CHAPTER

37

Sensory Organ Disorders (Retina, Auditory, Olfactory, Gustatory)

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OUTLINE

37.1 INTRODUCTION

Over the past several decades, many common historical causes of congenital sensory impairment have been eradicated or diminished by economic growth and by targeted programs combating disease and maternal health, among others. As a result, at some point in the last few decades, and perhaps for the first time in human history, inherited disorders have become the most common cause of congenital sensory impairment. Over the past 15 years, specific genes, protein function, and disease etiology have been identified at an accelerating rate. The growing number of animal models for developmental sensory disorders has been tremendously useful for understanding both normal and abnormal development and sensory processing.

37.2 HEARING IMPAIRMENT

Developmental auditory disorders may involve defects at any stage from the moment sound enters the external ear to the sensorineural synapse to the

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downstream processing pathways of the central nervous system. Disorders of the auditory organ are thus roughly classified as *conductive*, affecting primarily the mechanical structures of the external and middle ear; *sensorineural*, affecting primarily the sensory, neural, and supporting structures of the inner ear and central auditory pathway; or *mixed.* Because hearing impairment that precedes language acquisition can be especially significant, hearing loss is often characterized as *prelingual*, occurring before 2 years of age, or *postlingual.* Severity of hearing loss may be mild (<40 dB), moderate (40–70 dB), severe (70–90 dB), or profound (>90 dB).

37.2.1 Acquired Hearing Loss

Many forms of hearing loss are preventable. The hair cells, for example, are particularly vulnerable to acoustic trauma and to a wide range of ototoxic drugs (e.g., cisplatin, isoretinoin, alcohol, aminoglycoside antibiotics, loop-diuretics), and as mammalian hair cells do not regenerate, the inner hair cells constitute a scarce resource at only about 3500 cells per human cochlea. Infection has long been a major cause of hearing loss. Both acquired and congenital syphilis can produce otosyphilis, which if untreated causes endolymphatic hydrops (fluid accumulation) and subsequent degeneration accompanied by hearing loss and vestibular dysfunction. Although reports of congenital otosyphilis are rare in the current literature, there is concern that this disorder could rise with the reemergence of syphilis. Historically, rubella (German measles) was a major cause of hearing loss, and over half of all cases of congenital rubella syndrome, acquired through maternal infection, still lead to hearing loss. Vaccination programs have largely eliminated rubella from high-income countries, though the disease and its consequent hearing loss are still common in many low-income countries (Tucci et al., 2010). Hearing loss as a result of anoxia, maternal diabetes, and maternal herpes simplex virus are also still seen.

The infectious agent with greatest relevance to childhood hearing loss is perhaps the herpes virus cytomegalovirus (CMV), which is now considered a leading cause of congenital developmental disorders. CMV is widespread in humans, with CMV infection rates at birth estimated at 0.2–1%, and sensorineural hearing loss may develop in children who appear healthy at birth. Congenital CMV is estimated to cause 6% of hearing impairment in newborns and 15–25% of sensorineural hearing loss in children in the United States, and is now the primary cause of noninherited sensorineural hearing loss in children. Despite the incidence of this disorder, and the recent introduction of mouse models for CMV-induced hearing loss, the pathology of this CMV-induced hearing loss is still not well understood, and control remains focused on hygiene and on development of a vaccine or antiviral.

37.2.2 Inherited Hearing Loss

While a significant proportion of human congenital hearing loss was once due to disorders associated with maternal infection, in middle- and high-income countries today, the majority of congenital hearing loss has a genetic component. The most common form of sensory impairment, hearing loss, is also one of the most common birth abnormalities. Clinically, the various sensory disorders are typically categorized as nonsyndromic or primary (e.g., isolated deafness not accompanied by other apparent abnormalities) and syndromic (e.g., deafness accompanied by other sensory, morphological, or physiological abnormalities). Nonsyndromic disorders, though less numerous, account for a majority of cases of deafness of genetic origin; the various nonsyndromic disorders are identified by inheritance pattern, with DFN, DFNA, and DFNB referring to X-linked, autosomal-dominant, and autosomal-recessive deafness disorders (see Table 37.1). In practice, this increasingly long list can be confusing due to genetic heterogeneity and to overlap with some of the syndromic forms of deafness. As the list of mapped loci and identified genes for inherited deafness disorders is still growing, any attempt to encompass the known hereditary hearing disorders is quickly made obsolete by the description of new disorders in mouse and human. A selection from the wide range of auditory disorders will be briefly described here, and the reader is encouraged to consult updated websites and reviews for the most current, in-depth information (Dror and Avraham, 2009; Petit and Richardson, 2009).

37.2.2.1 Hereditary Conductive or Mixed Hearing Loss

In normal hearing, sound is collected at the external ear and focused into the external ear canal. The sound waves set up vibrations of the tympanic membrane that are transmitted by the three small bones of the ossicular chain through the air-filled cavity of the middle ear to the membranous oval window at the border between the middle and inner ear. The hinged lever-like mechanical advantage system of the interconnected ossicles, together with the reduction in surface area between the tympanic membrane and the oval window, allow pressure at the tympanic membrane to be amplified sufficiently to drive compressive waves in the fluid-filled cochlea of the inner ear. When conductive hearing loss presents in children, it is most often associated with otitis media, or middle ear infection, and its sequelae, which can include chronic perforation, mastoiditis, cholesteatoma, ossicular fixation, or tympanic membrane

