

Inheritance

- Autosomal recessive

Incidence

- 1/500 African-American births

Clinical Manifestations

- Severe anemia
- Painful swelling and crisis due to vaso-occlusive episodes usually affecting the limbs, back, abdomen, and chest
- Pneumococcal sepsis
- Leg ulcerations
- Enlarged spleen
- Pallor
- Acute chest syndrome (e.g., the presence of infiltrate on chest radiograph, sometimes including lower respiratory tract symptoms, fever, and hypoxemia)
- Autosplenectomy (i.e., the reduction in spleen size due to continual splenic infarctions resulting from the filtration of abnormal red blood cells)
- Chronic organ damage (e.g., renal or hepatic damage; retinopathy)
- Delayed growth and sexual development
- Repeated infections

Molecular Basis of Disease

- Sickle cell disease most commonly results from inheritance of a glutamic acid to valine substitution in position six of the *HBB* gene encoding the beta globin
- This mutation leads to the formation of hemoglobin S (Hb S), which alters the configuration of the hemoglobin molecule and causes the cells to sickle and obstruct blood flow in small vessels leading to ischemia of tissues and organs. Variable degrees of hemolysis also occur
- When inherited in a homozygous fashion, the condition is referred to as homozygous sickle cell disease or Hb SS
- Other forms of sickle cell disease result from inheritance of one Hb S allele along with another abnormal beta chain variant, such as Hb C

Laboratory

- Significant quantities of Hb S are identified by HPLC, isoelectric focusing, or electrophoresis
- Sickling and reduced oxygen tension of red cells and nucleated red blood cells are apparent in a peripheral blood smear
- There is also an increase in neutrophils and platelets
- All 50 states provide newborn screening for sickle cell disease
- Direct molecular testing for nucleotide substitution is clinically available and can be used for confirmatory testing, carrier testing for at-risk relatives, and prenatal diagnosis

Treatment

- Vaso-occlusive pain is treated with oral hydration and analgesics
- Transfusion is used during splenic or hepatic sequestration crises
- Acute chest syndrome is treated with oxygen, spirometry, analgesics, antibiotics, and transfusions
- Pulmonary hypertension is treated with transfusions, oxygen, hydroxyurea, and hypertension-specific investigational agents
- Preventative measures include hydration, prophylactic antibiotics, and immunizations
- Stem cell transplantation has been used on a limited basis
- A number of investigative therapies including gene therapy, nitric oxide (and its precursor L-arginine), therapies that increase the percentage of fetal hemoglobin, and therapies involving membrane cation transport systems are being studied
- Regular surveillance is necessary to assess development and for the early detection and treat organ damage, stroke risks, and cardiovascular manifestations

Hemophilia A

Chromosome and Gene Location

- Xq28

Inheritance

- X-linked recessive

Incidence

- 1 in 10,000 live male births, among all ethnic populations
- About 30% of cases result from new mutations occurring in families in whom there is no apparent family history of hemophilia A (HA)

Clinical Manifestations

- HA predominantly affects males
- Bleeding is main manifestation and occurs spontaneously in severe hemophilia, but only after major trauma or surgery in mild to moderate hemophilia
- Some female carriers have reduced FVIII levels and may have clinically significant bleeding, for example, lyonization of the normal X chromosome, Turner syndrome (XO karyotype)

Molecular Basis of Disease

- Reported deleterious mutations and polymorphisms are cataloged in an international database available on the Internet and updated periodically: (http://www.europium.csc.mrc.ac.uk/usr/WWW/WebPages/main.dir/main.htm)
- The most common deleterious mutation is an inversion within intron 22 found in approximately 40% of severe HA patients
- An additional inversion of exon 1 of the *FVIII* gene affecting up to 5% of patients with severe HA has also been described
- Deletions are common and account for about 5% of characterized mutations
- The remaining patients typically have single base pair changes (resulting in missense, frameshift splice junction

mutations), insertions, or duplications spread throughout the factor VIII gene

- X-autosome translocation involving a breakpoint within the factor VIII gene and uniparental isodisomy have been implicated

Laboratory

- The diagnosis of HA in males is established by assaying plasma FVIII coagulant activity (FVIII:C) for reduced or absent activity
- Classification (based on FVIII:C)
  - Severe FVIII:C <1%
  - Moderate FVIII:C 1–5%
  - Mild FVIII:C >5–40%
  - Estimated prevalence of severe, moderate, and mild are 43, 26, and 31%, respectively
- For carrier testing of at risk females, initially performing FVIII:C is reasonable; if it is reduced, carrier status is established; however, in the large majority of carriers, FVIII:C is normal; thus, carrier status is established by genetic testing
- Other laboratory findings include normal prothrombin time (PT), variably prolonged activated partial thromboplastin time (APTT), and normal von Willebrand factor (VWF) levels

Treatment

- Plasma-derived or recombinant FVIII concentrate is infused intravenously for prevention or treatment of bleeding episodes
- Current standard practice for severe hemophilia is to provide prophylactic clotting factor concentrate two to three times a week from childhood, so these patients currently lead relatively normal lives
- Patients with large deletions, nonsense mutations, and inversion mutations are susceptible to formation of FVIII inhibitor (antibodies) in response to therapy with FVIII concentrates

Hemophilia B

Chromosome and Gene Location

- Long arm of X chromosome (Xq27.1)

Inheritance

- X-linked recessive

Incidence

- Approximately 1 in 30,000 live male births across all ethnic groups
- Up to 30% of hemophilia B (HB) cases occur in families with no prior family history of HB

Clinical Manifestations

- HB is a bleeding disorder due to a deficiency in factor IX (FIX) and is clinically indistinguishable from HA
- HB predominantly affects males
- Bleeding is main manifestation and occurs spontaneously in severe hemophilia, but only after major trauma or surgery in mild to moderate hemophilia
- Some female carriers have reduced FIX levels and may have clinically significant bleeding, e.g., lyonization of the normal X chromosome, Turner syndrome (XO karyotype)

Molecular Basis of Disease

- Reported deleterious mutations and polymorphisms are cataloged in an international database available on the Internet and updated periodically (http://www.kcl.ac.uk/ip/petergreen/haemBdatabase.html)
- The majority of the mutations are missense, frameshift, or nonsense mutations. Short deletions (<30 nucleotides) account for ~7%, larger deletions ~3%, and insertions ~2% of mutations
- Mutations have been detected in all regions including the poly(A) signal
- An unusual FIX variant, due to mutation at Ala-10, is characterized by normal baseline FIX activity. However, warfarin therapy results in a severe and disproportionate reduction in FIX activity (typically <1%) and causes bleeding in patients being treated with warfarin who have an apparently therapeutic International Normalized Ratio (INR). An indication of such a situation is a disproportionate prolongation of the APTT, which should prompt clotting factor assays

Laboratory

- The diagnosis of HB in males is established by assaying plasma FIX coagulant activity (FIX:C) for reduced or absent activity
- Classification (based on FIX:C)
  - Severe FIX:C <1%
  - Moderate FIX:C 1–5%
  - Mild FIX:C >5–40%
- For carrier testing of at risk females, initially performing FIX:C is reasonable, if it is reduced, carrier status is established; however, in the large majority of carriers FIX:C is normal; thus, carrier status is established by genetic testing
- Other laboratory findings include normal PT, variably prolonged APTT, and normal VWF levels

Treatment

- Plasmas-derived or recombinant FIX concentrate is infused intravenously for prevention or treatment of bleeding episodes
- Current standard practice for severe hemophilia is to provide prophylactic clotting factor concentrate two to three times a week from childhood, so these patients currently need relatively normal lives
- Patients with large deletions are susceptible to formation of FIX inhibitors (antibodies) in response to therapy with FIX concentrates and may experience anaphylactic reactions in response to factor IX concentrate infusions

Von Willebrand Disease

Chromosome and Gene Location

- 12p
- A pseudogene is located on chromosome 22q11.2

Inheritance

- Autosomal dominant and autosomal recessive

Incidence

- Von Willebrand disease (VWD) is the most commonly recognized congenital bleeding disorder, with a prevalence varying from 0.82 to 2%

Clinical Manifestations

- Diagnosis is established based on a personal and family history of abnormal clinical bleeding and reduced plasma VWF antigen levels and/or functional activity (ristocetin cofactor activity) and analysis of distribution of the VWF multimers
- VWD is classified into quantitative (types 1 and 3) or qualitative (type 2) abnormalities of plasma VWF
- Quantitative abnormalities include a mild reduction of qualitatively normal VWF (type 1) or absent VWF (type 3)
- Qualitative abnormalities (type 2 VWD) types 2A, B, M, and N VWD
- Mild reductions in VWF do not typically result in spontaneous bleeding; however, patient will bleed after trauma or surgery
- Type 3 VWD patients have a severe reduction in a VWF levels, thus may bleed spontaneously

Molecular Basis of Disease

- Reported deleterious mutations and polymorphisms are cataloged in an international database available on the Internet and updated periodically: http://www.sheffield.ac.uk/VWF/
- Type 1 VWD
  - Autosomal dominant with variable penetrance
  - In the large majority of patients, mutations are not found, implying locus heterogeneity as an explanation for the mild quantitative deficiency of VWF associated with type 1 VWD, e.g., defects in glycosylation of the VWF protein
  - However, selected patients with type 1 VWD had missense mutations spread throughout *VWF* gene
- Type 3 VWD
  - Autosomal recessive
  - Deleterious mutations currently characterized include frameshifts, deletions, or nonsense mutations
  - Although most patients are typically compound heterozygous for such *VWF* mutations, homozygosity has been demonstrated in a few consanguineous families
- Type 2A VWD
  - Autosomal dominant, accounts for ~75% of all type 2 VWD
  - Missense mutations resulting in type 2A VWD occur predominantly in the A2 domain
- Type 2B VWD
  - Autosomal dominant, accounts ~20% of all type 2 VWD
  - This variant is distinguished from type 2A VWD by the presence of mild to moderate thrombocytopenia in type 2B
  - Causative missense mutations are found in the A domain and result in a dominant gain-of-function phenotype
- Type 2M VWD
  - Mutations in A1 domain can result in decreased binding affinity for platelet GPIb
- Type 2N (Normandy) VWD
  - Mutations in the FVIII binding domain of VWF result in suboptimal binding of FVIII to VWF. This binding defect results in a shorter half-life of plasma FVIII, and thus plasma FVIII activity is reduced
  - This subtype mimics mild HA; however, it is distinguished by its autosomal recessive pattern of inheritance rather than the X-linked recessive pattern of HA
  - Three *VWF* gene mutations Thr791Met, Arg816Trp, and Arg854Gln accounted for 96% of type 2N patients
  - Type 2N VWD should be considered in patients with a diagnosis of "mild HA" with a non-X-linked inheritance
  - Typically, heterozygotes have normal FVIII levels, and homozygotes have reduced FVIII activity. However, apparent heterozygotes with low FVIII levels typically have inherited a second allele resulting in VWD type 1 (compound heterozygotes)

Laboratory

- See Table 13.7
  - Currently, the most significant impact on clinical management and genetic counseling is the differentiation of VWD type 2N and mild HA. Both have a mild to moderate reduction in FVIII and normal levels of VWF antigen and ristocetin cofactor activity. The autosomal inheritance pattern and the need for the use of VWF concentrates rather than pure FVIII concentrates make this an important distinction
  - Differentiation of VWD types 2 A and B provides useful information that would alter clinical management. Although patients with type 2B are characterized by the presence of variable degrees of thrombocytopenia, such a clear distinction is not always possible. The importance of such a distinction affects management given that the therapeutic use of vasopressin (DDAVP) is contraindicated in patients with type 2B given the potential for worsening the thrombocytopenia

Treatment

- Intravenous infusion of plasma-derived VWF concentrate is used for prevention and treatment of bleeding

Table 13.7. **Typical laboratory Values in von Willebrand Disease**

VWD Subtype	*VWF: RCO*	*VWF Ag*	*FVIII:C*	*VWF: CBA*	*VWF: FVIIIB*	*Plt count*	*LD RIPA*	*Multimers*
Type 1	↓	↓	↓/N	↓/N	N	N	Absent	Decreased production of all multimeric forms
Type 2								
2A	↓	↓	↓/N	↓/N	N	N	Absent	↓
2B	↓	↓	↓/N	↓	N	↓	Present	↓
2M	↓	N/↓	N	↓	N	N	Absent	Normal
2N	N	N	↓	↓	↓	N	Absent	Normal
Type 3	↓↓↓/Absent	↓↓↓/Absent	↓↓↓	↓↓↓		N	Absent	Absent

VWD von Willebrand disease, VWF von Willebrand factor, RCO ristocetin cofactor, Ag antigen, FVIII:C factor VIII coagulant activity, VWF:CBA VWF collagen binding assay, VWF:FVIIIB VWF FVIII binding assay, LD RIPA low-dose ristocetin-induced platelet aggregation (0.5 mg/dL), HMWM high molecular weight multimers, N normal, Plt platelet, X decreased, XXX markedly decreased

- Occasionally, patients with type 1 VWD are treated with intravenous infusion of desmopressin (DDAVP) if they have had a documented response at a DDAVP trial

Factor V Leiden

Chromosome and Gene Location

- 1q21–25

Inheritance

- Autosomal dominant with variable penetrance

Incidence

- Factor V Leiden is considered to be a founder mutation
- Prevalence of the mutation varies with ethnic population and ranges from 2% in southern Europe to 15% in southern Sweden
- In the USA, approximately 3–7% of asymptomatic white populations of Northern European or Scandinavian ancestry are heterozygous carriers
- Prevalence varies from 1.2% in African Americans, 2.2% in Hispanics, 1.2% in Native Americans, and 0.45% in Asian Americans

Clinical Manifestations

- Large majority of patients are asymptomatic
- Patients may develop venous thromboembolism or pregnancy-related complications
- The large majority of asymptomatic carriers may never develop any clinical manifestations attributable to the presence of factor V Leiden mutation
- Selective patients may develop clinical manifestations of venous thromboembolism, especially when exposed to other acquired risk factors for venous thrombosis
- The incidence of recurrent venous thromboembolism attributable to heterozygous factor V Leiden mutation is debated; however, homozygotes are higher risk for recurrent venous thromboembolism

Molecular Basis of Disease

- The factor V Leiden mutation encodes for a single nucleotide substitution 1,691G>A within exon 10 of the factor V gene. This results in a missense mutation of a glutamine (Q) for arginine (R) at amino acid position 506 (506R>Q)

Laboratory

- Laboratory testing is used to evaluate for inherited risk factors for patients with venous thromboembolism (deep vein thrombosis and pulmonary embolism), recurrent fetal loss, and complications of pregnancy
- Initial screening test consists of a clot-based functional assay to detect activated protein C resistance (APC-R)
- If patient plasma is found to be resistant to activated protein C, reflexive molecular testing for the factor V Leiden mutation could be performed to determine genotype
- Alternatively, direct DNA-based testing could be considered

Treatment

- Carriers of the factor V Leiden mutation who have not had any venous thromboembolism are counseled regarding risks of venous thrombosis, and empiric anticoagulation is not indicated

- Heterozygous carriers of the factor V Leiden who have had venous thrombosis typically are treated with anticoagulants for 3–6 months
- Homozygous carriers of the factor V Leiden mutation who have had venous thrombosis are typically treated with long-term anticoagulation
- Patients who experience pregnancy-related complications attributable to the presence of the factor V Leiden typically receive heparin anticoagulation during subsequent pregnancies

Prothrombin Thrombophilia

Chromosome and Gene Location

- Chromosome 11p

Inheritance

- Autosomal dominant with variable penetrance

Incidence

- Overall prevalence in Europe is approximately 2% (1.7% in northern Europe to 3.0% in southern Europe)
- Prevalence among US Caucasians is 1–2%
- The prothrombin 20210G>A mutation is uncommon among African Americans, Asian Americans, and Native Americans

Clinical Manifestations

- Large majority of patients are asymptomatic
- Patients may develop venous thromboembolism or pregnancy-related complications
- Young women on estrogen-based oral contraceptives who carried the prothrombin G20210A mutation are at higher risk for cerebral venous sinus thrombosis
- The large majority of asymptomatic carriers may never develop any clinical manifestations attributable to the presence of prothrombin 20210G>A
- Selective patients may develop clinical manifestations of venous thromboembolism, especially when exposed to other acquired risk factors for venous thrombosis
- The incidence of recurrent venous thromboembolism attributable to heterozygous prothrombin 20210G>A mutation is debated; however, homozygotes are at higher risk for recurrent venous thromboembolism

Molecular Basis of Disease

- Prothrombin 20210G>A mutation is a common mutation in the gene encoding prothrombin (*FII* gene)
- The prothrombin 20210G>A mutation is located at 3′-untranslated region
- Presence of this mutation increases recognition of the polyadenylation cleavage signal, 3′ end RNA processing, and mRNA accumulation, thus increasing protein synthesis

Laboratory

- Direct DNA-based testing for the specific mutation is required for diagnosis
- Testing allows evaluation of inherited risk factors for patients with venous thromboembolism (deep vein thrombosis and pulmonary embolism), recurrent fetal loss, and complications of pregnancy

Treatment

- Carriers of the PT20210A mutation who have not had any venous thromboembolism are counseled regarding risks of venous thrombosis, and empiric anticoagulation is not indicated
- Heterozygous carriers of the PT20210A who have had venous thrombosis typically are treated with anticoagulants for 3–6 months
- Homozygous carriers of the PT20210A mutation who have had venous thrombosis are typically treated with long-term anticoagulation
- Patients who experience pregnancy-related complications attributable to the presence of the PT20210A typically receive heparin anticoagulation during subsequent pregnancies

OTHER GENETIC DISORDERS

Cystic Fibrosis

Chromosome and Gene Location

- 7q31.2 (*CFTR*)

Inheritance

- Autosomal recessive

Incidence

- 1/2,500 in the Caucasian population, varies in other ethnic groups

Clinical Manifestations

- Chronic pulmonary disease (inflammation and infection)
- Pancreatic insufficiency, failure to thrive
- Hepatobiliary disease
- Male infertility due to congenital absence of the vas deferens (CAVD)
- Meconium ileus in neonate (15–20%)
- Median survival age for classic CF is about 35 years

- Other *CFTR-related* disorders include isolated CAVD, *CFTR-related* pancreatitis, bronchiectasis, allergic bronchopulmonary aspergillosis, and chronic rhino-sinusitis

Molecular Basis of Disease

- Point mutations and large deletions in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene
- Over 1,000 mutations described are associated with a wide range of clinical severity and presentation of classic CF and CFTR-related disorders
- DeltaF508 most common mutation in Caucasian (75% of carriers)
- W1282X most common mutation in Ashkenazi Jews (60% of carriers)
- Polymorphic poly-T tract in intron 8 of the *CFTR* gene modifies the phenotype associated with certain *CFTR* genotypes; the number of repeats within the TG tract, just upstream of the poly-T tract, also modifies the splicing efficiency of intron 8
- 5T allele is associated with decreased efficiency in splicing of intron 8
- R117H in *trans* with 5T allele causes CAVD; therefore, evaluation of the poly-T tract should be considered in males being evaluated for CAVD