TABLE 37.1 Disorders of the ear

Name	Gene	Gene product	Reference
Nonsyndromic			
X-linked			
DFN3	POU3F4	POU domain, class 3, transcription factor 4	de Kok et al. (1995)
Autosomal-dominant			
DFNA1	DIAPH1	Protein diaphanous homolog 1	Lynch et al. (1997)
DFNA2A DFNA2B	KCNQ4 GJB3	Voltage-gated K^+ channel subfamily KQT member 4; Kv7.4 Gap–junction beta-3 protein; connexin 31	Kubisch et al. (1999) Xia et al. (1998)
DFNA3A DFNA3B	GJB2 GJB6	Gap–junction beta-2 protein; connexin 26 Gap–junction beta-6 protein; connexin 30	Kelsell et al. (1997) Grifa et al. (1999)
DFNA4	MYH14	Myosin-14	Donaudy et al. (2004)
DFNA5	DFNA5	Nonsyndromic hearing impairment protein 5	Van Laer et al. (1998)
DFNA6/14/38	WFS1	Wolframin	Bespalova et al. (2001) Young et al. (2001)
DFNA8/12	TECTA	Tectorin alpha	Verhoeven et al. (1998)
DFNA9	COCH	Cochlin	Robertson et al. (1998)
DFNA10	EYA4	Eyes-absent homolog 4	Wayne et al. (2001)
DFNA11	MYO7A	Myosin-7a	Liu et al. (1997)
DFNA13	COL11A2	Collagen, type XI, alpha 2	McGuirt et al. (1999)
DFNA15	POU4F3	POU class 4 homeobox 3	Vahava et al. (1998)
DFNA17	MYH9	Myosin-9	Lalwani et al. (2000)
DFNA20/26	ACTG1	Gamma actin	Zhu et al. (2003) van Wijk et al. (2003)
DFNA22	MYO6	Myosin-6	Melchionda et al. (2001)
DFNA23	SIX1	Sine-oculis homeobox homolog 1	Ruf et al. (2004)
DFNA25	SLC17A8	Solute carrier family 17, member 8; vesicular glutamate transporter 3	Ruel et al. (2008)
DFNA28	GRHL2	Grainyhead-like protein 2 homolog	Peters et al. (2002)
DFNA36	TMC1	Transmembrane channel-like protein 1	Kurima et al. (2002)
DFNA39	DSPP	Dentin sialophosphoprotein	Xiao et al. (2001)
DFNA44	CCDC50	Coiled-coil domain containing protein 50; Ymer	Modamio-Hoybjor et al. (2007)
DFNA48	MYO1A	Myosin-1a	Donaudy et al. (2003)
	CRYM	Mu-crystallin homolog	Abe et al. (2003)
Autosomal-recessive			
DFNB1A DFNB1B	GJB2 GJB6	Gap–junction beta-2 protein; connexin 26 Gap–junction beta-6 protein; connexin 30	Kelsell et al. (1997) del Castillo et al. (2002)
DFNB2	MYO7A	Myosin-7a	Liu et al. (1997) Weil et al. (1997)
DFNB3	MYO15	Myosin-15	Wang et al. (1998)
DFNB4	SLC26A4	Pendrin	Li et al. (1998)

Continued

TABLE 37.1 Disorders of the ear—cont'd

Name	Gene	Gene product	Reference
DFNB6	TMIE	Transmembrane inner ear expressed protein	Naz et al. (2002)
DFNB7/11	TMC1	Transmembrane channel-like protein 1	Kurima et al. (2002)
DFNB8/10	TMPRSS3	Transmembrane protease serine 3	Scott et al. (2001)
DFNB9	OTOF	Otoferlin	Yasunaga et al. (1999)
DFNB12	CDH23	Cadherin-23	Bork et al. (2001)
DFNB16	STRC	Stereocilin	Verpy et al. (2001)
DFNB18	USH1C	Harmonin	Ouyang et al. (2002) Ahmed et al. (2002)
DFNB21	TECTA	Tectorin alpha	Mustapha et al. (1999)
DFNB22	OTOA	Otoancorin	Zwaenepoel et al. (2002)
DFNB23	PCDH15	Protocadherin-15	Ahmed et al. (2003b)
DFNB24	RDX	Radixin	Khan et al. (2007)
DFNB28	TRIOBP	TRIO and F-actin-binding protein	Shahin et al. (2006) Riazuddin et al. (2006b)
DFNB29	CLDN14	Claudin-14	Wilcox et al. (2001)
DFNB30	MYO3A	Myosin-3a	Walsh et al. (2002)
DFNB31	WHRN	Whirlin	Mburu et al. (2003)
DFNB36	ESPN	Espin	Naz et al. (2004)
DFNB37	MYO6	Myosin-6	Ahmed et al. (2003a)
DFNB49	MARVELD2	MARVEL domain-containing protein 2; tricellulin	Riazuddin et al. (2006a)
DFNB53	COL11A2	Collagen, type XI, alpha 2	Chen et al. (2005)
DFNB59	PJVK	Deafness, autosomal-recessive 59; pejvakin	Delmaghani et al. (2006)
	SLC26A5	Prestin	Liu et al. (2003)
Syndromic			
Alport syndrome			
X-linked	COL4A5	Type IV collagen alpha-5	Barker et al. (1990)
Autosomal-recessive	COL4A3	Collagen alpha-3(IV) chain	Mochizuki et al. (1994)
Autosomal-recessive	COL4A4	Collagen alpha-4(IV) chain	Mochizuki et al. (1994)
Branchio–oto–renal syndrome			
BOR1	EYA1	Eyes-absent homolog 1	Abdelhak et al. (1997)
BOR2	SIX5	Homeobox protein SIX5	Hoskins et al. (2007)
BOS3	SIX1	Sine-oculis homeobox homolog 1	Ruf et al. (2004)
Keratitis–ichthyosis–deafness syndrome (KID)	GJB2	Gap–junction beta-2 protein; connexin 26	Richard et al. (2002)
Jervell and Lange-Nielsen syndrome			
JLNS1	KCNQ1	Voltage-gated K^+ channel subfamily KQT member 1	Neyroud et al. (1997)
JLNS2	KCNE1	Voltage-gated K^+ channel, Isk-related family, member 1	Tyson et al. (1997) Schulze-Bahr et al. (1997)
Norrie disease	NDP	Norrin	Berger et al. (1992)

TABLE 37.1 Disorders of the ear—cont'd

Name	Gene	Gene product	Reference
Pendred syndrome			
	SLC26A4	Pendrin	Everett et al. (1997)
	FOXI1	Forkhead box protein I1	Yang et al. (2007)
Stickler syndrome			
STL1	COL2A1	Collagen alpha-1(II) chain	Ahmad et al. (1991)
STL2	COL11A1	Collagen alpha-1(XI) chain	Richards et al. (1996)
STL3	COL11A2	collagen, type XI, alpha-2	Vikkula et al. (1995)
STL4	COL9A1	Collagen alpha-1(IX) chain	Van Camp et al. (2006)
Treacher–Collins syndrome	TCOF1	Treacle protein	TCSCG (1996)
Usher syndrome			
USH1B	MYO7A	Myosin-7a	Weil et al. (1995)
USH1C	USH1C	Harmonin	Verpy et al. (2000)
USH1D	CDH23	Cadherin-like 23	Bolz et al. (2001)
USH1F	PCDH15	Protocadherin-15	Ahmed et al. (2001)
USH1G	SANS	Usher syndrome type-1 G protein	Mustapha et al. (2002)
USH2A	USH2A	Usherin	Eudy et al. (1998)
USH2C	VLGR1	G protein-coupled receptor 98	Weston et al. (2004)
USH2D	WHRN	Whirlin	Ebermann et al. (2007)
USH3	USH3	Clarin 1	Joensuu et al. (2001)
Vohwinkel syndrome	GJB2	Gap–junction beta-2 protein; connexin 26	Maestrini et al. (1999)
Waardenburg syndrome			
WS1/3	PAX3	Paired box protein Pax-3	Tassabehji et al. (1992) Baldwin et al. (1992) Hoth et al. (1993)
WS2A	MITF	Microphthalmia-associated transcription factor	Tassabehji et al. (1994)
WS2D	SNAI2	Zinc finger protein SNAI2; slug	Sanchez-Martin et al. (2002)
WS2E	SOX10	SRY-BOX 10; SOX10 transcription factor	Bondurand et al. (1999)
WS4A	EDNRB	Endothelin B receptor	Puffenberger et al. (1994)
WS4B	EDN3	Endothelin-3	Edery et al. (1996)
WS4C	SOX10	SRY-BOX 10	Pingault et al. (1998)
Muckle–Wells syndrome	NLRP3	NACHT, LRR, and PYD domain-containing protein 3	Hoffman et al. (2001)
Bartter syndrome and deafness (DFNB73)			
Type 4A	BSND	Barttin	(Birkenhager et al. (2001)
Type 4b	CLCNKA CLCNKB	Chloride channel ClC-Ka; CLCK1 Chloride channel ClC-Kb; CLCKB	Schlingmann et al. (2004) Schlingmann et al. (2004)

Continued

TABLE 37.1 Disorders of the ear—cont'd

Name	Gene	Gene product	Reference
Hypoparathyroidism, deafness, and renal dysplasia	GATA3	Trans-acting T-cell-specific transcription factor GATA-3	Van Esch et al. (2000)
Renal tubular acidosis with deafness	ATP6B1	V-type proton ATPase subunit B	Karet et al. (1999)
Microtia, hearing impairment, and cleft palate	HOXA2	Homeobox A2	Alasti et al. (2008)
Otopalatodigital syndrome (OPD1)	FLNA	Filamin A	(Robertson et al. (2003)

Compiled in part from Online Mendelian Inheritance in Man (OMIM); OMIM gene symbols are used throughout

retraction, among others. Congenital conductive hearing loss most often results from malformations of the middle ear that cause fixation or disruption of the ossicular chain. As a group, the conductive losses are relatively tractable, as the various forms can often be successfully treated with surgery.

Deafness with perilymphatic Gusher is an X-linked disorder that involves congenital mixed conductive and sensorineural hearing loss and is caused by mutation of Brain 4 (Brn4, or POU3F4), a POU-domain transcription factor expressed in the developing otic mesenchyme. The conductive hearing loss results from stapes fixation to the oval window (with the name of the disorder arising from perilymph that gushes out from the cochlea during surgery to free the stapes). The sensorineural hearing loss in the mouse model likely results from a critical role of *Brn4* in establishing the endocochlear potential. Female carriers have been reported to have milder hearing loss that may be conductive or sensorineural. Mutation of the T-box transcription factor gene TBX1 is associated with velocardiofacial syndrome/DiGeorge syndrome, which is often accompanied by chronic otitis media. In mice, *Brn4* has been shown to interact with *Tbx1* to specify cochlear structure (Braunstein et al., 2008).

Several syndromes involving joint disorders, such as Cushing symphalangism, multiple synostoses, and the recently described Teunissen–Cremers syndrome ('stapes ankylosis with broad thumbs and toes'), result in moderate conductive hearing loss. These disorders can be caused by mutations affecting noggin (NOG) or growth and differentiation factor 5 (GDF5), both of which interact with bone morphogenetic proteins (BMP) during development. The secreted signaling proteins BMPs and GDFs induce bone formation, whereas the BMP antagonist NOG halts cartilage production at the site of joint initiation and is thus a critical player in joint development. GDF5 gain of function mutations and NOG loss of function mutations are both associated with ossicular fixation. In heterozygous $Nog^{+/-}$ mice with varying degrees of hearing loss, impairment is associated with the presence of an extra bone fragment of the stapes that interferes with normal stapedial movement, and complete loss of *Nog* results in a more extreme phenotype with fused ossicles (Hwang and Wu, 2008). Thus, in the developing middle ear, *Bmp4*, *Gdf5*, and *Nog* may cooperate to establish the stapes and to separate it from the styloid process during ossicular development.

As much as 2% of profound deafness in childhood may be caused by the autosomal-dominant disorder branchio–oto–renal syndrome (BOR), which is characterized by branchial arch and renal abnormalities, together with variable hearing loss of sensorineural, conductive, or mixed origin. BOR can include structural anomalies of the external, middle, and inner ear and is associated with mutations of *Drosophila* eyes-absent homolog 1 (EYA1). In mouse, *Eya1* is expressed in adult hair cells, as well as in the developing mouse otocyst, and deletion of *Eya1* halts development at the otocyst stage. The *Eya1* gene product is a transcriptional coregulator that translocates to the nucleus together with sine-oculis *Six1*, and mutations in SIX1 result in both BOR and the closely related branchiootic syndrome 3 (BOS3) (Kochhar et al., 2007).

Cholesteatoma occurs when keratin-producing squamous epithelium develops within the temporal bone or middle ear; as this mass expands, it impinges on nearby structures, causing conductive hearing loss. This disorder, which can present in childhood or adulthood, most often occurs after otitis media or injury to the tympanic membrane, occurring as a uni- or bilateral conductive hearing loss, and may result from a genetic predisposition to otitis media. A rare congenital cholesteatoma has also been reported in cases of BOR and in adenomatous polyposis coli, a disorder associated with mutations of the adenomatous polyposis coli (APC) gene, multiple adenomatous polyps, and colorectal cancer. Several forms of nonsyndromic and syndromic hearing loss may involve chronic otitis media. For example,

sensorineural hearing loss DFNA10 is a postlingual progressive hearing loss that typically presents late, in at least the second decade. This disorder involves the eyes-absent homolog EYA4, and the *Eya4*$^{-/-}$ mouse model displays a predisposition to otitis media. Several additional, as yet unidentified genes that function during development to direct middle ear anatomy likely also result in a susceptibility to otitis media (Rye et al., 2011). The rare autosomal-dominant craniofacial disorder, Treacher–Collins syndrome, is often accompanied by conductive hearing loss due to abnormalities of the ossicular chain. The syndrome is caused by a mutation affecting the nucleolar phosphoprotein treacle (TCOF1), which controls ribosome production and is required for proliferation of neural crest cells.