Laboratory

- Molecular analysis (sequencing and dosage) identifies mutations in *CFTR* gene
- Elevated sweat chloride (>60 mEql/L)
- Abnormal transepithelial nasal potential difference
- Semen analysis to evaluate for azoospermia

Treatment

- Antibiotics for control of respiratory infections
- Postural drainage and inhalation therapy
- Chest physiotherapy for airway clearance
- Pancreatic enzyme replacement therapy and supplemental feedings
- Oral ursodiol for biliary buildup/obstruction
- Assisted reproductive technologies for infertility
- Lung transplant for end-stage lung disease
- Surveillance
  - Blood glucose testing for diabetes
  - Chest radiograph and pulmonary function testing
  - Cultures of respiratory tract secretions to evaluate for the presence of *Pseudomonas aeruginosa*
  - Bone density

Albinism (Oculocutaneous Albinism Type 1)

Chromosome and Gene Location

- 11q14.3 (oculocutaneous albinism type 1 (OCA1))
- There are numerous other types of albinism

Inheritance

- Autosomal recessive

Incidence

- 1/40,000

Clinical Manifestations

- Hypopigmented skin and hair
- Nystagmus
- Reduced iris and retinal pigment
- Foveal hypoplasia with significantly reduced visual acuity
- Two subtypes
  - OCA1A – no melanin synthesis in any tissue
  - OCA1B – variable amounts of melanin synthesis in some tissues

Molecular Basis of Disease

- Point mutations and large deletions in the tyrosinase gene (*TYR*) alter melanin production
- Mutations in other genes involved in melanocyte production, transportation, or proliferation lead to various other types of albinism

Laboratory

- Molecular analysis (sequencing and dosage) identifies mutations in the *TYR* gene
- Deficient tyrosinase activity in hair bulb

Treatment

- Not curable, supportive/symptomatic
- Avoidance of direct sunlight
- Ophthalmologic care and correction

Neurofibromatosis Type 1 (von Recklinghausen)

Chromosome and Gene Location

- 17q11.2

Inheritance

- Autosomal dominant
  - 50% are new mutations (de novo)
  - 50% inherited from a parent

Incidence

- 1/3,000

Clinical Manifestations

- Diagnosis based on established clinical criteria
- Neurofibromas (cutaneous and plexiform)
- Café au lait spots (Fig. 13.6A)
- Axillary and inguinal freckling (Fig. 13.6A)
- Lisch nodules (Fig. 13.6B)
- Optic gliomas
- Scoliosis
- Tibial dysplasia
- Learning disabilities (50%)
- Peripheral nerve sheath tumors

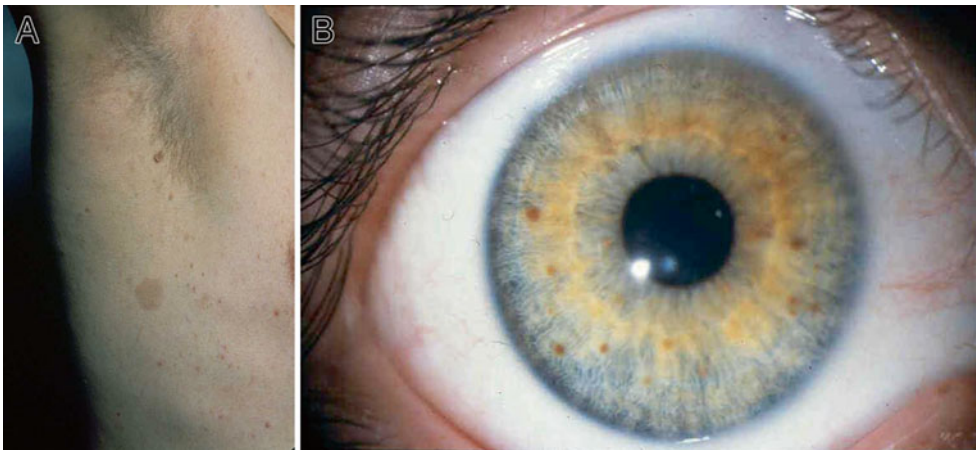

Fig. 13.6. Neurofibromatosis type 1 – Café au lait macule and axillary freckling (**A**). Lisch nodules (**B**).

- Osseous lesions
- Hypertension
- Noonan syndrome phenotype (12%)
  - Ocular hypertelorism, down-slanting palpebral fissures, low-set ears, webbed neck, and pulmonary stenosis

Molecular Basis of Disease

- Point mutations and large deletions in the *NFI* gene; large chromosomal rearrangements are also a rare cause of NF1
- Homozygous or compound heterozygous mutations in the four mismatch repair genes, *MLHI*, *MSH2*, *MSH6*, and *PMS2* result in childhood malignancies and features of NF1

Laboratory

- Molecular analysis (sequencing and dosage), in addition to cytogenetic analysis (standard chromosome analysis, FISH, chromosomal microarray), identifies mutations involving the *NFI* gene in approximately 95% of individuals

Treatment

- Not curable, supportive/symptomatic
- Surgical intervention when indicated
- Monitor by ophthalmologic examination and blood pressure measurements

Neurofibromatosis Type 2

Chromosome and Gene Location

- 22q12.2

Inheritance

- Autosomal dominant
  - 50% are new mutations (de novo)
  - 50% inherited from a parent

Incidence

- 1/35,000

Clinical Manifestations

- Diagnosis based on established clinical criteria
- Vestibular schwannomas (bilateral acoustic neuromas)
- Spinal tumors (schwannoma, astrocytoma, ependymoma)
- Meningiomas (50%)
- Loss of hearing
- Balance disturbance
- Ocular manifestations include subcapsular lens opacities that may progress to cataract, retinal hamartoma, and epiretinal membrane
- Childhood mononeuropathy and adult polyneuropathy
- Intellectual disability (associated with large deletions)

Molecular Basis of Disease

- Point mutations and large deletions in the *NF2* gene; large chromosomal rearrangements are also a rare cause of NF2
- Submicroscopic (10–600 kb) deletions (10–15%)
- Ring chromosome 22 (NF2 phenotype)

Laboratory

- Molecular analysis (sequencing and dosage), in addition to cytogenetic analysis involving the *NF2* gene in up to 93% of individuals with NF2

Treatment

- Not curable, supportive/symptomatic
- Surgical intervention when indicated
- Radiation therapy can induce or accelerate tumors
- Monitor by MRI for presence of tumors

Tuberous Sclerosis Complex

Chromosome and Gene Location

- 9q34.13 (*TSC1*)
- 16p13.3 (*TSC2*)

Inheritance

- Autosomal dominant
  - Two-thirds are new mutations (de novo)
  - One-third inherited from a parent

Incidence

- 1/6,000

Clinical Manifestations

- Diagnosis based on established clinical criteria
- Highly variable
- Skin abnormalities (~100%)
  - Facial angiofibromas (Fig. 13.7A)
  - Hypopigmented hypomelanocytic macules (by Wood lamp) (Fig. 13.7B)
  - Ungual fibroma
  - Shagreen patches
  - Fibrous facial plaques
- Central nervous system abnormalities
  - Cortical tubers
  - Subependymal nodules
  - Subependymal giant cell astrocytomas
  - Cerebral white matter radial migration lines
  - Seizures and epilepsy
  - Intellectual disability/learning difficulties (50%)
  - Behavioral and psychiatric disorders
- Renal abnormalities
  - Renal lesions (angiomyolipomas)
  - Renal cysts
  - Polycystic renal disease
  - Renal cell carcinoma
- Cardiac rhabdomyomas, retinal hamartomas, hamartomatous rectal polyps, and neuroendocrine tumors
- Bone cysts
- Lymphangiomyomatosis
- Dental enamel pits

Laboratory

- Molecular analysis (sequencing and dosage) for mutations in the *TSC1* and *TSC2* genes in about 85% of individuals with a definite diagnosis of TSC

Treatment

- Not curable, supportive/symptomatic
- Surgical removal of tumors
- Monitor for renal abnormalities by renal ultrasound
- Monitor for brain abnormalities by CT/MRI
- Chest CT for adult females to monitor for lymphangiomyomatosis

Beckwith–Wiedemann Syndrome

Chromosome and Gene Location

- 11p15.5 (includes multiple genes: *IGF2* and *H19* in domain 1 and *LIT1*/*KCNQ1OT1*, *CDKN1C*, and *KCNQ1* in domain 2)

Inheritance

- 85% sporadic
- 10–15% autosomal dominant (inherited from a parent)

Incidence

- 1/14,000

Clinical Manifestations

- Overgrowth syndrome: macroglossia, macrosomia, nephromegaly, splenomegaly, cardiomegaly, and hepatomegaly
- Hemihyperplasia and midface hypoplasia
- Ear creases and posterior helical ear pits
- Cryptorchidism
- Omphalocele observed by fetal ultrasound
- Neonatal hypoglycemia
- Cytomegaly of the fetal adrenal cortex
- Increased risk for embryonic tumors (Wilms tumor, hepatoblastoma, rhabdomyosarcoma, neuroblastoma)

Molecular Basis of Disease

- Beckwith–Wiedemann Syndrome (BWS) is due to dysregulation of imprinted genes at 11p15
- Imprinting refers to the difference in gene expression based on parent of origin

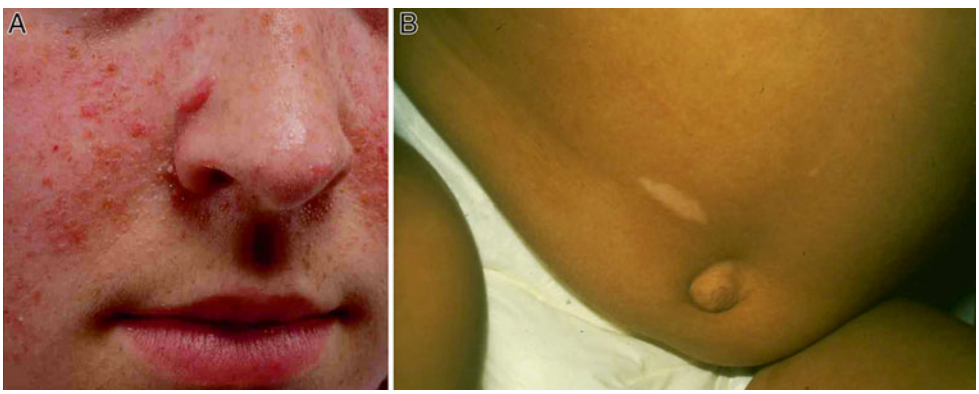

Fig. 13.7. Tuberous sclerosis – facial angiofibromas (**A**). Hypopigmented macule (**B**).

- Imprinted genes are usually regulated by methylation, which prevents a gene from being expressed
- Imprinted genes associated with BWS are regulated by imprinting center 1 (IC1) and imprinting center 2 (IC2)
  - *IGF2* (paternally expressed)
  - *KCNQ1OT1* (paternally expressed)
  - *H19* (maternally expressed)
  - *CDKN1C*/*p57*(*KIP2*) (maternally expressed)
- Molecular etiology of sporadic cases of BWS
  - Hypomethylation of *LIT1* (IC2) (50%)
  - Paternal UPD of chromosome 11 (20%)
  - Hypermethylation of *H19* (IC1) (5%)
  - Point mutation in *CDKN1C* (5–10%)
  - Cytogenetic abnormality (1–2%)
  - Unknown (10%)
- Molecular etiology of inherited cases of BWS
  - Point mutations in *CDKN1C* (40%)
  - Unknown

Laboratory

- Methylation analysis to detect methylation abnormalities of *LIT1* (IC2) and *H19* (IC1)
- UPD analysis of chromosome 11
- Molecular analysis of *CDKN1C* for point mutations
- Cytogenetic analysis identifies paternal duplications, translocations, or inversions of 11p15

Treatment

- Not curable, supportive/symptomatic
- Abdominal wall repair for abdominal wall defects in neonates
- Treatment of hypoglycemia
- Monitor for embryonic tumors by ultrasound and serum alpha-fetoprotein measurement

METABOLIC DISORDERS: INBORN ERRORS OF METABOLISM

Amino Acid Disorders

Phenylketonuria

Chromosome and Gene Location

- 12q24

Inheritance

- Autosomal recessive

Incidence

- 1/10,000–1/25,000 (lower in African Americans and Ashkenazi Jews)

Clinical Manifestations

- Intellectual disability
- Seizures
- Hyperactivity
- Eczema
- Hypopigmentation
- "Mousey" odor
- Maternal phenylketonuria (PKU) – children born to mothers with PKU have a high risk (90%) of having intellectual disability, microcephaly, impaired growth, and cardiac malformations, if mothers have not received dietary restriction of phenylalanine during pregnancy

Molecular Basis of Disease

- Mutations in phenylalanine hydroxylase (*PAH*) gene cause:
  - Inactivation of enzyme (more than 500 described)
  - Disruption of phenylalanine to tyrosine conversion with subsequent hyperphenylalaninemia

Laboratory

- Newborn screening detects blood phenylalanine (>0.13–1.2 mM) and phenylalanine/tyrosine ratio (>2.5) using tandem mass spectrometry
- Molecular genetic analysis available for positive cases

Treatment

- Low phenylalanine diet supplemented with tyrosine throughout life
- Sapropterin dihydrochloride (BH_4) at 20 mg/kg administration for BH_4-responsive forms of PKU

Tyrosinemia (Type I Most Prevalent)

Chromosome and Gene Location

- 15q23–q25

Inheritance

- Autosomal recessive

Incidence

- Varies by population, highest incidence along the St. Laurence waterway in Canada (1/1,846)

Clinical Manifestations

- Vomiting, acidosis, diarrhea, and failure to thrive
- Rickets
- Hepatic cirrhosis

- Fanconi renal tubular syndrome
- Urine odor of boiled cabbage (caused from methionine metabolites)
- Increased risk for hepatocellular carcinoma

Molecular Basis of Disease

- Mutations in the gene for tyrosinemia inactivate the enzyme fumarylacetoacetate hydrolase (FAH), which results in the accumulation of tyrosine and its metabolites (succinylacetoacetate, succinylacetone, and fumarylacetone) in the liver and kidney
- Numerous mutations have been found in the *FAH* gene and are generally family or population specific

Laboratory

- Increased urine tyrosine metabolites, serum alpha-fetoprotein concentration, and succinylacetone excretion. Reduced delta-ALA-dehydratase (PBG synthase) activity in erythrocytes due to inhibition by succinylacetone. Plasma or serum tyrosine is not 100% sensitive or specific
- Newborn screening detects succinylacetone by tandem mass spectrometry (an analyte not widely included in all newborn screening laboratories)
- Decreased fumarylacetoacetate hydrolase activity in liver biopsy specimens or cultured fibroblasts or chorionic villi sample
- Molecular analysis for targeted mutations and entire coding region is commercially available

Treatment

- Low phenylalanine, tyrosine, and methionine diet delays but does not stop progression of disease
- NTBC (2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione; nitisinone treatment reduces the accumulation of toxic metabolites by blocking the second step in the tyrosine degradation pathway and ameliorates the severe clinical manifestations

Maple Syrup Urine Disease

Chromosome and Gene Location

- 19q13.1–q13.2, (type 1-E1α subunit)
- 1p31 (type 2-E2 subunit)
- 6p14 (type 3-E1β subunit)
- 7q31–q32 (E3 subunit)

Inheritance

- Autosomal recessive

Incidence

- 1/125,000–1/300,000

Clinical Manifestations

- Variable based on type, level of enzyme deficiency, and management of acute episodes
- Features include
  - Apnea
  - Hypoglycemia
  - Cerebral edema
  - Poor feeding, vomiting, and lethargy
  - Maple syrup odor of urine and cerumen
  - Hypertonicity/hypotonicity
  - Muscle rigidity
  - Seizures

Molecular Basis of Disease

- The branched chain alpha keto acid dehydrogenase is a mitochondrial enzyme consisting of four subunits: E1α, E1β, E2, and E3 (each subunit is located on a different chromosome; see above)
- The enzyme system is responsible for the decarboxylation of the branched chain amino acids: leucine, isoleucine, and valine
- Mutations in the genes encoding the various subunits result in defective expression and buildup of the branched chain amino acids and their metabolites in the blood, urine, and cerebral spinal fluid

Laboratory

- Deficiency of branched chain alpha keto acid dehydrogenase activity in leukocytes and cultured skin fibroblasts (prenatal diagnosis also available)
- Elevation of leucine, isoleucine, valine, and alloisoleucine in plasma or serum. Elevation of branch-chain keto acids in urine, serum, or plasma

Treatment

- Thiamine for B1-responsive forms
- Not curable, supportive/symptomatic
- Manage acute episodes
- Reduce intake of branched chain amino acids by using special formulas and reducing protein intake

Homocystinuria

Chromosome and Gene Location

- 21q22.3

Inheritance

- Autosomal recessive

Incidence

- 1/100,000
- Clinical Manifestations
- Dislocation of ocular lens, myopia, strabismus, cataracts, and glaucoma
- Thinning and lengthening of the long bones, osteoporosis, and scoliosis

- High-arched palate, pes cavus, genu valgum, and biconcave vertebrae
- Thromboembolism
- Bluish mottling of the skin on legs and hands
- Developmental delay and seizures

Molecular Basis of Disease

- The enzyme, cystathionine-β-synthase (CBS), converts homocysteine to serine and cystathionine
- Mutations in the *CBS* gene result in inactivation of enzyme function, which leads to elevated methionine and homocysteine levels

Laboratory

- Increased levels of homocysteine in urine or plasma
- Hyperhomocysteinemia with increased methionine in plasma or serum. Decreased enzyme activity in fibroblasts, liver biopsy specimens, or PHA-stimulated lymphocytes (prenatal diagnosis available)
- Molecular analysis available for mutation detection

Treatment

- High doses of pyridoxine (vitamin B6), which is a cofactor of CBS, are given to decrease homocysteine levels (increases conversion of homocysteine to cysteine)
- Folic acid permits response to pyridoxine and optimizes conversion of homocysteine to methionine
- Betaine is used in pyridoxine-unresponsive patients to lower plasma homocysteine levels by allowing conversion to methionine
- Low-methionine diets reduce accumulation of methionine and homocysteine and their metabolites
- Patients treated from newborn period have fewer complications than those treated late or untreated

Urea Cycle Disorders

- The urea cycle functions to prevent the accumulation of toxic nitrogenous compounds and also contain several reactions required for the synthesis of arginine. The urea cycle consists of five biochemical reactions. Defects in the biosynthesis or function of any of the five enzymes in this pathway lead to disease

Chromosome and Gene Location

- See Table 13.8

Inheritance

- See Table 13.8

Incidence

- See Table 13.8

Clinical Manifestations

- All defects with the exception of arginase deficiency result in a similar clinical phenotype which includes:
  - Lethargy, persistent vomiting, and poor feeding coma
  - Hypotonia
  - Seizures
  - Hepatomegaly
- The onset usually occurs after feeding in newborn period or after infections or protein overload
- In arginase deficiency, children are often asymptomatic for the first few months to years of life
- Clinical features of arginase deficiency include:
  - Loss of developmental milestones
  - Increased clumsiness
  - Spastic quadriplegia with loss of ambulation
  - Loss of speech
  - Seizures
  - Progressive intellectual disability