Semicircular canal dehiscence is a rare condition in which an opening in the bone of the semicircular canal effectively creates a third window in the inner ear. This extra outlet acts as a relief valve, such that oval window vibrations that would normally drive only the cochlear perilymph toward the round window are transmitted in part toward this third window, stimulating the vestibular organs. In patients with this condition, acoustic stimuli or fullness of the middle ear can produce dizziness and nystagmus. Otopalatodigital syndrome and frontometaphyseal dysplasia are X-linked skeletal dysplasias that also result in moderate to profound conductive deafness and are linked to the actin-binding protein filamin A (FLNA). Finally, congenital atresia of the oval window and perilymph fistula (loss of perilymph into the middle ear) are rare conductive disorders of unknown etiology.

37.2.2.2 *Hereditary Sensorineural Hearing Loss*

Sensorineural hearing loss is most commonly related to defects within the cochlea, though a small percentage of hearing loss is more central. The mammalian inner ear, encased in the temporal bone, comprises six sensory organs: five belonging to the vestibular system and one, the cochlea, to the auditory system. The cochlea coils about 2.5 times in humans (less in certain disorders), narrowing toward its apex, and in cross section is divided into three fluid-filled ducts that run in parallel nearly the length of the coiled cochlea. Two of these ducts, the perilymph-filled scala vestibuli and scala tympani, join at the apical end of the cochlea to form a continuous chamber with the oval window at one end and the membranous round window at the other. The endolymph-filled scala media is sandwiched between the scalae vestibuli and tympani and contains the receptor organ itself, the organ of Corti, which comprises the mechanosensitive hair cells – one row of inner hair cells, the actual sensory receptor cells along the inside of the cochlear spiral, and three rows of outer hair cells that provide cochlear amplification – as well as several types of supporting cells. Each hair cell is a polarized neuroepithelial cell whose apical, mechanotransducing pole contains the stereocilia hair bundle, and whose basal, synaptic pole is surrounded by supporting cells of the basilar membrane. The stereocilia project into the endolymph, and the tallest stereocilia of the outer hair cells are inserted in the tectorial membrane, a gelatinous extracellular matrix. At the inner, coiled, core of the cochlea lies the spiral ganglion, containing the cell bodies that give rise to the afferent fibers of the auditory nerve.

Vibrations of the oval window are transmitted to the perilymph in the scala vestibuli, setting up a traveling wave that propagates along the basilar membrane, which is tuned by mechanical properties along its length to map low-frequency sounds near the apex and high-frequency sounds near the base of the cochlea. The traveling wave at the basilar membrane induces movement relative to the hair cell bundle. Tethered only at one end, the tectorial membrane can move in part independently of the organ of Corti, and the shearing motion of the tectorial membrane against the organ of Corti causes deflection of the hair bundles. Outer hair cells actively amplify the cochlear mechanics through a mechanism that is still controversial.

Inward current through the mechanoelectrical transduction channels produces a receptor potential that alters the tonic release of glutamate at the hair cell–ganglion cell synapse; the majority of hair cells innervated by ganglion cells of the cochlear nerve are inner hair cells. The active mechanical properties of the cochlea cause the healthy cochlea to emit faint sounds, both spontaneously and in response to auditory stimuli. These otoacoustic emissions (OAEs) can be recorded and used clinically to assess outer hair cell motility and/or to identify whether the site of hearing loss is cochlear. As a noninvasive test that does not require a behavioral response, OAE recording is also commonly used to screen newborns for hearing loss. Central dysfunction is indicated by abnormal auditory brainstem responses (ABRs), auditory evoked potentials recorded at surface electrodes. Auditory neuropathy refers to any one of several forms of nonsyndromic sensorineural hearing loss in which the deficit is localized to the inner hair cell–ganglion cell synapse, or to neurons of the auditory nerve and auditory brain stem.

37.2.2.3 *Hearing Loss and the Tectorial Membrane*

The longest stereocilia of each outer hair cell contact the tectorial membrane, a specialized extracellular matrix consisting of collagen fibril bundles, together with three non-collagenous glycoproteins – otogelin, α-tectorin, and β-tectorin – that are expressed only in the inner ear. As mRNA for both tectorins is only transiently expressed during cochlear development, whatever form the tectorial membrane takes during that

period likely persists for the lifetime of the organism. Though loss of otogelin in mouse causes early vestibular dysfunction, followed by a variable, progressive hearing loss and subtle abnormalities of the tectorial membrane, no human deafness associated with otogelin mutations has yet been identified (Simmler et al., 2000). In contrast to the subtle changes caused by the lack of otogelin, the absence of α-tectorin results in a failure to form the striated sheet matrix, the non-collagenous portion of the tectorial membrane. Mutations affecting α-tectorin (TECTA) are found in prelingual mid-frequency hearing loss of mild to profound severity, in both autosomal-dominant (DFNA8/12) and autosomal-recessive (DFNB21) forms of nonsyndromic hearing loss. In animal models lacking α-tectorin, otogelin and β-tectorin are not incorporated in the tectorial membrane and the tectorial membrane fails to associate normally with the spiral limbus and the organ of Corti, with the result that basilar membrane sensitivity is reduced and OAEs are abolished (Legan et al., 2000). To date, no mutations affecting β-tectorin (TECTB) have been associated with human hearing loss, though loss of *Tectb* in mouse results in a low-frequency hearing loss.

Two additional genes expressed uniquely in the inner ear are associated with sensorineural hearing loss. Otoancorin (OTOA) mutations associate with moderate to severe prelingual autosomal-recessive hearing loss DFNB22. Otoancorin is expressed at the apical surface of supporting cells adjacent to hair cells, but its role at the interface between the tectorial membrane and the sensory epithelium remains to be identified. Stereocilin (STRC) localizes to the distal portion of outer hair cell stereocilia. In humans, STRC mutations are associated with the early postlingual hearing loss DFNB16. In the mouse model $Strc^{-/-}$, which also experiences early hearing loss, the stereocilia array is established, but without the apical connectors between stereocilia or the links attaching stereocilia to the tectorial membrane, the stereocilia array rapidly deteriorates (Verpy et al., 2011).

37.2.2.4 *Hypothyroidism and Hearing Loss*

Congenital hypothyroidism in humans has been associated with a range of conductive and sensorineural hearing loss. Though none of these pathologies is entirely clear, animal studies point to a few possible pathways for hypothyroidism-induced hearing loss. The transcription factors thyroid receptor TRα1 (*Thra*) and T3 thyroid receptor TRβ (*Thrb*) are variably expressed during embryogenesis in the cochlea, *Thra* throughout the cochlea, and *Thrb* at high levels in the organ of Corti and at lower levels in the stria vascularis. Embryonic hypothyroidism delays development of the organ of Corti and prevents the normal transient developmental upregulation of β-tectorin mRNA. The Snell dwarf *Pou1f* ^{dw} mouse model highlights several effects of congenital hypothyroidism: (1) the tectorial membrane is abnormal, possibly due to altered β-tectorin expression; (2) KCNQ4 expression and function in outer hair cells is reduced; and (3) the endocochlear potential is decreased due to reduced expression of the inwardly rectifying K^+ channel KCNJ10 in intermediate cells of the stria vascularis (Mustapha et al., 2009).

37.2.2.5 *Pendred Syndrome*

Pendred syndrome (deafness with goiter) is the most common syndromic form of deafness, accounting for up to 7.8% of cases of congenital deafness and occurring in an estimated 7.5 of 100,000 births. Patients inheriting this autosomal-recessive disorder have variable degrees of deafness at birth and typically develop goiter in the second decade. The syndrome is accompanied by structural defects of the temporal bone such as Mondini dysplasia and enlarged vestibular aqueduct (EVA) that are likely driven in part by accumulation of endolymph. The vestibular aqueduct, embedded within the temporal bone, is a small canal containing the endolymphatic duct and extending from the vestibule between the cochlea and the labyrinth to the endolymphatic sac. In Mondini dysplasia, the apical turn of the cochlea fails to form, and patients are profoundly deaf at birth. In EVA, vestibular dysfunction may be present and the hearing loss is variable. The mutated Pendred syndrome gene PDS (SLC26A4) is a member of the solute carrier protein 26 anion transporter family, and the gene product pendrin is a transmembrane $Cl^-/I^-/HCO_3^-$ transporter. Allelic heterogeneity produces some SLC26A4 variants with Pendred syndrome and others with non-syndromic deafness with EVA (DFNB4).

Pendrin is expressed in the inner ear and kidney, and in the thyroid, where it mediates apical iodide transport in thyroid follicular cells (Kopp et al., 2008). Although Pendred syndrome is sometimes accompanied by hypothyroidism that could itself contribute to hearing loss, the distribution of the mouse pendrin throughout the endolymphatic duct and sac, and in specific areas of utricle, saccule, and external sulcus, points to a specific role of pendrin in fluid resorption and in regulating the ionic composition of the cochlear endolymph. The cochlear endolymph of the scala media is a unique extracellular fluid of high K^+ concentration and low Na^+ and Ca^{2+} concentrations. The unusual ionic makeup of the cochlear endolymph gives rise to a positive 'endocochlear potential' of about +80 mV and provides the driving force responsible for the large receptor potentials recorded from inner hair cells. Maintaining the ionic composition of the endolymph that underpins the endocochlear potential is critical to the generation of receptor potentials; this is a primary role of the stria vascularis, the extensively vascularized epithelium in the lateral wall of the scala media (Hibino et al., 2010).

Loss of pendrin in the knockout *Pds*$^{-/-}$ mouse leads to a thinned stria vascularis and a markedly reduced endocochlear potential. The Pendred syndrome alleles cause a complete loss of function, due to the retention of pendrin protein in the endoplasmic reticulum, whereas the nonsyndromic EVA alleles result in reduced anion transport and a less severe phenotype. In the absence of pendrin, both *Kcnj10* expression in the stria vascularis and the endocochlear potential are lost in early postnatal life. The decreased K^+ concentration of *Pds*$^{-/-}$ endolymph may be explained by the loss of *Kcnj10* expression, while the increased Ca^{2+} concentration results from disruption of pendrin-mediated transport of HCO_3^- into the endolymph. Loss of HCO_3^- exchange lowers the pH of the endolymph and can inhibit TRPV5/6 Ca^{2+} channels, increasing the endolymphic Ca^{2+} concentration (Nakaya et al., 2007). The winged helix/forkhead protein *Foxil* has similar expression patterns to pendrin and may be an upstream regulator, as *Foxil*$^{-/-}$ mice lack pendrin transcripts and display an enlarged endolymphatic chamber. Mutations of FOXI1 are also found in human patients with Pendred syndrome or nonsyndromic enlarged vestibular aqueduct.

To maintain the endolymphic concentration necessary for transduction, K^+ must be actively recycled; K^+ exits the hair cells and diffuses through the perilymph to the lateral wall, where it is transported by N^+–K^+–ATPase and/or Na^+–K^+–Cl^- cotransporter (NKCCl) into the stria vascularis, from which it is reintroduced into the endolymph by the voltage-gated K^+ channel KCNQ1. NKCCl is expressed during development in the stria vascularis and in immature epithelial cells lining the developing scala media, and its removal causes the collapse of the cochlear ducts. Mutations of KCNQ1 are also associated with the cardio-auditory Jervell and Lange-Nielsen syndrome, an autosomal-recessive disorder characterized by congenital deafness, prolonged QT syndrome, ventricular arrhythmia, and sudden death (Wangemann, 2006). Mouse models of this disorder display similar, though somewhat variable, defects.

Autosomal-dominant deafness DFNA2A – mild to severe progressive hearing loss with widely variable age of onset (early childhood to sixth decade) and occasional tinnitus – is associated with mutations affecting the voltage-gated potassium channel KCNQ4. In mouse, the native *Kcnq4* is expressed at high levels at the base of outer hair cells, where it forms a depolarization-activated K^+ channel with relatively slow kinetics. The slow progressive hearing loss seen in *Kcnq4*$^{-/-}$ mice may be due to degeneration of outer hair cells that are chronically depolarized (Kharkovets et al., 2006).

Mutations involving the connexins Cx26 (GJB2) and Cx30 (GJB6) may account for half of all cases of prelingual autosomal-recessive hearing loss, with loss of Cx26/30 leading to hair cell degeneration and subsequent degeneration of the spiral ganglion cells. The precise functions of Cx26 and 30 in the inner ear are unknown, though they are important for maintaining the high K^+ concentration of the endolymph. Cx26 and Cx30 are both highly expressed in adults in the supporting cells of the organ of Corti and in the stria vascularis, and though the connexins are not found in the developing hair cells themselves, both connexins are required for the survival of hair cells and the organ of Corti. Extensive gap junction coupling in the neonatal organ of Corti is likely supported by Cx26/30 gap junctions; the function of this coupling is unknown. In mice lacking Cx30, the capillary endothelial barrier in the stria vascularis breaks down, the endocochlear potential disappears, and the hair cells degenerate (Cohen-Salmon et al., 2007).