Molecular Basis of Disease

- See Table 13.8 for enzyme involved. Enzyme defects lead to the accumulation of ammonia and alter levels of other amino acids
- Ammonia is a neurotoxin that adversely affects the CNS

Table 13.8. **Urea Cycle Disorders**

	Chromosome	*Enzyme*	*Inheritance*	*Incidence*
Carbamoyl phosphate synthetase deficiency	2q35	Carbamoyl phosphate synthetase	Autosomal recessive	1/60,000
Ornithine transcarbamylase deficiency	Xp21.1	Ornithine transcarbamylase	X-linked recessive	1/30,000
Citrullinemia	9q34	Argininosuccinate synthetase	Autosomal recessive	Rare
Argininosuccinic aciduria	7cen-q11.2	Argininosuccinate lyase	Autosomal recessive	1/70,000
Argininemia	6q23	Arginase	Autosomal recessive	Rare

Laboratory

- Hyperammonemia, altered amino acid levels in plasma, which are specific to each reaction
- Deficient enzyme activity, molecular testing available for carrier and prenatal testing

Treatment

- Control of and avoidance of acute attacks, including supportive care during symptomatic episodes
- Restrict protein, high-caloric diet to minimize breakdown of protein
- Prognosis is better if disorder is treated promptly

Organic Acidemias

Isovaleric Acidemia

Chromosome and Gene Location

- 15q14–q15

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical Manifestations

- Usually presents within the first few days of life, symptoms include:
  - Acute attacks of vomiting and lethargy
  - Acidosis
  - Ataxia
  - Coma
  - Seizures
  - Intellectual disability
- Attacks are usually triggered by stresses such as infections or surgery

Molecular Basis of Disease

- Isovaleryl CoA dehydrogenase catalyzes the conversion of isovaleric acid to 3-methylcrotonic acid in the branch-chain amino acid, leucine, and degradation pathway
- Deficient isovaleryl CoA dehydrogenase results in the accumulation of isovaleric acid and its metabolites, which are toxic to the body
- A recurring mutation, A282V, is frequently found in asymptomatic and relatively mild IVA cases detected by newborn screening with tandem mass spectrometry

Laboratory

- Elevated isovaleric acid
- Hyperammonemia
- Hypocalcemia pancytopenia
- Neutropenia
- Thrombocytopenia
- Anemia
- Elevated urine isovalerylglycine during an acute attack
- Deficiency of isovaleryl CoA dehydrogenase in leukocytes or cultured skin fibroblasts (prenatal diagnosis available)

Treatment

- Not curable, supportive/symptomatic
- Avoidance of, and symptomatic control of, acute episodes
- Correct dehydration, electrolyte disturbances, and metabolic acidosis
- Reduce protein intake
- Remove excess isovalerylic acid by use of glycine and carnitine, which allows for urinary excretion

Propionic Acidemia

Chromosome and Gene Location

- 13q32
- 3q21–q22

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical Manifestations

- Onset may occur within the first few weeks of life
- Symptoms include:
  - Apnea
  - Hypoglycemia
  - Poor feeding, vomiting, and lethargy
  - Coma
  - Hypotonia
  - Seizures
  - Frequent infections
  - Osteoporosis
  - Intellectual disability
- Symptoms may be triggered by infections, constipation, and protein overload

Molecular Basis of Disease

- Propionyl-CoA-carboxylase (PCC) is a multimeric, mitochondrial enzyme consisting of alpha subunits, encoded by *PCCA*, and beta subunits, encoded by *PCCB*
- The gene for each subunit is located on different chromosomes: chromosome 13 (alpha) and chromosome 3 (beta)
- Propionic acidemia can arise from mutations in either the alpha or beta subunit
- PCC is involved in the catabolic pathway for the odd-chain length fatty acids: threonine, methionine, isoleucine, and valine

- Deficiencies of PCC lead to the accumulation of propionic acid, which results in the inhibition of citric acid cycle enzymes, acetylglutamate synthetase, granulocytes, and T- and B-cell development
- Numerous mutations have been described in the beta and alpha subunits

Laboratory

- Metabolic acidosis
- Hypoglycemia
- Hyperammonemia
- Carnitine deficiency
- Elevated glycine
- Elevated propionic and methylcitric acids
- Neutropenia
- Thrombocytopenia
- Deficiency of PCC activity in leukocytes or cultured skin fibroblasts (prenatal diagnosis available)

Treatment

- Not curative. Avoidance of, and symptomatic control of, acute episodes
- Correct dehydration, electrolytes disturbances, and metabolic acidosis (bicarbonate)
- Decrease protein intake
- Antibiotics prevent production of propionic acid by intestinal bacteria
- Some individuals respond to biotin treatment, as it is a cofactor for PCC

Methylmalonic Acidemia (Methylmalonyl-CoA Mutase and Other Forms)

Chromosome and Gene Location

- 6p21

Inheritance

- Autosomal recessive

Incidence

- 1/50,000

Clinical Manifestations

- Lethargy, failure to thrive, recurrent vomiting, and dehydration
- Respiratory distress
- Muscular hypotonia
- Growth retardation
- Psychomotor retardation
- Impairment of renal function
- Neurological abnormalities

Molecular Basis of Disease

- Methylmalonic acid is derived from propionic acid as part of the catabolic pathway of isoleucine, valine, threonine, methionine, cholesterol, and odd-chain fatty acids
- Methylmalonic acid is converted to succinic acid by methylmalonyl-CoA mutase and cobalamine (vitamin B12), which is a cofactor
- Defects in the mutase or reduced levels of its cofactor result in the accumulation of methylmalonic acid and its precursors
- The number of different genes involved in cobalamine metabolism and methylmalonic acidemia is uncertain; however, six complementation groups have been identified indicating multiple alleles
- Numerous mutations within the mutase gene on chromosome 6 have been reported

Laboratory

- Ketosis, acidosis, anemia, elevated urinary, and serum methylmalonic acid
- Decreased or absent mutase activity in cultured fibroblasts
- Prenatal diagnosis available

Treatment

- Restricted protein
- Vitamin B12 supplementation to lower MMA levels

Mitochondrial Fatty Acid Oxidation Disorders

- Mitochondrial fatty acid oxidation fuels ketogenesis in the liver and energy production during an unfed state or during activities requiring a high energetic demand. Thus, many disorders of mitochondrial fatty acid oxidation present with sudden death that is often triggered by an acute illness or other episode. In addition, several of these disorders affect liver function and may also be complicated by cardiac dysfunction
- Mitochondrial fatty acid oxidation consists of multiple biochemical reactions. Defects in the function of several of the enzymes in this pathway lead to disease

Medium-Chain Acetyl-CoA Dehydrogenase Deficiency

Chromosome and Gene Location

- 1p31

Inheritance

- Autosomal recessive

Incidence

- 1/15,000

Clinical Manifestations

- Onset may occur within the first few days of life if triggered by an illness or fasting
- Symptoms include:
  - Sudden, unexplained death
  - Hypoketotic hypoglycemia
  - Vomiting and lethargy
  - Seizures
  - Coma

- Reye-like syndrome
- Hepatomegaly and acute liver disease

Molecular Basis of Disease

- Medium-chain acetyl-CoA dehydrogenase (MCAD) is an enzyme encoded by *ACADM* on chromosome 1, and it is required for the beta oxidation of medium-chain fatty acids in the mitochondria
- A defect in MCAD results in the reduction of acetyl-CoA levels and in the accumulation of medium-chain fatty acids, which are further conjugated to glycine and carnitine–esters or metabolized to dicarboxylic acids
- The accumulation of medium-chain fats and their conjugates can be detected in the blood, urine, and tissue of patients with MCAD deficiency. The medium-chain, carnitine–ester conjugates are used as biomarkers for newborn screening of this disorder by tandem mass spectrometry
- A frequent cause of MCAD deficiency is homozygosity for the 985A>G mutation in exon 11 of *ACADM*, a mutation that has an estimated carrier frequency of 1/40 in peoples of Northern European descent
- Numerous mutations within the *ACADM* gene have been identified, and several may lead to a mild biochemical phenotype

Laboratory

- Hypoketotic hypoglycemia
- Hyperammonemia
- Carnitine deficiency
- Elevated medium-chain acylcarnitines with prominent octanoylcarnitine
- Elevated medium-chain acylglycines with prominent hexanoylglycine and suberylglycine
- Deficiency of MCAD activity in cultured skin fibroblasts
- *ACADM* mutations, such as 985A>G

Treatment

- Avoidance of fasting for more than 12 h
- Control of acute illnesses by intravenous glucose
- Uncooked cornstarch for toddlers at bedtime
- L-carnitine supplementation (100 mg/kg/day)
- Low-fat diet

Very Long-Chain Acetyl-CoA Dehydrogenase Deficiency

Chromosome and Gene Location

- 17p13

Inheritance

- Autosomal recessive

Incidence

- 1/40,000

Clinical Manifestations

- Onset often occurs during infancy where it can present with cardiomyopathy and hepatic dysfunction. It also occurs in childhood where it presents with hepatic symptoms and hypoglycemia. A few adult patients have been described with muscle symptoms and without hepatic or cardiac involvement
- Symptoms include:
  - Sudden, unexplained death
  - Hypoketotic hypoglycemia
  - Vomiting, lethargy
  - Seizures
  - Rhabdomyolysis
  - Myoglobinuria
  - Dilated or hypertrophic cardiomyopathy
  - Hepatomegaly and acute liver disease

Molecular Basis of Disease

- Very long-chain acetyl-CoA dehydrogenase (VLCAD) is an enzyme encoded by *ACADVL* on chromosome 17 that is essential for the beta oxidation of long-chain fatty acids in the mitochondria
- VLCAD leads to the accumulation of long-chain fatty acids, particularly the unsaturated C12–C14 chain-length fats, which are further conjugated to carnitine–esters or metabolized to dicarboxylic acids
- Accumulation of long-chain fats (unsaturated C12–C14) are found in VLCAD patient tissues and their carnitine–ester conjugates are used as biomarkers for newborn screening of this disorder by tandem mass spectrometry
- Numerous private mutations within the VLCAD gene account for this disorder

Laboratory

- Hypoketotic hypoglycemia
- Hyperammonemia
- Carnitine deficiency
- Elevated very long-chain plasma acylcarnitines with prominent unsaturated C14 species
- Elevated hepatic enzymes and creatine kinase (CK)
- Myoglobinuria
- Deficiency of VLCAD activity in cultured skin fibroblasts
- *ACADVL* mutation analysis is available for confirmation and prenatal diagnosis

Treatment

- Avoidance of fasting or prolonged exercise
- Control of acute illnesses by intravenous fluids
- High-carbohydrate and low-fat diet
- Supplementation with MCT-oil
- L-carnitine supplementation is controversial

Long-Chain 3-Hydroxylacetyl-CoA Dehydrogenase/Mitochondrial Trifunctional Protein Deficiency

Chromosome and Gene Location

- 2p23

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical Manifestations

- This presents as neonatal hypoglycemia, lactic acidosis, and sudden, unexplained death. It also occurs in childhood where it presents with additional symptoms, such as progressive neuropathy, myopathy, and ophthalmologic abnormalities. It is also associated with maternal, acute fatty liver of pregnancy or HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome in mothers of affected children
- Symptoms include:
  - Sudden, unexplained death
  - Hypoketotic hypoglycemia
  - Coma
  - Lactic academia
  - Hypotonia
  - Seizures
  - Progressive retinopathy
  - Peripheral neuropathy
  - Cardiomyopathy
  - Hepatic dysfunction

Molecular Basis of Disease

- Long-chain 3-hydroxylacetyl-CoA dehydrogenase/mitochondrial trifunctional protein deficiency (LCHAD/TFP) is caused by the deficiency of proteins encoded by *HADHA* and *HADHB*. Both genes are located in tandem on chromosome 2p23, and their protein products form a heteromer that is essential for the beta oxidation of long-chain fatty acids in the mitochondria. The heteromer functions as a long-chain 3-hydroxylacetyl-CoA dehydrogenase (LCHAD, encoded by HADHA), a long-chain enoyl-CoA hydratase, and a long-chain thiolase, hence the name, mitochondrial trifunctional protein (TFP)
- LCHAD/TFP leads to the accumulation of 3-hydroxyl long-chain fatty acids, particularly the hydroxylated C14–C18 chain-length fats, which are further conjugated to carnitine–esters or metabolized to dicarboxylic acids
- Accumulation of long-chain (hydroxylated C14–C18), fatty acid; carnitine–ester conjugates are used as biomarkers for newborn screening of this disorder by tandem mass spectrometry
- Private mutations are frequent within *HADHA* and *HADHB* genes

Laboratory

- Hypoketotic hypoglycemia
- Hyperammonemia and lactic acidemia
- Carnitine deficiency
- Elevated, long-chain, hydroxylated plasma acylcarnitines with prominent C14–C18 species
- Elevated hepatic enzymes and CK
- Deficiency of LCHAD/TFP activity in cultured skin fibroblasts
- *HADHA* and *HADHB* mutation analysis is available for confirmation and prenatal diagnosis

Treatment

- Avoidance of fasting or prolonged exercise
- Control of acute illnesses by intravenous fluids
- High-carbohydrate and low-fat diet
- Supplementation of diet with MCT-oil
- DHA supplementation is also commonplace with the aim to stabilize the retinopathy
- L-carnitine supplementation is controversial

Short-Chain Acetyl-CoA Dehydrogenase Deficiency

Chromosome and Gene Location

- 12q22–qter

Inheritance

- Autosomal recessive

Incidence

- 1/50,000

Clinical Manifestations

- Clinical heterogeneity of this disorder has complicated a complete understanding of its natural history. Several case reports have associated short-chain acetyl-CoA dehydrogenase (SCAD) deficiency with neonatal hypotonia and developmental delay, with or without seizures. However, with the advent of newborn screening by tandem mass spectrometry, of which SCAD deficiency is a secondary target, numerous SCAD-deficient patients have been found to be asymptomatic exclusive of persistent ethylmalonic aciduria. The presence of two common SCAD gene variants may account for the biochemical and clinical variability of this disorder
- Reported symptoms include:
  - Hypotonia
  - Seizures
  - Developmental and speech delay
  - Lethargy
  - Failure to thrive
  - Ethylmalonic aciduria without other symptoms

Molecular Basis of Disease

- Short-chain acetyl-CoA dehydrogenase (SCAD) is an enzyme encoded by *ACADS* on chromosome 12 and is required for the last chain-shortening step of mitochondrial fatty acid oxidation
- Reduction of SCAD function leads to the accumulation of short-chain fatty acids (of the C4 chain-length), which are further conjugated to glycine and carnitine–esters, or metabolized to dicarboxylic acids, ethylmalonic acid, and methylsuccinic acid
- Accumulation of short-chain fats and their conjugates can be detected in the blood and urine of patients with SCAD deficiency, and the carnitine–ester conjugate (C4 acylcarnitine) is used as a biomarker for newborn screening of this disorder by tandem mass spectrometry
- Two common *SCAD* gene variants, 625G>A and 511C>T, are frequently found in the normal population, lead to mild ethylmalonic aciduria, but do not confer disease
- Numerous SCAD-deficient patients who are compound heterozygous for an SCAD gene variant and a single mutation have been identified by newborn screening. It does not appear that compound heterozygosity for a mutation and a variant will lead to a clinical phenotype. However, additional studies are needed to understand the possible complex multifactorial components that lead to a phenotype

Laboratory

- Hypoglycemia
- Elevated short-chain plasma acylcarnitines with prominent butyrylcarnitine
- Elevated ethylmalonic acid excretion detectable by urine organic acids or acylglycines
- Deficiency of SCAD activity in cultured skin fibroblasts
- *SCAD* gene sequence analysis is commercially available and will detect gene variants and most missense mutations

Treatment

- Avoidance of fasting
- Control of acute illnesses by intravenous fluids
- L-carnitine supplementation (100 mg/kg/day)
- Low-fat diet

Carbohydrate Metabolism Disorders

Glycogen Storage Disease (Type I)

Chromosome and Gene Location

- 17q21

Inheritance

- Autosomal recessive

Incidence

- 1/100,000

Clinical Manifestations

- Hypoglycemia
- Hypertension
- Excessive perspiration
- Bruising and nosebleeds
- Short stature
- Delayed puberty
- Protuberant abdomen
- Liver adenomas, hepatomegaly, hepatoblastoma, and hepatocellular carcinoma
- Chronic pancreatitis
- Renal insufficiency

Molecular Basis of Disease

- The enzyme glucose-6-phosphatase catalyzes the conversion of glucose-6-phosphate to glucose
- Mutations in the gene encoding glucose-6-phosphatase result in a deficiency of this enzyme and the subsequent inability to free glucose for use in the body
- Mutations in the glucose-6-phosphatase gene (*G6PC*) have been found in about 80% of patients studied
- There are various types of glycogen storage diseases, which result from deficiencies of other enzymes involved in the glycogen metabolism pathway

Laboratory

- Deficiency of glucose-6-phosphatase in liver biopsy (enzyme not present in skin fibroblasts)
- Lipidemia
- Hyperuricemia
- Lactic acidemia
- Ketonemia
- Molecular analysis available

Treatment

- Maintenance of normal blood glucose concentration, by supplementation of glucose, pancreatic enzymes, and cornstarch
- Limit intake of fructose and galactose
- Low-fat diet
- Liver transplantation if necessary

Galactosemia

Chromosome and Gene Location

- 9p13

Inheritance

- Autosomal recessive

Incidence

- 1/30,000

Clinical Manifestations

- Babies with galactosemia may appear normal at birth
  - Symptoms begin soon after milk feedings have begun

- Symptoms include:
  - Lethargy, irritability, vomiting, feeding difficulties, poor weight gain, and failure to thrive
  - Seizures
  - Jaundice
  - Hepatomegaly, hepatic cirrhosis, and splenomegaly
  - Hypoglycemia
  - Ascites
  - Lens opacities
  - Increased susceptibility to infections
- Long-term complications include:
  - Speech deficits
  - Ataxia
  - Dysmetria
  - Diminished bone density
  - Premature ovarian failure

Molecular Basis of Disease

- Galactose-1-P uridyltransferase (GALT) catalyzes the conversion of galactose-1-phosphate to glucose-1-phosphate
- Deficiency of GALT results in the accumulation of galactose-1-phosphate, which causes injury to the parenchymal cells of the kidney, liver, brain, ovaries, and eyes
- A single mutation (Q188R) accounts for about 70% of galactosemia alleles in Northern Europeans
- 12% carry the Duarte variant, which decreases enzyme activity, but does not result in phenotypic consequence

Laboratory

- Newborn screening uses an enzyme fluorescent assay and/or measurement of total galactose in dried blood spots
- Classic and variant alleles can be detected with isoelectric focusing
- Molecular analysis is used in conjunction with biochemical testing for prognostication, heterozygote detection, and prenatal diagnosis
- Serum in affected individual shows elevated transaminase, hyperbilirubinemia, follicular-stimulating hormone, luteinizing hormone, decreased estrogen, and anemia
- *E. coli* septicemia frequently occurs

Treatment

- Eliminate lactose and galactose from the diet; special formula is necessary
- Even with good dietary control, there may be poor intellectual function, speech problems, and ovarian dysfunction

Galactokinase Deficiency

Chromosome and Gene Location

- 17q24

Inheritance

- Autosomal recessive

Incidence

- 1/40,000

Clinical Manifestations

- Cataracts
- Neonatal jaundice
- Normal intelligence

Molecular Basis of Disease

- Galactokinase catalyzes the conversion of galactose to galactose-1-phosphate
- Galactokinase deficiency results in the accumulation of galactose
- Some galactose is converted to galactitol, which may be responsible for the cataract formation

Laboratory

- Deficiency of galactokinase activity in red blood cells

Treatment

- Elimination of lactose and galactose from the diet

Transport Disorders

Familial Hypophosphatemic Rickets

Chromosome and Gene Location

- Xp22.2–p22.1

Inheritance

- X-linked dominant (also autosomal recessive and sporadic forms)

Incidence

- 1/1,000,000

Clinical Manifestations

- Bowing of lower extremities
- Waddling gait
- Short stature
- Decreased femur/shaft angle
- Dolichocephaly
- Tooth deformities

Molecular Basis of Disease

- Deficiency interferes with phosphate reabsorption in kidney and conversion of 25-hydroxy-D to 1,25-hydroxy-2D

Laboratory

- Hyperphosphaturia
- Normal amino acids
- X-rays show metaphyseal widening and fraying and cupping of metaphyses at tibia, femur, radius, and ulna
- Molecular analysis of the *PHEX* gene is available

Treatment

- Phosphate supplements and surgery for limb deformities

Cystinuria

Chromosome and Gene Location

- 2p16.3 and 19q13.1

Inheritance

- Complex inheritance that is mostly autosomal recessive with genetic components from multiple alleles producing three clinical types

Incidence

- 1/2,000 in England to 1/100,000 in Sweden
- Overall approximately 1/7,000

Clinical Manifestations

- Urinary tract calculus
- Cystine stones are formed and crystals appear in the urine
- Increased risk for impaired cerebral function

Molecular Basis of Disease

- Mutations in the *SLC3A1* gene on chromosome 2p are responsible for type I, which is recessive; mutations in *SLC7A9* are responsible for types II and III, which show incomplete penetrance
- The relationship between *SLC3A1* and *SLC7A9* gene products and their influence on the complex inheritance of cystinuria is not completely understood

Laboratory

- Dibasic aminoaciduria (excess excretion of cystine) and increased urinary lysine, arginine, and ornithine
- Molecular analysis of *SLC3A1* and *SLC7A* is available

Treatment

- Dietary therapy to reduce cystine excretion and increase solubility
- Decreased methionine
- Low-sodium diets
- High fluid intake
- Alkalization of urine by sodium bicarbonate or sodium citrate to increase solubility of cystine
- Surgery to remove stones
- Penicillamine treatment for dissolving stones

Hartnup Disease

Chromosome and Gene Location

- 5p15

Inheritance

- Autosomal recessive

Incidence

- 1/30,000

Clinical Manifestations

- Cerebellar ataxia
- Emotional instability, psychosis
- Delayed development
- Severe retardation
- Photosensitive skin

Molecular Basis of Disease

- Caused by mutations in *SLC6A19*, which leads to a defect in neutral amino acid transport across the brush-border membrane of the renal and intestinal epithelium

Laboratory

- Characteristic pattern of increased secretion of neutral amino acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, histidine, glutamine, and asparagine)

Treatment

- Nicotinic acid or nicotinamide for deficiency of this vitamin reduces rash, ataxia, and psychotic behavior
- High-protein diet or supplementation

Cystinosis

Chromosome and Gene Location

- 17p13

Inheritance

- Autosomal recessive

Incidence

- 1/100,000–1/200,000

Clinical Manifestations

- There appears to be three types of cystinosis with varying degrees of involvement:
  - Nephrotic-classic renal and systemic disease in which children develop dehydration, acidosis, vomiting, electrolyte imbalances, hypophosphatemic rickets, failure to grow, photophobia, corneal crystals, hypothyroidism, myopathy, decreased ability to sweat, and renal failure by age 9–10
  - Intermediate late onset of nephrotic cystinosis
  - Non-nephrotic, clinically affecting only the corneas

Molecular Basis of Disease

- Defective carrier-mediated transport of cystine causes accumulation of cystine and formation of crystals in the lysosomes of most tissues
- Mutations in the *CTNS* gene are responsible for all three types of cystinosis

Laboratory

- Generalized aminoaciduria
- Glucosuria with normal blood glucose
- Elevated leukocyte cystine

- Cystine crystals in tissue biopsy of bone marrow, conjunctiva, kidney, liver, intestine, and other tissues (not present in skin biopsy) and cystine storage in pancreatic islet cells, aorta, atrophic ovaries, and brain
- Molecular mutation analysis and prenatal diagnosis are available

Treatment

- Management of electrolyte imbalance
- Renal allografts
- Growth hormones
- Therapy with cysteamine averts the otherwise inevitable renal failure, but systemic therapy does not improve the corneal keratopathy; cysteamine eye drops may prevent photophobia

Metal Metabolism Disorders

Wilson Disease

Chromosome and Gene Location

- 13q14

Inheritance

- Autosomal recessive

Incidence

- 1/30,000

Clinical Manifestations

- Liver disease
- Neurologic disturbance
- Acute jaundice
- Hemolysis
- Dysarthria
- Involuntary movement
- Renal tubular acidosis
- Osteoarthropathy
- Cardiomyopathy
- Golden-brown granular pigmentation is seen in the outer crescent of the iris ("Kayser–Fleischer" rings)

Molecular Basis of Disease

- Wilson disease is caused by mutations in the *ATP7B* gene, which encodes a copper-binding P-type ATPase
- Expression occurs primarily in the liver, kidney, and placenta
- Defects in the gene lead to defective liver-specific copper transport and defective copper excretion into the bile
- Copper accumulates in the liver and other tissues and inhibits various enzymatic reactions
- Numerous mutations in *ATP7B* have been identified

Laboratory

- Reduced serum copper level and ceruloplasmin and increased urinary copper excretion
- Elevated copper in liver biopsy
- Diagnosis by quantitating hepatic copper stores which are increased
- Molecular analysis clinically available

Treatment

- Zinc acetate, which inhibits intestinal absorption of copper
- Penicillamine, tetrathiomolybdate, or trientine (which may have fewer side effects) increases urinary copper excretion
- Liver transplantation when necessary

Acrodermatitis Enteropathica

Chromosome and Gene Location

- 8q24.3

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical Manifestations

- Symptoms most often occur early in infancy after transition from breast milk to cow milk
- Features include:
  - Dry, scaly, reddish skin lesions on the face, knees, elbows, and perineal areas
  - Reddish hair
  - Hair loss
  - Photophobia
  - Conjunctivitis
  - Corneal dystrophy
  - Chronic diarrhea
  - Growth retardation
  - Delayed wound healing
  - Immune defects

Molecular Basis of Disease

- Impaired zinc absorption due to an absent or defective zinc-specific transporter, which is encoded by *SLC39A4* and facilitates zinc absorption
- Variety of clinical features is likely because zinc plays a role in numerous metabolic pathways
- Without therapy, plasma zinc concentration and serum alkaline phosphatase, as well as urinary excretion of zinc, are very low

Treatment

- Oral zinc compounds abolish the manifestations of the disease

Menkes Disease

Chromosome and Gene Location

- Xq13

Inheritance

- X-linked recessive

Incidence

- 1/40,000–1/350,000

Clinical Manifestations

- Hypothermia
- Hypotonia
- Myoclonic seizures
- Chubby, rosy cheeks
- Kinky, colorless friable hair (Fig. 13.8)
- Failure to thrive
- Severe intellectual disability
- Optic atrophy
- Osteopenia with pathologic fractures (may be mistaken for child abuse)

Molecular Basis of Disease

- Caused by mutations in the copper-transporting ATPase, *ATP7A*
- Mutations in *ATP7A* result in defective copper absorption and transport
- A wide spectrum of mutations has been identified

Laboratory

- Low serum copper and ceruloplasmin levels
- Intracellular accumulation of copper in cultured cells
- Molecular analysis of *ATP7A* is available; prenatal diagnosis is also available

Fig. 13.8. Menkes disease – magnified image of pili torti of hair.

Treatment

- Copper histidine treatment has had limited success. Many patients deteriorate and die of complications from seizures before 2 years of age

Hemochromatosis

Chromosome and Gene Location

- 6p21.3

Inheritance

- Autosomal recessive

Incidence

- Varies by population
- 1/200–1/300 in Northern European populations
- Lower in others

Clinical Manifestations

- Fatigue
- Palpitations
- Premature arthritis
- Impotence in males
- Amenorrhea in females
- Cardiac arrhythmias
- Congestive heart failure due to cardiomyopathy
- Cirrhosis with hepatosplenomegaly
- Ascites
- Hyperpigmentation
- Onset is generally between ages 40 and 60
- Females have later onset due to menses/child birthing

Molecular Basis of Disease

- A gene called *HLA-H* or *HFE* has been shown to be altered in the majority of hemochromatosis patients
- The most common mutation causes an amino acid substitution at codon 282 (C282Y)
- Approximately 85% of hemochromatosis patients of Northern European descent are homozygous, 5–10% are heterozygous, and an additional 5–10% do not carry the C282Y mutation
- A second less frequent alteration is an amino acid substitution at codon 63 (H63D); its role in this disease is controversial, but may increase one's risk for developing hemochromatosis
- It has been hypothesized that the C282Y mutation results in an abnormal protein trafficking or cell surface expression of the *HFE* gene

Laboratory

- Elevated serum transferrin saturation and concentration
- Elevated hepatic iron concentration on liver biopsy
- Molecular mutation analysis is available

Treatment

- Phlebotomy reduces iron stores to normal
- Chelating agents remove smaller amounts of iron, but are not as effective as phlebotomy

Purine Metabolism Disorders

Lesch–Nyhan Syndrome

Chromosome and Gene Location

- Xq26–q27

Inheritance

- X-linked recessive

Incidence

- 1/300,000

Clinical Manifestations

- Hypotonia
- Delayed motor development
- Choreoathetosis
- Spastic movements
- Hyperreflexia
- Self-injurious behavior
- Gouty arthritis
- Kidney stones composed of uric acid
- Carrier females develop gout in later years

Molecular Basis of Disease

- The enzyme, hypoxanthine-guanine phosphoribosyltransferase, converts hypoxanthine and xanthine to nucleotides, inosinic acid, and guanylic acid
- Deficiency in enzyme activity results in accelerated purine production de novo and increased uric acid
- Deficiencies may also result in decreased synthesis of nucleotides

Laboratory

- Elevated serum uric acid concentration
- Elevated urate to creatinine ratio in urine
- Marked increases in the production and excretion of uric acid
- Absence of hypoxanthine-guanine phosphoribosyltransferase activity in erythrocytes and fibroblasts (prenatal diagnosis available)
- Molecular mutation analysis is available, including prenatal diagnosis

Treatment

- Avoidance of dehydration
- Adequate nutrition
- Behavior control and modification
- Allopurinol to prevent damage to kidneys
- Experimental gene therapy

Adenosine Deaminase

Chromosome and Gene Location

- 20q13

Inheritance

- Autosomal recessive

Incidence

- 1/200,000–1,000,000

Clinical Manifestations

- Severe immunodeficiency
- Complete impairment of T-cell function
- Rib cage abnormalities
- Chondro-osseous dysplasia

Molecular Basis of Disease

- Mutations in the *ADA* gene encoding the enzyme adenosine deaminase result in the accumulation of adenosine, 2′ deoxyadenosine and 2′-*O*-methyladenosine, which leads to lymphocyte toxicity and subsequent immunodeficiency

Laboratory

- Absence of adenosine deaminase in red blood cells or cultured fibroblasts

Treatment

- Enzyme replacement therapy has resulted in clinical and immunologic improvement in some patients
- Bone marrow transplantation

Peroxisomal Disease

Zellweger Syndrome, Neonatal Adrenoleukodystrophy, and Infantile Refsum Disease

Chromosome and Gene Location

- 7q11.23 (also chromosomes 1, 2, 6, 8, 11, 12, 17, and 22)

Inheritance

- Autosomal recessive

Incidence

- 1/25,000–1/50,000

Clinical Manifestations

- Clinical spectrum with Zellweger syndrome representing the most severe presentation; infantile Refsum disease is the least severe phenotype
- High forehead
- Upslanting palpebral fissures
- Hypoplastic supraorbital ridges
- Epicanthal folds

- Severe weakness
- Hypotonia
- Seizures
- Eye abnormalities
- Profound intellectual disability
- Early lethality
- Liver cysts
- Chondrodysplasia punctata
- Hearing loss and visual impairment

Molecular Basis of Disease

- Peroxisome biogenesis disorders are caused by mutations in several different genes involved in peroxisome biogenesis
- Mutations have been identified in numerous peroxisome biogenesis factor (*PEX*) genes as well as the peroxisomal membrane protein-3 gene

Laboratory

- Reduced or absent peroxisomes
- Catalase in cytosol
- Reduced plasmalogens
- Accumulation of very long-chain fatty acids
- Increased phytanic acid
- Bile acid precursors are elevated
- Increased L-pipecolic acid
- Increased urinary excretion of dicarboxylic acids
- Molecular mutation analysis available

Treatment

- Not curable, supportive/symptomatic

Adrenoleukodystrophy (X linked)

Chromosome and Gene Location

- Xq28

Inheritance

- X-linked recessive

Incidence

- 1/42,000

Clinical Manifestations

- Learning deficits (attention deficit disorder, hyperactivity), followed by regression of academic performance
- Leg weakness, loss of sphincter control, and sexual dysfunction
- Progressive spastic paresis
- Loss of hearing and vision
- Dementia
- Demyelination of cerebral hemispheres

Molecular Basis of Disease

- Mutations in the *ABCD1* gene result in defective peroxisomal beta oxidation of very long-chain fatty acids (VLCFAs); the protein is an ATP-binding cassette (ABC) protein transporter
- Deficiency results in the accumulation of VLCFAs in the adrenal cortex and brain gangliosides, plasma, blood cells, and cultured fibroblasts
- Numerous mutations have been identified in the *ABCD1* gene

Laboratory

- Accumulation of unbranched saturated fatty acids with a chain length of 24–30 carbons in plasma, cultured skin fibroblasts, and prenatal diagnosis available
- Molecular mutation analysis is available

Treatment

- VLCFA-restricted diet
- Hematopoietic stem cell transplantation for affected males
- Corticosteroid replacement therapy for adrenal insufficiency

LYSOSOMAL STORAGE DISORDERS

Mucopolysaccharidoses

Chromosome and Gene Location

- See Table 13.9

Inheritance

- See Table 13.9

Incidence

- See Table 13.9

Clinical Manifestations

- Onset typically by 2 years
- Coarse facial features
- Corneal clouding
- Organomegaly
- Skeletal dysplasia (dysostosis multiplex)
- Intellectual disability (not observed in MPS IV or MPS VI)
- Loss of developmental milestones
- Behavioral problems (MPS III)
- Hearing loss
- Decreased range of motion in joints
- Heart valve abnormalities

Table 13.9. **Mucopolysaccharidoses**

Name	*Inheritance*	*Gene location*	*Enzyme deficiency*	*Excess excretion*	*Clinical features*	*Incidence*
Hurler syndrome (MPS IH)	Autosomal recessive	4pl6.3	Alpha-L-iduronidase	Dermatan sulfate, heparan sulfate	Corneal clouding, dysostosis multiplex, organomegaly, heart disease, intellectual disability, death in childhood	1/100,000
Scheie syndrome (MPS IS)	Autosomal recessive	4pl6.3	Alpha-L-iduronidase	Dermatan sulfate, heparan sulfate	Corneal clouding, stiff joints, normal intelligence, normal life span	1/500,000
Hunter syndrome (MPS II)	X-linked	Xq28	Iduronate sulfatase	Dermatan sulfate, heparan sulfate	Dysostosis multiplex, organomegaly, intellectual disability, death typically before 15 years	1/100,000–1/170,000 male births
Sanfilippo syndrome (MPS III)	Autosomal recessive	17q25.3	Sanfilippo A – heparan *N*-sulfatase Sanfilippo B – alpha-*N*-acetylglucosaminidase Sanfilippo C – acetyl-CoA: alpha glucosaminide *N*-acetyltransferase Sanfilippo D – *N*-acetylglucosamine-6-sulfatase	Heparan sulfate	Profound mental deterioration, hyperactivity	1/75,000–1/300,000
Morquio syndrome (MPS IVA and	Autosomal recessive	MPS IVA: 16q24.3	Galactose-6-sulfatase	Keratan sulfate, chondroitin 6-sulfate	Skeletal abnormalities, corneal clouding, odontoid hypoplasia	1/75,000–1/300,000
MPS IVB)		MPS IVB: 3p21.33	Beta galactosidase	Keratan sulfate		Unknown
Maroteaux–Lamy syndrome (MPS VI)	Autosomal recessive	5qll–ql3	*N*-acetylgalactosamine-4-sulfatase (arylsulfatase B)	Dermatan sulfate	Dysostosis multiplex, corneal clouding, normal intelligence	1/800,000–1/1,300,000
Sly syndrome (MPS VII)	Autosomal recessive	7q21.11	Beta glucuronidase	Dermatan sulfate, heparan sulfate, chondroitin 4-,6-sulfates	Dysostosis multiplex, hepatosplenomegaly	1/800,000–1/1,300,000
Hyaluronidase deficiency (MPS IX)	Autosomal recessive	3p21.3–p21.2	Hyaluronidase	Hyaluronan	Short stature, periarticular soft tissue masses	Unknown

- Inguinal or umbilical hernias

Molecular Basis of Disease

- The mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans)
- Accumulation of glycosaminoglycans (previously called mucopolysaccharides) in the lysosomes interferes with the normal functioning of cells, tissues, and organs

Laboratory

- Increased urinary excretion of glycosaminoglycans
- Decreased enzyme activity in cultured fibroblasts, leukocytes, serum, or plasma
- Radiographs show skeletal abnormalities
- Molecular sequencing is available for most types
- Prenatal diagnosis available for known familial mutations

Treatment

- Hematopoietic stem cell transplantation (bone marrow or cord blood) can improve somatic features for some patients with severe forms of MPS I and MPS VI; neurological outcomes are still being investigated
- Enzyme replacement therapy is available for patients with MPS I, MPS II, and MPS VI and in clinical trials for other MPS disorders
- Treatment remains primarily supportive/symptomatic
- Bacterial endocarditis prophylaxis for patients with cardiac abnormalities
- Orthopedic surgery for skeletal complications

Mucolipidosis

- Mucolipidosis consists of a group of disorders, which result from abnormal lysosomal enzyme transport