The SLC26 family protein prestin (SLC26A5), which is closely related to pendrin, is linked to mild to profound hearing loss DFNB61, presenting from birth to the fourth decade. Prestin is expressed specifically in cochlear outer hair cells, where it functions as an anion transporter in the lateral membrane of outer hair cells. Electromotility, the hair cells' ability to change shape in an applied electric field, is driven by a physical change in the lateral membrane of outer hair cells and underlies cochlear amplification. Prestin is likely the critical voltage-driven motor protein for electromotility, and the loss of prestin and hair cell electromotility may yield a loss in cochlear amplification of 40–60 dB (Liu et al., 2003).

37.2.2.6 *Other Hearing Disorders*

Although hereditary hearing loss affecting primarily low frequencies (<2 kHz) is rare, a few distinct forms have been reported. The nonsyndromic hearing loss DFNA1 is an autosomal-dominant sensorineural disorder that manifests at about 10 years with low-frequency hearing loss and progresses to entail profound deafness at all frequencies by age 30. The disorder results from mutations affecting the homolog of *Drosophila* diaphanous (DIAPH1), which is widely expressed in many tissues in addition to the cochlea. As diaphanous is a member of the family of highly conserved formin proteins, which stabilize microtubules and regulate actin nucleation and elongation (Chesarone et al., 2010), the disorder likely affects the actin skeleton of hair cells or stereocilia. A second form of low-frequency sensorineural deafness, DFN6/14/38, results in moderate hearing loss with occasional tinnitus. Little is known of the pathology of this disorder, which involves wolframin (WFS1), a membrane glycoprotein found at the endoplasmic reticulum.

Several forms of inherited hearing loss are associated with mutations in mitochondrial DNA and can present as prelingual or postlingual hearing loss. In particular, Mohr–Tranebjaerg syndrome (MTS), or dystonia–deafness

syndrome, is an X-linked progressive syndrome (DFN1) involving early postlingual hearing loss and dystonia that can also be accompanied by myopia, cortical blindness, and mental impairment. The mutation is due to a loss of function in the TIMM8A gene (translocase of inner mitochondrial membrane 8), but the mechanism of hearing loss is unknown. Additional disorders linked to mutations in mitochondrial genes include diabetes–deafness syndrome, Ballinger–Wallace syndrome, multisystem disorder, and a number of nonsyndromic sensorineural deafness disorders.

37.2.2.7 *Auditory Neuropathy*

Auditory neuropathy accounts for about 10% of profound childhood hearing loss. Some of the major preventable causes of auditory neuropathy include anoxia, certain infectious diseases, and hyperbilirubinemia. Neonatal hyperbilirubinemia is easily treatable, but it is also common, and bilirubin neurotoxicity may account for 50% of all cases of auditory neuropathy. Various genetic mutations underlying auditory neuropathies of mild to profound hearing loss have also been identified.

One of the first auditory neuropathy genes identified was found in a candidate gene search for the profound prelingual hearing loss DFNB9 (Yasunaga et al., 1999). The membrane-anchored Ca^{2+}-binding protein otoferlin (OTOF) is expressed in hair cells and in the spiral ganglion during development in the mouse, and in adult localizes to vesicles of the ribbon synapses at the basal pole of the inner hair cells. Though otoferlin is not required for the development of ribbon synapses, it is required both for Ca^{2+}-dependent exocytosis at ribbon synapses of inner hair cells and at ribbon synapses that are transiently expressed during development at the outer hair cells. Otoferlin mutations may also result in minor defects in hair bundle structure.

The postlingual progressive hearing loss of variable severity DFNA15 is linked to mutations in POU4F3. *Brn-3.1*, a member of the Class IV POU-domain transcription factor family, is expressed exclusively in hair cells of the inner ear; *Brn-3.1*$^{-/-}$ mice show severe balance deficits and are completely deaf at a young age. In *Brn-3.1*$^{-/-}$ mice, the overall structure of the cochlea and spiral ganglion is normal at birth, but the hair cells do not differentiate and extend stereocilia; within a short period, the hair cells and supporting cells of the cochlea and the neurons of the spiral ganglion, degenerate (Erkman et al., 1996). Brn-3.1 likely mediates terminal differentiation of the hair cells, and the failure of hair cell differentiation may lead to secondary degeneration of supporting cells and postsynaptic neurons.

Glutamate release at the synapse between inner hair cell and spiral ganglion cell requires the vesicular glutamate transporter VGLUT3 (SLC17A8), and mutation of the SLC17A8 gene in humans is associated with the progressive sensorineural hearing loss DFNA25. Loss of SLC17A8 in mouse results in deafness, seizing, and deficits in central auditory circuit refinement; the central deficits may be due to a role for VGLUT3 in inhibitory synapse maturation (Seal et al., 2008). The gene for SLC17A8 is one of a few known to have effects both early in the cochlea and more centrally in the auditory pathway. Another is pejvakin (Persian for "echo"), which is associated with recessive auditory neuropathy DFNB59, causing prelingual severe hearing impairment. Pejvakin is expressed in cell bodies in the cochlea, spiral ganglion, and neuronal subpopulations in the auditory brain stem and midbrain in mouse, and though the function is unknown, the pathology likely affects both outer hair cells and downstream auditory pathways.

Charcot–Marie–Tooth disease describes a diverse group of inherited peripheral neuropathies, with onset in the first or second decade, of which the most common is the demyelinating form CMT1. About 5% of patients with CMT exhibit sensorineural hearing loss, with a likely locus in the cochlear nerve, specifically those with point mutations or deletions in the genes for peripheral myelin protein 22 (PMP22), myelin protein zero (MPZ), or connexin-32 (GJB1).

37.3 MIXED AUDITORY AND VISUAL IMPAIRMENT – USHER SYNDROME

Hereditary deafness–blindness in its most common form, Usher syndrome, is an autosomal-recessive disorder that involves bilateral sensorineural hearing loss and retinitis pigmentosa, in addition to vestibular deficits in some cases. Over half of all cases of hereditary deafness–blindness are associated with Usher syndrome, which has an estimated global prevalence of 1:16,000–1:50,000. The three clinically recognized subtypes of the syndrome are distinguished from one another by severity of hearing loss, age of onset of retinitis pigmentosa and the presence or absence of vestibular dysfunction. Usher syndrome types 1 and 2 are most common, type 1 being more severe and type 2 more frequent. Patients with the rarer form of type 3 Usher syndrome exhibit progressive hearing loss of intermediate severity, together with vestibular dysfunction and retinitis pigmentosa of varying severity and onset. Examination of the hair cells in Usher syndrome reveals significant disorder of the hair bundles, and the syndrome is considered a ciliopathy, as the primary deficit is at hair cell stereocilia in the cochlea and at the ciliated stalk connecting inner and outer photoreceptor segments in the retina.