I-Cell Disease (Mucolipidosis II Alpha/Beta)

Chromosome and Gene Location

- 12q23.3

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical Manifestations

- Mucolipidosis II is a severe type of mucolipidosis. Presentation is similar to the mucopolysaccharidoses

Molecular Basis of Disease

- *GNPTAB* (*N*-acetylglucosamine-1-phosphotransferase, alpha/beta subunits gene) is the only gene known to be associated with ML II alpha/beta
- Mutations in the *GNPTAB* gene disrupt interactions and recognition of the phosphotransferase, resulting in secretion of lysosomal enzymes into the extracellular medium instead of being correctly targeted to the lysosomes

Laboratory

- Increased activity of lysosomal hydrolases in plasma and other body fluids (in particular: beta-D-hexosaminidase, beta-D-glucuronidase, beta-D-galactosidase, alpha-L-fucosidase, and arylsulfatase A); diagnosis cannot be made in leukocytes
- Increased urinary excretion of oligosaccharides
- Cytoplasmic granular *inclusions* in skin fibroblasts (swollen lysosomes called I-cells)
- Molecular sequencing of the *GNPTAB* gene is available
- Prenatal diagnosis available for known familial mutations

Treatment

- Not curable, supportive/symptomatic

Pseudo-Hurler Polydystrophy (Mucolipidosis III Alpha/Beta)

Chromosome and Gene Location

- 12q23.3

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical Manifestations

- Onset is typically between 2 and 4 years. Clinical presentation resembles the mucopolysaccharidoses

Molecular Basis of Disease

- *GNPTAB* (*N*-acetylglucosamine-1-phosphotransferase, alpha/beta subunits gene) is the only gene known to be associated with ML III alpha/beta
- Mutations within the gene disrupt interactions and recognition of the phosphotransferase, resulting in secretion of lysosomal enzymes into the extracellular medium instead of being targeted correctly to the lysosomes
- A milder variant of I-cell disease (ML II alpha/beta) is caused by the same enzyme deficiency

Laboratory

- Increased activity of lysosomal hydrolases in plasma and other body fluids (in particular: beta-D-hexosaminidase, beta-D-glucuronidase, beta-D-galactosidase, and beta-D-mannosidase); the diagnosis cannot be made in leukocytes
- Increased urinary excretion of oligosaccharides
- Cytoplasmic granular inclusions in skin fibroblasts (swollen lysosomes)
- Molecular sequencing of the *GNPTAB* gene is available
- Prenatal diagnosis available for known familial mutations

Treatment

- Not curable, supportive/symptomatic

Sphingolipidoses

GM1 Gangliosidosis

Chromosome and Gene Location

- 3p21.33

Inheritance

- Autosomal recessive

Incidence

- 1 in 100,000–200,000

Clinical Manifestations

- Onset
  - Type 1 (infantile) – between birth and 6 months
  - Type 2 (late infantile or juvenile) – between 7 months and 3 years
  - Type 3 (adult or late-onset) – between 3 and 30 years
- Psychomotor deterioration
- Hepatosplenomegaly
- Skeletal abnormalities (widening of the long bones and ribs, broad short stubby fingers, contractures)
- Coarse facial features
- Failure to thrive
- Gum hypertrophy
- Macroglossia
- Macrocephaly
- Protuberant abdomen
- Frontal bossing
- Depressed nasal bridge
- Hypertelorism
- Cherry red spot on macula
- Cardiomyopathy
- Exaggerated startle response

Molecular Basis of Disease

- *GLBI* is the only gene known to be associated with GM1 gangliosidosis
- Mutations in the *GLBI* gene lead to a deficiency of beta galactosidase enzyme activity and subsequently results in an accumulation of GM1gangliosides, oligosaccharides, and keratan sulfate derivatives

Laboratory

- Deficient beta galactosidase in leukocytes or cultured fibroblasts
- Empty-appearing vacuoles on electron microscopy
- Large foam cells in bone marrow
- Radiographs show skeletal abnormalities
- Molecular sequencing of the *GLBI* gene is available
- Prenatal diagnosis available for known familial mutations

Treatment

- Not curable, supportive/symptomatic

GM2 Gangliosidoses (Tay–Sachs Disease and Sandhoff Disease)

- The GM2 gangliosidoses are a group of disorders caused by excessive accumulation of GM2 ganglioside and other glycolipids in the lysosomes, particularly in neuronal cells

Tay–Sachs Disease

Chromosome and Gene Location

- 15q23–q24

Inheritance

- Autosomal recessive

Incidence

- The incidence of Tay–Sachs has been substantially reduced in the Ashkenazi Jewish population in North America as a result of population-based carrier screening programs, education, counseling, and subsequent monitoring and testing of at-risk pregnancies
- Carrier frequency in Ashkenazi Jewish population: 1 in 30
- Carrier frequency in non-Ashkenazi Jewish population: ~1 in 300

Clinical Manifestations

- Onset typically between 3 and 6 months
- Other forms may present with later onset (through adulthood) and have a more mild and varied clinical presentation
- Progressive mental and motor deterioration
- Exaggerated startle response
- Cherry red spot on macula
- Macrocephaly
- Decreased attentiveness
- Convulsions
- Blindness
- Usually fatal by 4 years of age

Molecular Basis of Disease

- *HEXA*, the gene encoding the alpha subunit of the HEX A enzyme, is the only gene associated with hexosaminidase A deficiency
- Hexosaminidase A is made up of one alpha subunit (encoded by *HEXA*) and one beta subunit (encoded by *HEXB*)
- Mutations in the alpha chain lead to a deficiency of hexosaminidase A, and mutations in the beta chain lead to Sandhoff disease (see below). Six common mutations include four deleterious mutations (three null alleles (+TATC1278, +1IVS12, and +1IVS9), one adult-onset allele (G269S)), and two pseudodeficiency alleles: R247W and R249W. Pseudodeficiency alleles result in low enzyme level on biochemical testing, but are not true deficiency alleles

- Hexosaminidase A deficiency results in the accumulation of GM2 gangliosides in the brain, nervous system, liver, spleen, and heart, leading to the disruption of cell function and cell death

Laboratory

- Decreased hexosaminidase A in serum, leukocytes, or cultured fibroblasts
- Pseudodeficiency alleles account for approximately 35% of non-Ashkenazi Jewish individuals and 2% of Ashkenazi Jewish individuals identified as carriers through enzyme-based testing and may falsely indicate carrier status
- Carrier screening can be performed by molecular analysis, biochemical analysis, or both
- Targeted mutation analysis for common mutations and sequence analysis are available
- Prenatal diagnosis available for known familial mutations

Treatment

- Not curable, supportive/symptomatic
- Hematopoietic stem cell transplantation (bone marrow or cord blood) is investigational

Sandhoff Disease

Chromosome and Gene Location

- 5q13

Inheritance

- Autosomal recessive

Incidence

- ~1/300,000 (non-Ashkenazi Jewish)
- ~1/1,000,000 (Ashkenazi Jewish)

Clinical Manifestations

- Neurological presentation and clinical course similar to Tay–Sachs (note: Sandhoff does not demonstrate increased incidence in the Ashkenazi Jewish population)
- Hepatosplenomegaly
- Skeletal abnormalities
- Macrocephaly

Molecular Basis of Disease

- Mutations in *HEXB*, the gene encoding the beta subunit of the HEX B enzyme, result in deficiencies of both hexosaminidase A and B enzymes
- Deficiency results in the accumulation of GM2 gangliosides in the brain, nervous system, liver, spleen, and heart, leading to the disruption of cell function and cell death

Laboratory

- Deficient hexosaminidase A and hexosaminidase B in serum, leukocytes, or cultured fibroblasts
- Molecular sequence analysis is available
- Prenatal diagnosis available for known familial mutations

Treatment

- Not curable, supportive/symptomatic

Niemann–Pick Disease, Types A and B

Chromosome and Gene Location

- 11p15.4–p15.1

Inheritance

- Autosomal recessive

Incidence

- 1/250,000
- Carrier frequency for type A is increased in the Ashkenazi Jewish population (1/80–1/100), although carrier screening and subsequent prenatal diagnosis have resulted in a decreased incidence in this population

Clinical Manifestations

- Type A
  - Onset typically by 3 months
  - Hepatosplenomegaly
  - Progressive neurodegeneration
  - Interstitial lung disease
  - Cherry red spot on macula
  - Usually fatal by 3 years of age
- Type B
  - Typically later onset with milder presentation
  - Hepatosplenomegaly
  - Respiratory insufficiency
  - A minority have neurologic involvement
  - Life expectancy may extend into adolescence or adulthood

Molecular Basis of Disease

- Mutations in the *SMPD1* gene coding for acid sphingomyelinase result in an accumulation of sphingomyelin in cells and tissues
- Three common mutations causing type A have been described in the Ashkenazi Jewish population (L302P, R496L, and fsP330) and account for >90% of the mutations in this population
- Only one common mutation for type B has been described (R608del) and is more common in individuals of North African background

Laboratory

- Deficiency of acid sphingomyelinase in leukocytes (or lymphocytes) or cultured fibroblasts
- Targeted mutation analysis for common mutations and sequence analysis are available
- Prenatal diagnosis available for known familial mutations

Treatment

- Bone marrow transplantation may be able to improve blood counts and reduce liver and spleen volumes. Improvement in neurologic features has not been reported

Niemann–Pick Disease Type C

Chromosome and Gene Location

- 18q11–q12 (Niemann–Pick disease type C [*NPC1*]), 14q24.3 (*NPC2*)

Inheritance

- Autosomal recessive

Incidence

- 1/150,000

Clinical Manifestations

- Typically late infantile or juvenile onset (ranges from infantile to adult)
- Neonatal jaundice
- Sea-blue histiocytes in marrow
- Hepatosplenomegaly
- Progressive neurological deterioration: ataxia, dysarthria, dystonia, dementia, and seizures
- Vertical supranuclear gaze palsy

Molecular Basis of Disease

- Mutations in two genes (*NPC1* and *NPC2*) result in a complex defect involving cellular lipid trafficking and subsequent cholesterol and glycosphingolipid accumulation in the lysosomes
- Most patients (~90%) have mutations in the *NPC1* gene

Laboratory

- Delayed induction of cholesterol esterification following LDL uptake
- Increased filipin staining of accumulated cholesterol in fibroblasts
- Molecular sequencing of the *NPC1* and *NPC2* genes is available
- Prenatal diagnosis available for known familial mutations

Treatment

- Not curable, supportive/symptomatic

Gaucher Disease

Chromosome and Gene Location

- 1q21

Inheritance

- Autosomal recessive

Incidence

- Type 1: 1/855 (Ashkenazi Jewish)
- The prevalence is difficult to ascertain in non-Ashkenazi Jewish populations and for types 2 and 3

Clinical Manifestations

- Type 1
  - Adult onset is most common, though can present at any age
  - Disease severity is variable
  - Bone disease (osteopenia, bone pain, pathologic fractures)
  - Hepatosplenomegaly
  - Anemia
  - Thrombocytopenia
  - Acquired coagulation deficiencies of factor IX and XI and von Willebrand
- Type 2
  - Onset is typically within first few months of life
  - Strabismus
  - Hypertonia of neck muscles results in extreme arching of the neck
  - Loss of head control
  - Hepatosplenomegaly
  - Poor sucking and swallowing
  - Failure to thrive
  - Spasticity
  - Seizures
  - Usually fatal by 2 years of age
- Type 3
  - Clinically heterogeneous
  - Onset typically in adolescence or early adulthood
  - Strabismus
  - Myoclonus
  - Ataxia
  - Seizures
  - Hepatosplenomegaly
  - Life expectancy is extremely variable (5–50 years) and dependent on severity of clinical manifestations

Molecular Basis of Disease

- Mutations in the *GBA* gene result in the deficiency of glucocerebrosidase (glucosylceramidase or acid β-glucosidase) and subsequent accumulation of glucocerebroside (glucosylceramide) in the lysosomes
- There are four common mutations: N370S, L444P, 84GG, and IVS2(+1G>A), which account for >90% of the mutations in the Ashkenazi Jewish population
- Individuals with at least one N370S allele are not predicted to have central nervous system involvement (it is not found in types 2 or 3) and are thought to confer a less severe phenotype when compounded with other mutations

Laboratory

- Deficiency of glucocerebrosidase activity in leukocytes or cultured fibroblasts (not accurate for carrier determination)

- Elevated glucopsychosine (glucosylsphingosine) level in blood
- Presence of Gaucher storage cells in bone marrow
- Targeted mutation analysis for common mutations and sequence analysis are available
- Prenatal diagnosis available for known familial mutations

Treatment

- Enzyme replacement therapy available since l994 (effective for somatic symptoms but not CNS)
- Skeletal problems may be treated with limitation of physical activity, prostheses, analgesics, and surgical intervention

Krabbe Disease

Chromosome and Gene Location

- 14q31

Inheritance

- Autosomal recessive

Incidence

- 1/100,000

Clinical Manifestations

- Onset typically within first 6 months
- Extreme irritability and hypersensitivity to external stimuli
- Feeding difficulties
- Spasticity
- Progressive neurologic deterioration
- Cortical blindness with optic atrophy
- Deafness
- Usually fatal by 2 years of age
- Also late-onset variants

Molecular Basis of Disease

- The *GALC* gene codes for galactosylceramidase (galactocerebrosidase), a lysosomal enzyme, which degrades galactocerebroside to ceramide and galactose
- Mutations in the gene cause deficient enzyme activity resulting in an accumulation of enzyme substrates and early destruction of oligodendroglia (type of glial cell that forms the myelin sheath of nerve fibers in the central nervous system)

Laboratory

- Deficient galactosylceramide beta galactosidase activity in leukocytes or cultured fibroblasts
- Elevated protein in cerebral spinal fluid
- Elevated psychosine level in blood
- Neuroimaging demonstrates progressive, diffuse, and symmetrical, cerebral atrophy
- Targeted mutation analysis for common mutations and sequence analysis are available
- Prenatal diagnosis available for known familial mutations
- Newborn screening has been instituted in some states despite lack of effective treatment

Treatment

- Hematopoietic stem cell transplantation may slow the course of disease progression in asymptomatic patients and individuals with only minimal neurologic involvement
- Treatment remains primarily supportive/symptomatic

Metachromatic Leukodystrophy

Chromosome and Gene Location

- 22q13.31–qter

Inheritance

- Autosomal recessive

Incidence

- 1/40,000–1/160,000

Clinical Manifestations

- Late infantile (50–60% of cases)
  - Onset typically between 1 and 2 years
  - Hypotonia, weakness, clumsiness, frequent falls, toe walking, and inability to stand
  - Progressive neurologic deterioration
  - Increased muscle tone
  - Slurred speech
  - Blindness
  - Unaware of surroundings
  - Death typically occurs approximately 5 years after the onset of symptoms
- Juvenile (20–30% of cases)
  - Onset typically between 4 and 14 years
  - Decline in school performance and behavioral problems
  - Clumsiness and gait problems
  - Slurred speech
  - Seizures
  - Death typically by 20 years of age
- Adult (15–20% of cases)
  - Onset typically after puberty and into the sixth decade of life
  - Problems in school or job performance and personality changes
  - Weakness, loss of coordination, and peripheral neuropathy
  - Seizures
  - Duration of disease may range from a few years to several decades before the patient reaches a vegetative state and, ultimately, death

Molecular Basis of Disease

- The *ARSA* (arylsulfatase A) gene is the only known gene associated with MLD

- Mutations in this gene lead to a deficiency in the enzymatic hydrolysis of sulfatide and subsequent accumulation of sulfatides, mainly within the lysosomes

Laboratory

- Deficient arylsulfatase A enzyme activity in leukocytes or cultured fibroblasts
- The presence of individuals with pseudodeficiency (unaffected individuals whose ARSA activity in leukocytes is 5–20% of controls) makes establishing a diagnosis of true ARSA deficiency difficult by biochemical analysis alone
- Increased protein in the cerebrospinal fluid
- Metachromatic lipid deposits in a nerve or brain biopsy
- Increased urinary sulfatide excretion
- Targeted mutation analysis for common mutations and sequence analysis are available
- Prenatal diagnosis available for known familial mutations

Treatment

- Not curable, supportive/symptomatic
- Bone marrow transplantation may be able to slow disease progression when performed prior to symptoms occurring in juvenile and adult-onset forms. BMT does not appear to alleviate peripheral nervous system manifestations and has not been shown to be effective in symptomatic patients with the late infantile form. BMT remains controversial due to risks and uncertain long-term effects

Fabry Disease

Chromosome and Gene Location

- Xq22.1

Inheritance

- X linked

Incidence

- 1/40,000 males; newborn screening studies including late-onset variants are finding a prevalence closer to 1/5,000 males

Clinical Manifestations

- Onset typically in childhood or adolescence
- Also cardiac and renal variants with variable presentation; late-onset variants are likely underdiagnosed
- Pain in distal extremities (acroparesthesias)
- Fever due to hypohidrosis (reduced sweating)
- Corneal opacities
- Angiokeratomas (Fig. 13.9)

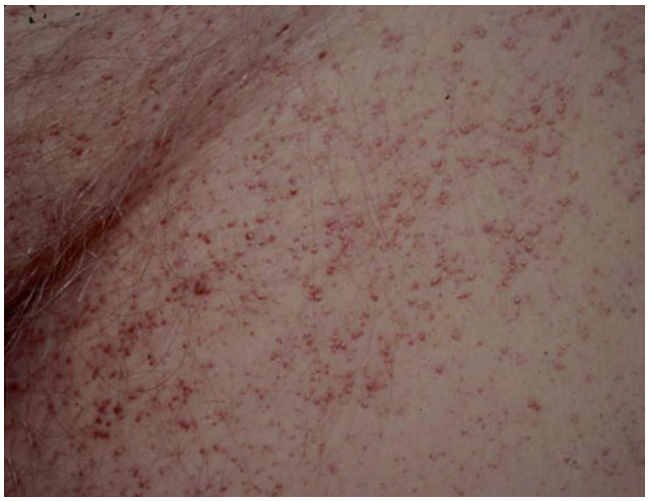

Fig. 13.9. Fabry disease – angiokeratomas.