Usher syndrome can result from mutations in any one of at least nine genes, all of which are involved in the

organization of the stereocilia during development of the hair bundle. The stereocilia are not true cilia, but rather are specialized microvilli formed of tightly packed cross-linked actin filaments. During development, however, each hair bundle expresses a single true cilium, the kinocilium, which in mammalian cochlear hair cells eventually degenerates. During early development of the hair bundle, a central kinocilium, surrounded by microvilli at apparently random locations, is first extended at the apical pole of the hair cell. The kinocilium migrates to one side of the hair bundle, and then the kinocilia of all hair cells align to the same side of their hair cells. A height-ordered array of stereocilia begins to form, with those stereocilia nearest the kinocilium elongating first, followed sequentially by stereocilia farther removed from the kinocilium, and an organized, hexagonal array of stereocilia forms, in stepwise order of increasing height. Stereocilia are continually extended from the apical surface during this period, many to be later resorbed. Once elongation is complete, the addition of actin filaments to the stereocilia increases stereocilia width, the stereocilia extend actin rootlets into the cytoplasm of the hair cell, and the basal ends of the stereocilia taper to a point (Goodyear et al., 2006; Tilney et al., 1992).

Mature stereocilia are linked at their apical tips by tip links, filamentous strands oriented in parallel with the direction of hair bundle deflection that connect the tip of each stereocilium to the side of its taller, adjacent stereocilium. In addition to the tip links, several additional filamentous links between stereocilia are also expressed, especially during development. In the E17.5 mouse, lateral links, tip links, and some kinociliary links are present. Ankle links appear at around P2 and remain until about P9. The different links can be distinguished by their position along the stereocilia, from apical tip to basal ankle, and by their distinct antibody binding.

37.3.1 Usher Syndrome Type 1

Individuals with USH1 typically exhibit severe hearing loss (≥90 dB) and vestibular dysfunction at birth. Balance problems contribute to an average 12-month delay in walking, and onset of retinitis pigmentosa occurs before puberty. Although Usher type 1 is genetically heterogeneous, all identified relevant gene products are expressed in cochlear hair cells, where they function during development to organize and hold together the hair bundle. The five known gene products are myosin VIIa (USH1B), an actin-based motor protein, harmonin (USH1C), cadherin 23 (USH1D), protocadherin-15 (USH1F), and the putative scaffolding protein Sans (USH1G). Harmonin can bind to F-actin, as well as to the four other USH1 proteins. Harmonin, cadherin 23, and protocadherin-15 are expressed at the hair bundle as soon as stereocilia are extended, and cadherin 23 and protocadherin-15 together form the tip link connecting the tip of one stereocilia to its taller neighbor. The various *Pcdh15* isoforms differ in sites of expression along the stereocilia and in timing of expression during development, and may direct distinct aspects of hair bundle development. Myosin VIIa is expressed throughout the hair cell, and likely plays several roles in development of the hair bundle. One function involves directing harmonin to its appropriate position on the stereocilia, as harmonin remains at the base of the hair bundle in the absence of *Myo7a* (Boeda et al., 2002). Sans function is less well understood; this transiently expressed protein can interact with myosin VIIa or with harmonin and may be a component of the developmentally expressed lateral links.

37.3.2 Usher Syndrome Type 2

Usher syndrome type 2, which accounts for 3–6% of congenital hearing loss, is characterized by mild congenital nonprogressive hearing loss, onset of retinitis pigmentosa in the first to second decades, and a lack of vestibular dysfunction. Three causative genes have been identified for USH2; all proteins are expressed in the cochlea during development. Type 2A, the most common form of Usher syndrome, results from mutations in usherin (USH2A), type 2C from mutations in GPR98, and type 2D from mutations in whirlin (WHRN).

The highly conserved 600 kDa long usherin variant is transiently associated with the growing stereocilia of inner and outer hair cells. The long isoform, found in both retina and inner ear, contains a PDZ-binding motif on its cytoplasmic tail, as do harmonin b and whirlin, which are also present in the differentiating hair bundle. GPR98 (VLGR1) is a transmembrane, calcium-binding G protein-coupled receptor that is transiently expressed at the base of the hair bundle during development. Both usherin and Vlgr1 bind to whirlin and myo7a, and association of Vlgr with usherin allows the formation of the ankle links at the base of the hair bundle. Ankle links are required for controlling the shape of the hair bundle, and loss of Vlgr during development leads to reduced transduction currents in the outer hair cells, alteration of the overall hair bundle structure, and deafness. Whirlin localizes to the stereocilia tips, where it interacts with myo15a or with myo7a in the control of stereocilia length during the growth of the hair bundle. In mice, targeted N-terminus whirlin mutants exhibit loss of both vision and hearing, whereas C-terminus mutants exhibit an isolated auditory disorder (Yang et al., 2010).

37.3.3 Usher Syndrome Type 3

Type 3 (USH3) is a relatively rare form of Usher syndrome reported primarily in Finland and among Ashkenazi Jewish populations, usually diagnosed in

the first decade. The disorder results from mutations in the transmembrane protein clarin-1 (CLRN1), most instances occurring due to a single amino acid substitution that affects glycosylation and membrane insertion of the protein. *Clarin-1* is expressed transiently in the cochlea during development, and in Muller cells of the retina. In the Clrn1 knockout mouse, loss of clarin-1 results in disorganized stereocilia of the outer hair cells, followed by slow progressive disorganization of the hair bundle and age-related stereocilia lengthening and eventual hair cell degeneration, leading to vestibular dysfunction and complete loss of hearing (Geller et al., 2009). The protein's ability to interact with cell adhesion molecules and induce actin filament reorganization suggests that the pathology results from disruption of interactions between cell-adhesion molecules and the actin cytoskeleton.

37.3.4 Retinitis Pigmentosa in Usher Syndrome

As this disease is characterized by the progressive degeneration of the rod photoreceptors, the cone photoreceptors, and finally retinal pigment epithelium (RPE) cells, patients present first with night blindness (nyctalopia). Progressive loss of peripheral vision leads to tunnel vision, whereas central vision (color and high acuity) may be compromised after a variable period. The pigment deposits for which the disorder is named appear late in the disease, after photoreceptors degenerate and cells of the RPE detach and migrate through the eye (Milam et al., 1998).