- Proteinuria; this can lead to end-stage renal disease typically occurs in the third to fifth decades
- Cardiovascular disease
- Carrier females are usually asymptomatic but may be as severely affected as males or have an attenuated form of the disease due to random X-inactivation

Molecular Basis of Disease

- The *GLA* gene codes for alpha galactosidase A, an enzyme involved in the degradation of glycosphingolipids
- Mutations in the *GLA* gene result in the accumulation of globotriaosylceramide (Gb3) and other glycosphingolipids in bodily fluids, lysosomes, and cell types of various other tissues in organs

Laboratory

- Deficient alpha galactosidase A activity in leukocytes, tears, cultured fibroblasts, plasma, or serum (unreliable for carrier determination)
- Molecular sequence analysis is available
- Prenatal diagnosis available for known familial mutations
- Newborn screening has been instituted in some states

Treatment

- Enzyme replacement therapy
- Symptoms of peripheral neuropathy may respond to carbamazepine or diphenylhydantoin; however, the neuropathy does not diminish
- Renal dialysis and transplantation

FAMILIAL CANCER SYNDROMES

Familial Adenomatous Polyposis

Chromosome and Gene Location

- 5q22.2 (*APC*)

Inheritance

- Autosomal dominant
- 75–80% have an affected parent
- 20–25% are the result of new (de novo) mutations

Incidence

- 3 in 100,000

Clinical Manifestations

- Multiple (>100) polyps early in life, on average at 16 years of age with a range of 7–36 (by age 35 over 95% of gene carriers will develop polyps)
- Polyps progress to colonic carcinoma on average by age 39 (range 34–43)
- Other tumors and/or carcinomas may occur including duodenal, thyroid, brain, liver, and pancreatic desmoid tumors (Fig. 13.10), and childhood hepatoblastomas
- Additional features include congenital hypertrophy of the retinal pigment epithelium (CHRPE) and dental anomalies, such as supernumerary teeth
- "Gardner syndrome" refers to individuals with familial adenomatous polyposis (FAP) who have extracolonic manifestations such as tumors of the jaw (osteomas), lipomas, and fibromas
- "Turcot syndrome" refers to individuals with FAP and central nervous tumors (CNS), specifically medulloblastoma

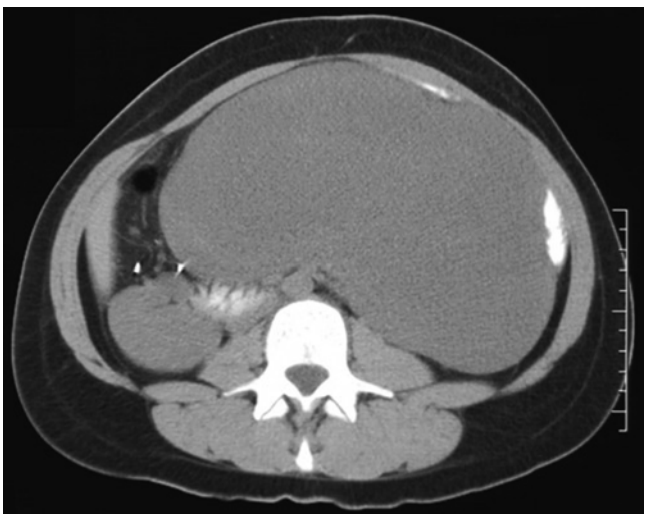

Fig. 13.10. Familial adenomatous polyposis – desmoid tumor.

- Attenuated FAP refers to individuals who still have a significant increased risk for colonic carcinoma, with fewer than 100 polyps (on average 30)

Molecular Basis of Disease

- Numerous mutations have been identified in the adenomatous polyposis coli (*APC*) gene; most mutations lead to truncated protein product
- The protein is thought to be involved in maintaining normal apoptosis and decreasing cell proliferation and may also be involved in maintaining chromosomal stability

Laboratory

- Direct mutation analysis is available. Linkage testing is also available for families without an identifiable mutation
- Less than 30% of individuals clinically diagnosed with attenuated FAP will have an identifiable *APC* mutation

Treatment/Surveillance

- Genetic consultation is necessary to determine the utility of genetic testing in these families
- For individuals with a diagnosis of FAP, colectomy is advised when polyps become too numerous to remove or watch, to prevent colorectal carcinoma
- For individuals who have a positive gene test, flexible sigmoidoscopy or colonoscopy every year beginning at age 10–15 years, colonoscopy when polyps are detected
- For individuals who have not had genetic testing and are at risk, flexible sigmoidoscopy or colonoscopy every year beginning at 10–15 years to 24 years, every 2 years until age 34 if polyps are not detected, every 3 years to age 44 if polyps are not detected, and every 3–5 years thereafter
- Esophagogastroduodenoscopy should be initiated when colonoscopies are started or by age 25
- Annual thyroid palpation beginning in late teens
- Ophthalmologic examination for CHRPE is done if confirmation of diagnosis is sought; however, note these lesions are harmless
- For children at risk, liver palpitation, abdominal ultrasound, and alpha-fetoprotein testing are recommended for hepatoblastoma every 3–6 months until age 5

MYH-Associated Polyposis

Chromosome and Gene Location

- 1p34.1 (*MUTYH*)

Inheritance

- Autosomal recessive

Incidence

- 1 in 20,000 to 1 in 40,000

- Approximately 1–2% of the general population are carriers of one *MUTYH* mutation

Clinical Manifestations

- Multiple (>10–100) adenomatous polyps early in life, similar to the presentation of attenuated FAP, evident by the mean age of 50
- Polyps are likely to progress to carcinoma if left untreated (80% cumulative risk to age 80 years)
- Additional features include similar extracolonic manifestations exhibited with FAP; approximately 65% of individuals will have at least one
- Duodenal adenomas occur in 17–25% of individuals with a lifetime duodenal cancer risk of approximately 4%
- Additional risk for colon cancer remains unclear related to carriers of one *MUTYH* mutation; some suggest a 2–3 time increased risk over the general population; however, the evidence has not been enough to warrant additional screening

Molecular Basis of Disease

- Two mutations account for ~90% of mutations within the Northern European population (Y179C, G396D). Therefore, only ~2% of people with biallelic mutations will have a negative DNA test, when only these two mutations are studied
- Other founder mutations exist in certain ethnic groups (i.e., Indian, Dutch, Pakistani)
- The *MUTYH* protein repairs DNA by removing adenine residues that are mispaired with 8-oxoguanine during replication of oxidized DNA. Deficiency in this base excision repair leads to somatic mutations in *APC*, hence the clinical similarity to FAP
- Biallelic *MUTYH* mutations are identified in up to 30% of individuals with 10–100 polyps and 7–14% with greater than 100 polyps

Laboratory

- Direct mutation analysis for the two common mutations is clinical available; full gene sequencing can also be performed
- Predictive genetic testing can be offered once mutations have been identified within a family

Treatment/Surveillance

- Genetic consultation is necessary to determine the utility of genetic testing in these families
- For individuals with a diagnosis of attenuated FAP without clear evidence of dominant inheritance, testing for *MUTYH* should be offered
- *MUTYH* testing should be offered for those suspected to have FAP or attenuated FAP with negative *APC* testing
- Treatment/surveillance of families with biallelic *MUTYH* mutations should include colonoscopy every 2–3 years beginning at 25–30 years and every 1–2 years if polyps are noted
- Esophagogastroduodenoscopy is advised at 30–35 years and repeated based on findings, at minimum every 4 years. If adenomas are found, management proceeds akin to that of classical FAP

Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome, Basal Cell Nevus Syndrome)

Chromosome and Gene Location

- 9q22.32 (*PTCH1*)

Inheritance

- Autosomal dominant

Incidence

- 1 in 30–50,000 (in United Kingdom)

Clinical Manifestations

- The following criteria have been proposed for making a diagnosis. (The sensitivity and specificity are not known) A diagnosis is made when two major or two minor and one major criteria are fulfilled:
  - Major criteria
    - More than 2 basal cell carcinomas (BCC) or 1 in an individual before 20
    - Odontogenic keratocyst of the jaw
    - Three or more palmar or plantar pits
    - Bilamellar calcification of falx cerebri (90% of individuals have by age 20)
    - Bifid, fused, or markedly splayed ribs
    - Family history of NBCC syndrome
  - Minor criteria
    - Macrocephaly (head circumference >97th percentile)
    - Congenital skeletal malformations (cleft lip/palate, frontal bossing, "coarse facies," ocular hypertelorism, pectus, polydactyly, syndactyly)
    - Radiologic abnormalities (hemivertebrae, fusion or elongation of the vertebral bodies, bridging of the sella turcica)
    - Cardiac or ovarian fibroma
    - Medulloblastoma
- Rate of BCC risk increases with age; 51% risk for age >20 and 71% risk for age >40
- Variable expressivity is noted

Molecular Basis of Disease

- Majority of mutations are nonsense mutations leading to a premature stop codon resulting in a truncated protein
- 20–30% are the result of de novo mutations
- The protein is thought to be involved in controlling cell fates, patterning, and growth in numerous tissues

Laboratory

- Molecular genetic testing is available

- Failure to detect a *PTCH1* mutation does not exclude a clinical diagnosis of NBCCS
- 9q22.3 microdeletion syndrome involves *PTCH1*; however, beyond NBCCS causes developmental and intellectual delays, metopic craniosynostosis, obstructive hydrocephalus, pre- and postnatal macrosomia and seizures

Treatment/Surveillance

- Advice regarding avoidance of sun exposure and radiation
- Developmental and physical assessment every 6 months in the first few years of life due to increased medulloblastoma risk
- Screening by dermatologist in puberty and every 4–12 months thereafter with early excision of basal cell cancers
- Jaw radiograph every 12–18 months after the age of 8 for keratocysts
- Gynecologic exam done annually in adulthood

Birt–Hogg–Dube Syndrome

Chromosome and Gene Location

- 17p11.2 (*FLCN*)

Inheritance

- Autosomal dominant

Incidence

- Unknown; under recognized, current estimate is 1 in 200,000

Clinical Manifestations

- The clinical triad of BHDS is comprised of:
  - Cutaneous lesions including multiple fibrofolliculomas (specific for BHDS) as well as trichodiscomas and acrochordons (associated with BHDS). These skin lesions are easily overlooked and usually initially develop in the third to fourth decades of life
  - Pulmonary cysts (present in 90%) with spontaneous pneumothorax (~25%) may be the presenting feature
  - Bilateral and multiple renal tumors, developing at a median age of 48 years (25–35% with BDHS have lesions before 50). The histology is variable including oncocytomas, chromophobe, clear cell, or papillary renal cell carcinomas and hybrid oncocytic neoplasms
- A range of 1–28 renal tumors have been reported with an average number of 5.3
- Nonrenal carcinomas have been described but are rare

Molecular Basis of Disease

- *FLCN* encodes a protein called folliculin, which appears to be involved in AMPK and mTOR signaling
- Approximately 90% fulfilling diagnostic criteria will have an identifiable *FLCN* mutation
- Approximately 50% will have a mutation identified in the gene's hotspot, exon 11

Laboratory

- Skin biopsy is required to confirm a diagnosis of fibrofolliculomas and trichodiscomas, both of which are fibroepithelial hamartomas of the hair follicles

Treatment/Surveillance

- Genetic consultation is necessary to determine if clinical genetic testing will be of utility in a given family
- Due to concern for an increased risk for melanoma, dermatology visits may be considered and an avoidance of radiation exposure advised
- Surveillance is not indicated for the cutaneous lesions as they are not premalignant
- Annual renal imaging by MRI (optimal) or abdominal/pelvic CT scan with contrast is appropriate beginning at age 18, when the diagnosis is made or if a *FLCN* mutation is confirmed
- Renal sparing surgery should be offered due to the propensity for multifocal tumor development
- Affected individuals should be counseled on the signs, symptoms, and management of spontaneous pneumothorax and to avoid smoking and high ambient pressures

Hereditary Breast and Ovarian Cancer (HBOC) Syndrome

Chromosome and Gene Location

- 17q21.31 (*BRCA1*)
- 13q13.1 (*BRCA2*)

Inheritance

- Autosomal dominant

Incidence

- Varies by population
  - Approximately 1/400 non-Ashkenazi Caucasian individuals carry a *BRCA1* or *BRCA2* mutation
  - Approximately 1/40 Ashkenazi Jewish individuals carry one of three founder mutations in *BRCA1* or *BRCA2*
  - Less is known about mutation frequency in other populations

Clinical Manifestations

- Early onset (premenopausal) adenocarcinoma of the breast, often bilateral disease
- Additionally, ovarian, fallopian, and primary peritoneal cancer occurs less frequently for *BRCA2* families (11–18%) than *BRCA1* families (24–40%)
- *BRCA2* is known to have an ovarian cancer cluster region (OCCR) in exon 11 in which the risk for ovarian cancer is higher than that for any other region in which a *BRCA2* mutation is found
- Breast cancer in males is more common in *BRCA2* families (5–10%) but also present in *BRCA1* families (1–2%)

- Males carrying a *BRCA1* or *BRCA2* mutation are at an increased risk of developing prostate cancer (up to 39%)
- Males and females carrying a *BRCA1 or BRCA2* mutation are at an increased risk for pancreatic cancer (1–3% and 2–7%, respectively)
- *BRCA1* mutations are estimated to account for 50% of all familial early-onset cases (2.5–5% of all breast cancer) and about 80% of inherited breast and ovarian cancer
- *BRCA2* mutations are estimated to account for 17–35% of hereditary breast cancer
- It is estimated that individuals who carry a *BRCA1* or *BRCA2* gene mutation may have as high as 40–80% risk of developing breast cancer and 11–40% risk of developing ovarian cancer by age 70, compared with the lifetime general population risk of 12.5% for breast cancer and 1.4% for ovarian cancer
- The following criteria have been established to determine when further evaluation for a mutation is warranted
  - Breast cancer at or below the age of 45
  - Breast cancer at or below the age of 50 with:
    - An additional primary
    - One or more close blood relatives with breast cancer at any age
    - Unknown or limited family history
  - Ovarian, fallopian, or primary peritoneal cancer at any age
  - Diagnosed at or under 60 with a triple negative (ER-, PR-, Her2-) breast cancer
  - Breast cancer at any age and:
    - One or more close blood relatives with breast cancer at or under 50
    - One or more close blood relative with ovarian cancer at any age
    - Two or more close blood relatives with breast, pancreatic, and/or prostate cancer at any age
    - Close male blood relative with breast cancer
  - Male breast cancer
  - Pancreatic or prostate cancer at any age with two or more close blood relatives with breast and/or ovarian cancer and or pancreatic or prostate cancer on the same side of the family
  - Previous BRCA mutation identified in the family

Molecular Basis of Disease

- Various mutations (deletions, insertion, point mutations) have been identified; most result in truncation or absence of *BRCA1* and *BRCA2* proteins
- Both are thought to be tumor suppressor genes

Laboratory

- Molecular testing available for *BRCA1* and *BRCA2*

Treatment/Surveillance

- Breast awareness starting at age 18 and clinical breast exams every 6–12 months starting at age 25
- Breast screening recommendations include:
  - Annual breast MRI (mammogram if MRI is unavailable) beginning at age 25–29 or individualized based on earliest age of onset in family
  - Annual breast MRI and mammogram age 30–75
- Additional screening beyond age 75 should be considered on an individual basis
- Discuss risk-reducing mastectomy including degree of protection, reconstruction options, and risks
- Recommend risk-reducing salpingo-oophorectomy between 35 and 40 or upon completion of childbearing or individualized based on earliest age of onset in family; counseling includes discussion of reproductive desires, extent of risk, degree of protection, and management of related medical issues
- For those electing not to undergo risk-reducing BSO, consideration of semiannual screening using transvaginal ultrasound and serum CA-125 starting at age 30 or 5–10 years before earliest ovarian cancer diagnosis in the family
- Caution: less than half of early stage ovarian tumors produce elevated levels of CA-125; there is no evidence of efficacy of screening for ovarian cancer
- Consider chemoprevention options for breast and ovarian cancer; tamoxifen or related compounds confer up to a 50% reduction in risk contralaterally
- For males, self-breast exam training and education, as well clinical breast exams every 6–12 months should begin at age 35 with consideration of baseline mammography at age 40
- Prostate cancer screening should begin at age 40 for *BRCA2* mutation carriers and can be considered for *BRCA1* mutation carriers
- Additional screening guidelines should be considered and individualized based on cancers observed in the family (i.e., pancreatic, melanoma, etc.)

Lynch Syndrome

- Previously referred to as hereditary nonpolyposis colon cancer syndrome (HNPCC)

Chromosome and Gene Location

- Caused by of mutations in one of four DNA mismatch repair genes
  - 3p22.1 (*MLH1*)
  - 2p21 (*MSH2*)
  - 2p16.3 (*MSH6*)
  - 7p22.1 (*PMS2*)
  - 2p21 (*EPCAM*, upstream of *MSH2*)

Inheritance

- Autosomal dominant

Incidence

- Estimated at 1 in 440
- Accounts for 2–3% of all colon cancer

Clinical Manifestations

- Risks vary dependent upon the underlying genetic cause
- Colorectal cancer
  - 70–85% noted to occur in the proximal region (right sided)
  - Average age at diagnosis is 44 (range 44–61)
  - 80% lifetime risk for colon cancer
- Endometrial adenocarcinoma lifetime risk may be up to 60%; average age of diagnosis is 62
- Increased risk for ovarian, transitional cell renal collecting system, ureter, stomach, small bowel, hepatobiliary tract, and pancreatic cancers. Cumulative lifetime risk for women is 47% and for men is 27%
- Increased risk for sebaceous carcinomas and basal and squamous cell carcinomas of the skin
- Muir–Torre syndrome is a variant form of Lynch syndrome characterized by a combination of benign or malignant sebaceous skin tumors and internal malignancy most commonly associated with a mutation in *MSH2*
- Turcot syndrome is characterized by brain tumor (glioblastoma multiforme) and colorectal tumors and is also associated with Lynch syndrome
- While reports have indicated a potential associated breast cancer risk, the relationship remains unclear
- Biallelic pathogenic mutations are possible and likely incur an increased risk
- The following Amsterdam II criteria were developed to define HNPCC. All four conditions need to be fulfilled to meet the Amsterdam criterion. However, the criteria have been found to be over-restrictive for clinical use:
  - Three or more family members with a HNPCC-related cancer, one of which is a first degree relative of the other two
  - Two successive generations affected
  - One or more HNPCC-related cancers diagnosed before age 50
  - The family does not have FAP
- Note that only about half of families that fulfill these strict criteria actually have defective DNA mismatch repair (i.e., have Lynch syndrome)
- 50% of families that meet criteria and do not have a detected Lynch syndrome mutation have a familial risk of uncertain etiology

Molecular Basis of Disease

- The products of the genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* participate in a DNA mismatch repair (MMR) complex
- *EPCAM* is not part of the MMR complex; however, it can disrupt it due to its inactivation of *MSH2*
- *MLH1* and *MSH2* account for 50% and 40%, respectively, of the mutations found in Lynch syndrome to date
- Colon cancer is a multistep process, meaning that a number of mutations in different genes need to occur before the onset of colon cancer
- When a mutation occurs in a mismatch repair complex, the ability to repair other random mutations is compromised, thus leading to an accumulation of mutations (microsatellite instability [MSI])
- The mutations may inactivate tumor suppresser genes and lead to the subsequent penetrance of colon cancer

Laboratory

- Nearly all colorectal tumors in Lynch syndrome show widespread MSI, and Bethesda guidelines have been developed to assist in what tumors should be tested
- MSI in combination with immunostaining is a useful tool to identify which gene may be involved
- Immunohistochemistry (IHC) can be utilized on the tumor tissue to identify the presence or absence of protein expression for *MLH1*, *MSH2*, *MSH6*, and *PMS2* proteins, helping to determine the gene of interest for a given individual
- BRAF and MLH1 hypermethylation are useful to distinguish sporadic cancers from those that may be due to a MMR gene; mutational analysis is available

Treatment/Surveillance

- Surveillance depends upon the gene involved and the family history
- For asymptomatic, suspected, or known gene carriers, a colonoscopy every beginning between ages 20–30 or 2–5 years prior to the earliest diagnosis, repeating every 1–2 years
- Prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy considered after childbearing complete
- Annual screening for endometrial and ovarian cancer may be considered; however, there is no clear evidence supporting its use
- Consider annual urinalysis and cytology beginning at age 25–30
- Consideration of upper gastrointestinal endoscopy every 3–5 years beginning at age 30–35 for families in which gastric cancer has occurred
- Annual physical/neurological exam beginning at age 25–30 for CNS tumors
- Breast cancer surveillance has been suggested; however, no guidelines exist at this time; suggest to base upon family history

Juvenile Polyposis Syndrome (JPS)

Chromosome and Gene Location

- 10q23.2 (*BMPR1A*)
- 18q21.2 (*SMAD4*)
- Each accounts for approximately 20–25% of mutations detected in families who meet criteria; 50–60% of families do not have a detected mutation in either

Inheritance

- Autosomal dominant
- Estimated 25% are due to de novo mutations

Incidence

- Estimated to range between 1 in 16,000 to 1 in 100,000

Clinical Manifestations

- Increased risk for gastrointestinal and pancreatic cancer
- Note: juvenile polyps are a type of polyp, not the age of onset of polyps. They are typically less than 3 cm in diameter and comprised of focal malformations of mucosa and lamina propria
- Individuals typically have between 50 and 200 polyps, but the number can be variable
- Solitary juvenile polyps occur in approximately 2% of adults and children
- JPS is clinically diagnosed if an individual has:
  - 5 or more juvenile polyps in the colon or rectum *or*
  - Multiple juvenile polyps throughout the gastrointestinal tract *or*
  - Any number of juvenile polyps and a family history of JPS
- Lifetime estimates of GI cancers range from 9 to 50%
- Incident of colon cancer is 17–22% by 35 years, approaching 68% by age 60 with a median age of diagnosis of 42
- 15–22% of individuals with *SMAD4* mutations are likely to have JPS and hereditary hemorrhagic telangiectasia (HHT); recent discussion includes the suggestion that those with a *SMAD4* mutation and JPS also have HHT
- HHT includes mucocutaneous telangiectases, pulmonary, hepatic, cerebral, and/or GI arteriovenous malformations, epistaxis, and intracranial bleeding
- Myhre syndrome and thoracic aortic disease have also been noted to be caused by *SMAD4* mutations

Molecular Basis of Disease

- It is unclear how germ line mutations of *SMAD4* or *BMPR1A* cause juvenile polyps to form; *SMAD4* is a tumor suppressor gene, *BMPR1A*'s protein product mediates intracellular signaling through *SMAD4*

Laboratory

- Pathologic confirmation of the type of polyp necessary to apply clinical diagnosis
- Molecular mutation analysis is available
- If molecular testing is negative, consideration of *PTEN* testing is appropriate to determine if an individual has *PTEN* hamartoma tumor syndrome rather than JPS

Treatment/Surveillance

- Colonoscopy and upper endoscopy to begin at approximately age 15 with repeat annually if polyps are noted and every 2–3 years if polyps are not noted
- If SMAD4 mutation, screen for vascular lesions associated with HHT within the first 6 months of life
- Due to the rare and undefined nature of small intestine and pancreatic cancer risk, no recommendations have been made at this time

Cowden Syndrome (One of the PTEN Hamartoma Tumor Syndromes)

Chromosome and Gene Location

- 10q23.31 (*PTEN*)

Inheritance

- Autosomal dominant

Incidence

- Estimated to be 1 in 200,000, likely underestimated

Clinical Manifestations

- Clinical criteria exist to determine those at risk to have Cowden syndrome
  - Major criteria include breast cancer, endometrial cancer, follicular thyroid cancer, multiple GI hamartomas or ganglioneuromas, macrocephaly, macular pigmentation of glans penis, and mucocutaneous lesions
  - Minor criteria include colon cancer, autism spectrum disorder, lipomas, intellectual delay, esophageal glycogenic acanthuses, papillary or follicular variants of papillary thyroid cancer, structural thyroid lesions, renal cell carcinoma, testicular lipomatosis, single GI hamartoma or ganglioneuroma, and vascular anomalies
- 85% of individuals meeting clinical diagnostic criteria have an identified *PTEN* mutation
- 80% of individuals will have dermatologic findings, and these pathognomic criteria include trichilemmomas, acral keratoses, papillomatous lesions, and mucosal lesions
- Hamartomatous polyps of the stomach, small bowel, and colon occur in 35–60%; the intestinal polyps are indistinguishable from those noted in JPS
- Breast cancer occurs in 30–50% of female mutation carriers; 85% lifetime risk
- Increased risk for endometrial cancer (28%) and thyroid adenoma and carcinomas (mainly follicular, 35%)
- Condition overlaps with Bannayan–Ruvalcaba–Riley syndrome

Molecular Basis of Disease

- Mutations in *PTEN* gene thought to disrupt the tyrosine/dual-specificity phosphatase domain of this gene

Laboratory

- Molecular mutation analysis is available

Treatment/Surveillance

- Annual thyroid ultrasound beginning at age 18

- Breast awareness beginning at age 18, clinical breast exams every 6–12 months beginning at age 25, and annual mammography and breast MRI beginning at age 30–35
- Consideration of endometrial biopsy and/or ultrasound beginning at age 30–35
- Consideration of risk-reducing mastectomy and hysterectomy
- Colonoscopy every 5 years or as findings appropriate beginning at age 35
- Consider renal ultrasound every 1–2 years beginning at age 40
- Additional screening guidelines should be considered and individualized based upon cancers observed in the family

Li–Fraumeni Syndrome

Chromosome and Gene Location

- 17p13.1 (*Tp53*)

Inheritance

- Autosomal dominant
- Approximately 7–20% due to de novo mutations

Incidence

- Approximately 1 in 5,000 to 1 in 20,000

Clinical Manifestations

- Soft tissue sarcomas
- Early onset breast cancer; estimated that 4–8% of individuals diagnosed under age 30 who test negative for *BRCA1* and *BRCA2* mutations test positive for a *Tp53* mutation
- Adrenocortical and brain tumors
- Osteosarcomas
- Leukemia
- Risk of developing invasive cancer is approximately 50% by age 30 and 90% by age 60
- Classical definition requires:
  - One patient with sarcoma under age 45
  - A first degree relative under age 45 with any cancer
  - A third affected first- or second-degree relative with either sarcoma at any age or any cancer under age 45
- About 70–83% of families meeting these criteria have identifiable mutation in *Tp53*
- Several additional guidelines exist, such as Chompret

Molecular Basis of Disease

- Mutation types include nonsense mutations and splice site mutations, which generate truncated protein products

Laboratory

- Mutation analysis available for *Tp53*

Treatment/Surveillance

- Efficacy not well established
- Annual comprehensive physical exam and promptly seek medical care for the evaluation of lingering symptoms or illnesses
- Breast surveillance includes clinical breast exams every 6 months beginning at 20–25 years, annual breast MRI beginning at 20–29 years, and annual mammography and breast MRI after age 30
- Consider colonoscopy screening no later than 25 years with repeat every 2–5 years
- Consider organ-targeted screening based upon family history
- Whole-body MRI protocols are currently under investigation but could be considered
- Additional surveillance strategies have been published, and discussion to participate in novel screening approaches using technologies such as whole-body MRI, abdominal ultrasound, and brain MRI should be offered

Multiple Endocrine Neoplasia Type 1 (MEN1)

Chromosome and Gene Location

- 11q13.1 (*MEN1*)

Inheritance

- Autosomal dominant

Incidence

- 1 in 20,000 to 1 in 40,000
- 10% are the result of de novo mutations

Clinical Manifestations (Also See Chap. 20)

- Parathyroid adenomas
- Pituitary adenoma (prolactinoma)
- Pancreatic islet cell tumors (most commonly gastrinomas)
- Insulinoma
- Peptic ulcer disease
- Hyperparathyroidism
- Other findings include lipoma and leiomyoma and dermatologic findings such as facial angiofibroma and collagenoma
- Features are variable within and between families
- 80% penetrance by age 50
- Diagnostic criteria include the presence of two of the following three endocrine tumors:
  - Parathyroid tumor (hypercalcemia, primary hyperparathyroidism)
  - Pituitary tumors (prolactinomas)
  - Well-differentiated endocrine tumors of the gastroenteropancreatic (GEP) tract (gastroma, insulinoma, VIPoma)

Molecular Basis of Disease

- *MEN1* encodes a transcript called menin
- Numerous frameshift, nonsense, missense, and in-frame deletions have been reported

- Function of protein is not known but thought to have a role in DNA replication and repair, transcription, and chromatin modification

Laboratory

- Elevated ACTH
- Abnormal secretion test
- Hypoglycemia
- Hypergastrinemia
- Hyperparathyroidism
- Glucose intolerance
- Molecular analysis is available

Treatment/Surveillance

- Screening recommendations begin at age 5 and include an annual evaluation for prolactin, cortisol, glucose, calcium, and phosphorus
- Physical exam with endocrinologic review of systems
- Annual head MRI beginning at age 5 and abdominal CT or MRI beginning at age 20

Multiple Endocrine Neoplasia Types 2A and 2B and Familial Medullary Thyroid Carcinoma

Chromosome and Gene Location

- 10q11.21 (*RET*)

Inheritance

- Autosomal dominant

Incidence

- 1 in 35,000
- About 10% of thyroid cancers are of the medullary type; of these, 25–30% are due to germ line RET mutations
- Approximately 5% of MEN2A diagnoses are the result of de novo *RET* mutations; approximately 50% of MEN2B diagnoses are the result of de novo *RET* mutations

Clinical Manifestations (Also See Chap. 20)

- MEN2A
  - Medullary thyroid carcinoma (>95%)
  - Pheochromocytoma (50%)
- Hyperparathyroidism (parathyroid hyperplasia or adenoma) (20–30%)
- MEN2B
  - Same features as MEN2A but earlier onset (10 years; 100%)
  - Parathyroid disease is rare
- Additional findings include
  - Mucosal neuromas (Fig. 13.11)
  - Thickened corneal nerves

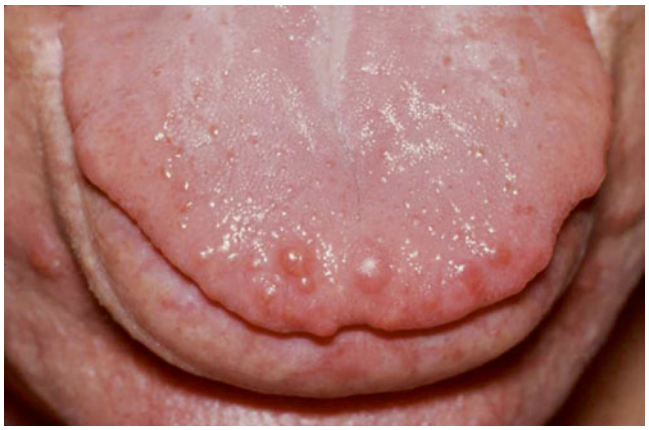

Fig. 13.11. Multiple endocrine neoplasia type 2b – mucosal ganglioneuroma.

  - Marfanoid habitus (75%)
  - Gastrointestinal involvement
- Familial medullary thyroid carcinoma (FMTC)
  - Medullary thyroid carcinoma only
- More indolent than MEN2A or 2B

Molecular Basis of Disease

- Mutations in cysteine residues of extracellular binding domain in exons 10, 11, and 13–16 of the RET proto-oncogene account for most of the cases of MEN2A and FMTC; mutations can occur in exon 5 and 8 but are rare
- A single point mutation in *RET* exon 16 (M918T) is the most common cause for MEN2B
- Mutations of codon 634Cys in exon 11 account for over 85% of MEN2A mutations
- Mutations within these exons of the RET proto-oncogene account for ~98% of MEN2A families, 95% of FMTC, and 98% of MEN2B families
- Strong genotype/phenotype correlations exist

Laboratory

- Mutations in *RET*
- Elevated calcitonin after stimulation
- Metanephrines may be elevated if pheochromocytoma is present
- Parathyroid hormone and calcium elevation may also be present

Treatment/Surveillance

- Screening recommendations include genetic testing for at risk individuals
- For positive individuals, prophylactic thyroidectomy and annual screening for pheochromocytoma and hyperparathyroidism are indicated
- Those at risk for pheochromocytoma should avoid dopamine (D_2) receptor antagonists

Peutz–Jeghers Syndrome

Chromosome and Gene Location

- 19p13.3 (*STK11*, previously known as *LKB1*)

Inheritance

- Autosomal dominant

Incidence

- Estimate ranges from 1 in 25,000 to 1 in 280,000

Clinical Manifestations

- Numerous pigmented spots found on lips and buccal mucosa (more rarely on face, forearms hands, feet, and perianal area) (Fig. 13.12). Many fade over time, and some individuals do not have pigmentation
- Multiple gastrointestinal hamartomatous polyps found in the jejunum (malignant transformation not common) can also occur in the stomach and colon
- Most individuals present with intussusception, small bowel obstruction, or rectal bleeding
- Colon cancer risk estimated to be 39% by age 70 and breast cancer risk estimated to be 54% by age 65
- Cancers of the ovary, cervix, testis, pancreas, uterus, and lung also reported
- Risk of any malignancy estimated as 67–85% by age 70 years
- Clinical diagnosis may be made when any one of the following is present:
  - Two or more histologically confirmed PJS-type hamartomatous polyps
  - Any number of PJS-type polyps detected in one individual with a PJS family history
  - Characteristic mucocutaneous pigmentation in an individual with a PJS family history
  - Any number of PJS-type polyps in an individual who also has characteristic mucocutaneous pigmentation
  - Individual found to have STK11 mutation

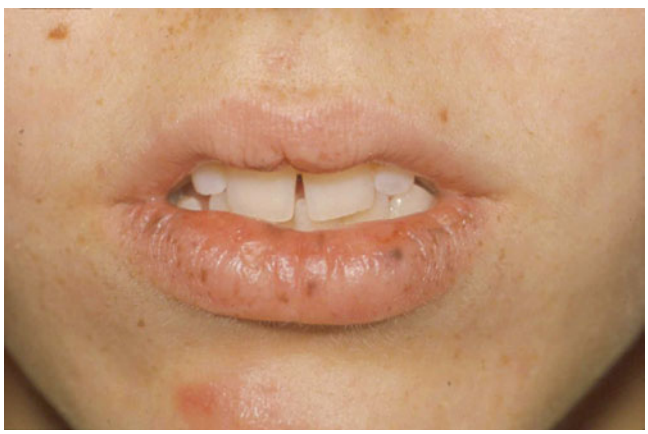

Fig. 13.12. Peutz–Jeghers syndrome with freckles on lips.

- 80–94% of those with clinical diagnosis will have identifiable *STK11* mutation

Molecular Basis of Disease

- Disorder is due to mutations in the serine threonine kinase, *STK11*
- About 45% thought due to a de novo mutation, however, and may also be underdiagnosed within a family

Laboratory

- Polyps can have a unique cellular morphology imparting branching treelike appearance of mucosa with interdigitating smooth muscle
- Molecular testing available

Treatment/Surveillance

- CT or MRI of small bowel beginning at age 8–10, following up based upon findings, and then every 2–3 years beginning at age 18
- Colonoscopy and upper endoscopy every 2–3 years beginning in the late teens
- Removal of polyps if feasible to prevent small bowel intussusception
- Clinical breast exams every 6 months and annual mammography and breast MRI beginning at age 25
- MR cholangiopancreatography or endoscopic ultrasound every 1–2 years beginning at age 30–35
- Annual pelvic ultrasound and pap smear with consideration of transvaginal ultrasound beginning at 18–20 years
- Annual testicular exam with observation for feminizing changes beginning at age 10

Retinoblastoma

Chromosome and Gene Location

- 13q14.2 (*RB1*)

Inheritance

- Autosomal dominant with incomplete penetrance
- Approximately 65–75% are unilateral and sporadic with a mean diagnosis age of 24 months
- 25–35% are bilateral and hereditary with a mean diagnosis age of 15 months

Incidence

- 1 in 15,000–1 in 20,000

Clinical Manifestations

- Strabismus and/or leukocoria, multifocal, and bilateral tumors of the retina
- Other secondary cancers include:
  - Osteosarcoma
  - Fibrosarcoma
  - Melanoma
  - Pineoblastoma
- May also be at an increased risk for lung, prostate, and breast cancer

Molecular Basis of Disease

- *RB1* protein is involved in cell cycle and cell growth regulation

Laboratory

- Probability of detecting *RB1* mutation in WBC DNA of index case will depend upon whether the tumors are bilateral or unilateral and whether there is positive family history or index case and the sensitivity of the testing method
- Deletions and point mutations are noted
- Chromosome analysis to detect large rearrangements and deletions
- Linkage analysis is available

Treatment/Surveillance

- Surgical options include enucleation and cryosurgery; additional options of chemotherapy and radiation also utilized
- Screening includes ophthalmologic examination at birth and every 4–6 weeks for 6 months and then at increasing intervals (3–6 months) until age 7 and then every 6–12 months thereafter

Von Hippel–Lindau

Chromosome and Gene Location

- 3p25.3 (*VHL*)

Inheritance

- Autosomal dominant
- Approximately 100% penetrant by age 65

Incidence

- 1 in 36,000
- 20% due to de novo mutations

Clinical Manifestations (Used Prior to Advent of Molecular Testing)

- Hemangioblastoma of the brain, spinal cord, and retina:
  - Retinal hemangioblastomas (25–60%)
  - Cerebellar hemangioma (44–72%)
  - Spinal hemangiomas (13–50%)
- Pancreatic cysts (35–70%)
- Pancreatic neuroendocrine tumors
- Renal cysts
- Clear cell renal cell carcinoma (occurs in approximately 70% by age 60), leading cause of mortality
- Endolymphatic sac tumors and epididymal tumors are also common
- Four VHL disease phenotypes:
  - Type 1: low risk for pheochromocytoma, high risk for renal cell carcinoma
  - Type 2A: high risk for pheochromocytoma, low risk for renal cell carcinoma
  - Type 2B: high risk for pheochromocytoma, high risk for renal cell carcinoma
  - Type 2C: high risk for pheochromocytoma, very low risk for renal cell carcinoma

Molecular Basis of Disease

- Numerous deletions, insertions, nonsense, and missense mutations in *VHL*
- *VHL* is a tumor suppressor gene, the gene product functions to negatively regulate transcription
- Genotype/phenotype correlations

Laboratory

- Mutation analysis of *VHL* available

Treatment/Surveillance

- Annual eye and retinal ophthalmologic exam beginning at age 1
- Annual blood pressure evaluation at age 1
- Annual labs including catecholamines and metanephrines beginning at age 5
- Annual abdominal ultrasound beginning at age 16
- Complete audiologic assessment every 2–3 years, with MRI if recurrent ear infections, beginning at age 5
- Brain, cervical spine, and abdominal MRI every 2 years beginning at age 16

MITOCHONDRIAL DISORDERS

- Mitochondria are cellular organelles, which generate energy for cellular processes by producing ATP by means of the electron transport chain and the oxidative phosphorylation system (the "respiratory chain"). The respiratory chain is located in the inner mitochondrial membrane. It consists of five multimeric protein complexes:
  - Reduced nicotinamide adenine dinucleotide (NADH) dehydrogenase–ubiquinone oxidoreductase (complex I, 45 subunits)
  - Succinate dehydrogenase–ubiquinone oxidoreductase (complex II, four subunits)
  - Ubiquinone–cytochrome *c* oxidoreductase (complex III, 11 subunits)
  - Cytochrome c oxidase (complex IV, 13 subunits)
  - ATP synthase (complex V, 16 subunits)

Chromosome and Gene Location

- Apart from the nucleus, mitochondria are the only cellular organelles that contain their *own* DNA (called mtDNA) for

synthesizing RNA and proteins. Cells contain hundreds to thousands mitochondria, and each has approximately five mitochondrial genomes

- The mtDNA contains 37 genes, but most of the gene products (approximately 1,000) required for mitochondrial functioning are encoded by nuclear DNA (nDNA) and imported from the cytoplasm
- Mitochondrial DNA is a double-stranded circular molecule, which encodes 13 protein respiratory chain subunits and 24 RNAs (two ribosomal RNAs and 22 transfer RNAs) required within the mitochondria for translation of the protein-coding units

Inheritance

- Mitochondrial inheritance (mtDNA) (maternal inheritance)
  - Generally, all mitochondria in the zygote are derived from the ovum. Therefore, a mother carrying an mtDNA mutation may pass it onto each of her children, but only her daughters will transmit it to their offspring. Most mtDNA-related diseases are maternally inherited, but there are exceptions. The occurrence of large deletions is almost always sporadic, probably taking place in oogenesis or early embryogenesis
  - *Homoplasmy* refers to the presence of all normal or all mutant mitochondrial DNA
  - *Heteroplasmy*: mtDNA pathogenic mutations are present in some, but not all mtDNA molecules in each cell. As a result, cells and tissues harbor both normal (wild type) and mutant mtDNA
  - A minimal number of mutant mtDNAs must be present before oxidative dysfunction occurs and clinical signs become apparent: *threshold effect*
  - During mitotic segregation, the random redistribution of organelles during cell division might alter the proportion of mutant mtDNAs received by daughter cells; if the pathogenic threshold in a previously unaffected tissue is surpassed, the phenotype might also change. This underlies the age-related and tissue-related variability of clinical features in mtDNA-related diseases
- Mendelian inheritance
  - Most mitochondrial dysfunction is due to alterations in nuclear genes and is inherited according to Mendelian laws with autosomal recessive pattern thought to be the most common

Incidence

- Mitochondrial diseases are not rare; incidence 1:10,000 live births

Clinical Manifestations

- Nearly all tissues depend on oxidative metabolism. Therefore, mitochondrial diseases are complex multisystem disorders, which include a variety of neurologic, ophthalmologic, cardiac, endocrine, gastrointestinal, renal, hematologic, audiologic, and pulmonary manifestations. Specific examples are provided below

Molecular Basis of Disease

- Mutations in mtDNA can affect specific structural respiratory chain proteins or the synthesis of all/many mitochondrial proteins (mutations in RNA genes or mtDNA rearrangements)
- Examples of the clinical manifestation of various mutation types are provided below

Respiratory chain disorders due to defects in mtDNA

- Point mutations in protein-encoding genes
  - Neurogenic weakness, ataxia, and retinitis pigmentosa (NARP)
- Mutation in transfer RNA
  - Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
    - Seizures
    - Stroke-like episodes
    - Psychomotor regression
    - Weakness and exercise intolerance
    - Intestinal pseudo-obstruction
    - Sensorineural hearing loss
  - Myoclonic epilepsy with ragged-red fibers (MERRF)
    - Myoclonus
    - Seizures
    - Cerebellar ataxia
    - Mitochondrial myopathy
- Mutation in messenger RNA
  - Leber hereditary optic neuropathy (LHON)
    - Bilateral visual loss
    - Central scotomas
    - Abnormal color vision
- Mutation in ribosomal RNA
  - Aminoglycoside-induced non-syndromic deafness
- Rearrangements/deletions in mtDNA
  - Kearns–Sayre syndrome (KSS)
    - Chronic progressive external ophthalmoplegia
    - Ptosis
    - Pigmentary retinopathy
    - Heart block
    - Elevated CSF protein greater than 100 mg/dL
    - Ataxia

Nuclear-encoded mitochondrial diseases, which exhibit Mendelian inheritance (examples)

- Structural *OXPHOS* gene defects
  - Complex I deficiency

- Leigh (–like) syndrome – *NDUFS4* (NADH dehydrogenase (ubiquinone) Fe–S protein), *NDUFS7*, *NDUFS8* genes
  - Progressive central nervous system neurological deterioration
  - Characteristic radiographic features with symmetric involvement of brainstem and basal ganglia
- Hypertrophic cardiomyopathy and encephalomyopathy – *NDUFS2* gene
- Macrocephaly, leukodystrophy, and myoclonic epilepsy – *NDUFV1* gene

– Complex II deficiency (all complex II enzymes are nuclear encoded [none are in the maternally inherited genome])
- Leigh (–like) syndrome – flavoprotein (Fp) gene

♦ Nonstructural *OXPHOS* gene defects

– Intergenomic (mitochondrial and nuclear DNA) communication defects
- Mitochondrial neurogastrointestinal encephalomyopathy syndrome (MNGIE)
  - Mutations in thymidine phosphorylase gene
  - Ophthalmoparesis
  - Peripheral neuropathy
  - Leukoencephalopathy
  - Gastrointestinal dysmotility
  - Myopathy

– Assembling defects
- Complex IV deficiencies (Leigh syndrome, mutations in *SURF1* gene)

– Homeostasis and import defects
- Deafness–dystonia syndrome – *DDP* gene (involved in protein transport)
  - X-linked recessive
  - Sensorineural hearing loss
  - Dystonia
  - Dementia
  - Psychotic features
  - Optic atrophy

Laboratory

♦ Biochemical investigations – elevated serum and cerebrospinal fluid lactate

♦ Tissue evaluation – ragged-red fibers and ragged-blue cox negative fibers in skeletal muscle; defective oxidative phosphorylation enzyme activity on biopsied (affected) tissue

♦ Electromyography, nerve conduction studies – myopathic potentials; axonal and demyelinating peripheral neuropathy

♦ ECG and ECHO – cardiac conduction defects and cardiomyopathy

♦ Mitochondrial and nuclear gene mutations

Treatment

♦ Supportive/symptomatic

SUGGESTED READING

Online Resources

GeneReviews. http://www.geneclinics.org.

Online Mendelian Inheritance in Man (OMIM). http://www.ncbi.nlm.nih.gov.

General Genetic Resources

Jones KL. Smith's recognizable patterns of human malformation. 6th ed. Philadelphia: Elsevier; 2006.

Rimoin DL, Connor JM, Pyeritz RE, Korf BR, editors. Emery and Rimoin's principles and practice of medical genetics. 5th ed. New York: Churchill Livingstone; 2007.

Scriver CR, et al., editors. The metabolic and molecular basis of inherited disease. 8th ed. New York: McGraw-Hill; 2001.

Chromosomal Disorders

ACOG Practice Bulletin – Clinical Management Guidelines for Obstetrician-Gynecologists. ACOG Practice Bulletin No. 77: screening for fetal chromosomal abnormalities. Obstet Gynecol. 2007;109:217–27.

De Decker HP, Lawrenson JB. The 22q11.2 deletion: from diversity to a single gene theory. Genet Med. 2001;3:2–5.

Duker NJ. Chromosome breakage syndromes and cancer. Am J Med Genet. 2002;115:125–9.

Gardner RJ, Sutherland G. Chromosome abnormalities and genetic counseling. New York: Oxford University Press; 2004.

Horsthemke B, Wagstaff J. Mechanisms of imprinting of the Prader-Willi/Angelman region. Am J Med Genet A. 2008;146A:2041–52.

Joenje H, Patel KJ. The emerging genetic and molecular basis of Fanconi anaemia. Nat Rev Genet. 2001;2:446–57.

Mitchell EB, et al. Ready reference to common segmental aneusomies by syndromic names, major features and chromosomal locations. J Assoc Genet Technol. 2008;34:5–7.

Trinucleotide Repeat Disorders

Evidente VG, Gwinn-Hardy KA, Caviness JN, Gilman S. Hereditary ataxias. Mayo Clin Proc. 2000;75:475–90.

Shao J, Diamond MI. Polyglutamine diseases: emerging concepts in pathogenesis and therapy. Hum Mol Genet. 2007;16:R115–23.

Wenstrom KD. Fragile X, and other trinucleotide repeat diseases. Obstet Gynecol Clin North Am. 2002;29:367–88.

Neuromuscular Disorders

Ogino S, Wilson RB. Genetic testing and risk assessment for spinal muscular atrophy (SMA). Hum Genet. 2002;111:477–500.

Saifi GM, Szigeti K, Snipes GJ, et al. Molecular mechanisms, diagnosis, and rational approaches to management of and therapy for Charcot-Marie-Tooth disease and related peripheral neuropathies. J Invest Med. 2003;51:261–8.

Zatz M, de Paula F, Starling A, et al. The 10 autosomal recessive limb-girdle muscular dystrophies. Neuromuscul Disord. 2003;13:532–44.

Skeletal Disorders

Kimonis V, et al. Genetics of craniosynostosis. Semin Pediatr Neurol. 2007;14:150–61.

Valadares ER, Carneiro TB, Santos PM, et al. What is new in genetics and osteogenesis imperfecta classification? J Pediatr (RioJ). 2014;90:536–41.

Warman ML, Cormier-Daire V, Hall C, et al. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet A. 2011;115:943–68.

Wilkie AO, Patey SJ, Kan SH, et al. FGFs, their receptors, and human limb malformations: clinical and molecular correlations. Am J Med Genet. 2002;112:266–78.

Connective Tissue Disorders

Colige A, Nuytinck L, et al. Novel types of mutation responsible for the dermatosparactic type of Ehlers-Danlos syndrome (Type VIIC) and common polymorphisms in the ADAMTS2 gene. J Invest Dermatol. 2004;123:656–63.

Kashtan CE. Alport syndrome and thin basement membrane nephropathy. 2001 Aug 28 [Updated 2013 Feb 28]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle, WA: University of Washington, Seattle; 1993–2014. http://www.ncbi.nlm.nih.gov/books/NBK1207/.

Levy M, Feingold J. Estimating prevalence in single-gene kidney diseases progressing to renal failure. Kidney Int. 2000;58:925–43.

Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-B receptor. N Engl J Med. 2006;355:788–98.

MacCarrick G, Black III J, et al. Loeys–Dietz syndrome: a primer for diagnosis and management. Genet Med. 2014;16:576–87.

Milewicz DM, Guo DC, Tran-Fandulu V, et al. Genetic basis of thoracic aortic aneurysms and dissections: focus on smooth muscle cell contractile dysfunction. Annu Rev Genomics Hum Genet. 2008;9:283–302.

Muller T, Mizumoto S, et al. Loss of dermatan sulfate epimerase (DSE) function results in musculocontractural Ehlers-Danlos syndrome. Hum Mol Genet. 2013;22:3761–72.

Paterick T, Humphries J, et al. Aortopathies: etiologies, genetics, differential diagnosis, prognosis and management. Am J Med. 2013;126:670–8.

Robin NH, Moran RT, Ala-Kokko L. Stickler syndrome. 2000 Jun 9 [Updated 2014 Sep 11]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle, WA: University of Washington, Seattle; 1993–2014. http://www.ncbi.nlm.nih.gov/books/NBK1302/.

Hematologic Disorders

Old JM. Screening and genetic diagnosis of haemoglobin disorders. Blood Rev. 2003;17:43–5.

Pruthi RK. Hemophilia: a practical approach to genetic testing. Mayo Clin Proc. 2005;80:1485–99.

Schrier SL. Pathophysiology of thalassemia. Curr Opin Hematol. 2002;9:123–6.

Thein SL. Genetic insights into the clinical diversity of beta thalassaemia. Br J Haematol. 2004;124:264–74.

Other Genetic Disorders

Coffee B, Keith K, Albizua I, Malone T, Mowrey J, Sherman SL, Warren ST. Incidence of fragile X syndrome by newborn screening for methylated FMR1 DNA. Am J Hum Genet. 2009;85:503–14.

Kulczycki LL, Kostuch M, Bellanti JA. A clinical perspective of cystic fibrosis and new genetic findings: relationship of CFTR mutations to genotype-phenotype manifestations. Am J Med Genet A. 2003;116A:262–7.

Roach ES, Sparagana SP. Diagnosis of tuberous sclerosis complex. J Child Neurol. 2004;19:643–9.

Rossi M, Perez-Lloret S, Doldan L, et al. Autosomal dominant cerebellar ataxias: a systematic review of clinical features. Eur J Neurol. 2004;21:607–15.

Suominen T, Bachinski LL, Auvinen S, et al. Population frequency of myotonic dystrophy: higher than expected frequency of myotonic dystrophy type 2 (DM2) mutation in Finland. Eur J Hum Genet. 2011;19:776–82.

Turner C, Hilton-Jones D. Myotonic dystrophy: diagnosis, management and new therapies. Curr Opin Neurol. 2014;27:599–606.

Udd B, Meola G, Krahe R, et al. 140th ENMC International Workshop: myotonic dystrophy DM2/PROMM and other myotonic dystrophies with guidelines on management. Neuromuscul Disord. 2006;16:403–13.

Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med. 2004;6:387–91.

Metabolic Disorders: Inborn Errors of Metabolism

Blau N, Duran M, Gibson MK. Laboratory guide to the methods in biochemical genetics. Berlin: Springer; 2008.

Blau N, Duran M, Gibson KM, Dionisi-Vici C. Physician's guide to the diagnosis, treatment, and follow-up of inherited metabolic diseases. Berlin: Springer; 2014.

Fearing MK, Levy HL. Expanded newborn screening using tandem mass spectrometry. Adv Pediatr. 2003;50:81–111.

Fernandes J, Saudubray JM, van den Berghe G, Walter JH, editors. Inborn metabolic diseases diagnosis and treatment. 4th ed. Heidelberg: Springer; 2006.

Rinaldo P, Lim JS, Tortorelli S, Gavrilov D, Matern D. Newborn screening of metabolic disorders: recent progress and future developments. Nestle Nutr Workshop Ser Paediatr Program. 2008;62:81–93. discussion 93–96.

Lysosomal Storage Diseases

Beck M. New therapeutic options for lysosomal storage disorders: enzyme replacement, small molecules and gene therapy. Hum Genet. 2007;121:1–22.

Staretz-Chacham O, Lang TC, LaMarca ME, Krasnewich D, Sidransky E. Lysosomal storage disorders in the newborn (review). Pediatrics. 2009;123:1191–207.

Familial Cancer Syndromes

Alsanea O, Clark OH. Familial thyroid cancer. Curr Opin Oncol. 2001;13:44–51.

Bausch B, Jilg C, Glasker S, et al. Renal cancer in von Hippel-Lindau disease and related syndromes. Nat Rev Nephrol. 2013;9:529–38.

Boardman LA. Heritable colorectal cancer syndromes: recognition and preventive management. Gastroenterol Clin North Am. 2002;31:1107–31.

Callender GG, Rich TA, Perrier ND. Multiple endocrine neoplasia syndromes. Surg Clin North Am. 2008;88:863–95. viii.

Classon M, Harlow E. The retinoblastoma tumour suppressor in development and cancer. Nat Rev Cancer. 2002;2:910–7.

Cohen SA, Leininger A. The genetic basis of Lynch syndrome and its implications for clinical practice and risk management. Appl Clin Genet. 2014;7:147–58.

Economopoulou P, Dimitriadis G, Psyrri A. Beyond BRCA: new hereditary breast cancer susceptibility genes. Cancer Treat Rev. 2015;41:1–8.

Eng C. PTEN: one gene, many syndromes. Hum Mutat. 2003;22:183–98.

Fleischmann C, Peto J, Cheadle J, Shah B, Sampson J, Houlston RS. Comprehensive analysis of the contribution of germline MYH variation to early-onset colorectal cancer. Int J Cancer. 2004;109:554–8.

Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. J Clin Oncol. 2002;20:1480–90.

Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. Am J Gastroenterol. 2014;109:1159–79.

Kuroda N, Furuya M, Nagashima Y, et al. Review of renal tumors associated with Birt-Hogg-Dube syndrome with focus on clinical and pathobiological aspects. Pol J Pathol. 2014;65:93–9.

Larsen MJ, Thomassen M, Gerdes AM, Kruse TA. Hereditary breast cancer: clinical, pathological and molecular characteristics. Breast Cancer (Auckl). 2014;8:145–55.

Leggett BA, Young JP, Barker M. Peutz-Jeghers syndrome: genetic screening. Expert Rev Anticancer Ther. 2003;3:518–24.

Lindor NM, McMaster ML, Lindor CJ, Greene MH, National Cancer Institute DoCPCO, Prevention Trials Research Group. Concise handbook of familial cancer susceptibility syndromes – second edition. J Natl Cancer Inst Monogr. 2008;1–93.

Markey K, Axel L, Ahnen D. Basic concepts for genetic testing in common hereditary colorectal cancer syndromes. Curr Gastroenterol Rep. 2002;4:404–13.

Mester J, Eng C. Cowden syndrome: recognizing and managing a not-so-rare hereditary cancer syndrome. J Surg Oncol. 2015;111:125–30.

Metzger R, Milas M. Inherited cancer syndromes and the thyroid: an update. Curr Opin Oncol. 2014;26:51–61.

Robbins DH, Itzkowitz SH. The molecular and genetic basis of colon cancer. Med Clin North Am. 2002;86:1467–95.

Sims KB. Von Hippel-Lindau disease: gene to bedside. Curr Opin Neurol. 2001;14:695–703.

Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. J Clin Oncol. 2015;33:209–17.

Varley JM. Germline TP53 mutations and Li-Fraumeni syndrome. Hum Mutat. 2003;21:313–20.

Villani A, Tabori U, Schiffman J, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. Lancet Oncol. 2011;12:559–67.

Wooster R, Weber BL. Breast and ovarian cancer. N Engl J Med. 2003;348:2339–47.

Mitochondrial Disorders

DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. N Engl J Med. 2003;348:2656–68.

Haas RH, Parikh S, Falk MJ, et al. The in-depth evaluation of suspected mitochondrial disease. Mol Genet Metab. 2008;94:16–37.

Smeitink J, van den Heuvel L, DiMauro S. The genetics and pathology of oxidative phosphorylation. Nat Rev Genet. 2007;2:342–52.

Van den Heuvel L, Smeitink J. The oxidative phosphorylation (OXPHOS) system: nuclear genes and human genetic diseases. Bioessays. 2001;23: 518–25.