The ciliary defect in hearing loss in Usher syndrome, and the existence of a ciliary stalk between the inner and outer segments of retinal photoreceptors, points to photoreceptors as the primary site of the visual deficit in Usher syndrome, and the first measurable retinal loss in humans with USH 1B, 1 F, 2A, and 2C is of photoreceptors. Despite the existence of various animal models for Usher syndrome, an ongoing challenge has been that affected animals exhibit hearing loss and vestibular dysfunction but most mouse models fail to develop the retinitis pigmentosa characteristic of Usher syndrome in humans. Additionally, many well-known mouse models of deafness (e.g., waltzer, shaker-1, deaf circler, Ames waltzer, and Jackson shaker) possess mutated USH1 genes and exhibit vestibular but not visual impairment. In the retina, usherin is expressed at all ages at the connecting cilium in photoreceptors, and one promising development is the mouse model for USH2A, which loses large numbers of photoreceptors (Liu et al., 2007).

37.4 VISUAL IMPAIRMENT

Many historical forms of childhood blindness have been largely eradicated in middle- and high-income countries, and are being eliminated from low-income countries, where programs combating measles and vitamin A deficiency have been especially successful. Corneal disorders still account for 19% of childhood blindness worldwide, however, and are disproportionately common in the developing world, amounting to perhaps 1% of all cases of blindness in the highest income regions and as much as 36% of all cases in sub-Saharan Africa (Gilbert, 2009). Most of these cases are preventable, resulting from vitamin A (retinol) deficiency, measles, and/or use of traditional treatments. Prenatal or neonatal lack of dietary vitamin A, increased demand for vitamin A during infection, and malabsorption of vitamin A due to illness can singly or together lead to retinol deficiency, a risk factor for xerophthalmia (dry eye), which commonly leads to corneal ulceration and scarring. Corneal ulceration and scarring can also result from measles infection, an effect that is potentiated if vitamin A deficiency is already present.

Microphthalmia, an abnormally small eye with normal structure, develops in response to genetic or environmental factors, and may be present in as much as one-tenth of all childhood blindness. Microphthalmia most often occurs bilaterally as part of a heritable syndrome, and most of the genes linked to this disorder code for transcription factors and homeobox genes involved in early development of the eye, for example in neuronal differentiation, proliferation of retinal progenitor cells, or formation of the lens placode. Some of the known genes include transcription factor SOX-2 (SOX2), retina homeobox protein Rx (RAX), and visual system homeobox 2 (VSX, also CHX10), among others (see Table 37.2).

37.4.1 Disorders of the Anterior Segment

The anterior segment of the eye includes the cornea, iris, and lens, together with their supporting structures. As the first structure through which light passes, and as part of the interface with the most refractive power, the cornea occupies a special position; hence, environmental insults or genetic disorders that affect the cornea can profoundly affect visual sensation. Transparency of the lens also plays a critical role in conducting light to the retina. Disorders of the anterior segment can commonly include glaucoma of unknown etiology. Aniridia, for example, the complete or partial absence of the iris, may occur with glaucoma, as well as with cataracts or photophobia. Aniridia is associated with over 100 different mutations of the transcription factor paired box 6 (PAX6), which is linked to several additional disorders of abnormal eye development, such as morning glory disc (a dysplasia of the optic disc), ectopic pupil, optic nerve hypoplasia, and foveal hypoplasia. Corneal dystrophy refers to a group of disorders that lead to accumulation of deposits in the corneal layers and to a loss of corneal transparency; depending on the specific type of dystrophy, the

TABLE 37.2 Disorders of the eye

Name	Gene	Gene product	Reference
Microphthalmia			
MCOPCT2	SIX6	Homeobox protein SIX6	Gallardo et al. (2004)
MCOP3	RAX	Retina homeobox protein Rx	Voronina et al. (2004)
MCOP5	MFRP	Membrane frizzled-related protein	Sundin et al. (2005)
MCOPS2	BCOR	BCL-6 corepressor	Ng et al. (2004)
MCOPS3	SOX2	Transcription factor SOX-2	Fantes et al. (2003)
MCOPS5	OTX2	Orthodenticle homeobox 2	Ragge et al. (2005)
MCOPS6	BMP4	Bone-morphogenic protein 4	Bakrania et al. (2008)
MCOPS7	HCCS	Holocytochrome c synthase	Wimplinger et al. (2006)
MCOPS9	STRA6	Stimulated by retinoic acid gene 6 protein	Pasutto et al. (2007)
Corneal dystrophy			
CHED2	SLC4A11	Sodium bicarbonate transporter-like protein 11	Vithana et al. (2006) Desir et al. (2007)
CDGDL	TACSTD2	Tumor-associated calcium signal transducer 2	Tsujikawa et al. (1999)
MECD	KRT3 KRT12	Keratin 3 Keratin 12	Irvine et al. (1997)
Congenital cataract			
	CRYAA	Alpha crystallin A	Litt et al. (1998)
	CRYAB	Alpha crystallin B	Berry et al. (2001)
	CRYBA1	Beta crystallin A1	Kannabiran et al. (1998)
	CRYBB1	Beta crystallin B1	Cohen et al. (2007)
	CRYBB2	Beta crystallin B2	Litt et al. (1997)
	CRYGC	Gamma C crystallin	Heon et al. (1999)
	CRYGD	Gamma D crystallin	Nandrot et al. (2003)
	CRYGS	Gamma S crystallin	Sun et al. (2005)
Retinitis pigmentosa			
RP1	RP1	Retinitis pigmentosa RP1 protein	Pierce et al. (1999) Sullivan et al. (1999)
RP2	RPGR	Retinitis pigmentosa 2	Schwahn et al. (1998)
RP3	RPGR	Retinitis pigmentosa GTPase regulator	Meindl et al. (1996)
RP4	RHO	Rhodopsin	Dryja et al. (1990) Humphries et al. (1997)
RP7	PRPH2 ROM1	Peripherin-2 (retinal degeneration slow) Rod outer segment protein 1	Farrar et al. (1991) Kajiwara et al. (1994)
RP8	MTTS2	tRNA, mitochondrial, serine, 2	Mansergh et al. (1999)
RP9	RP9	Retinitis pigmentosa 9 protein	Keen et al. (2002)
RP10	IMPDH1	Inosine-5′-monophosphate dehydrogenase 1	Bowne et al. (2006)
RP11	PRPF31	Pre-mRNA processing factor 31	Vithana et al. (2001)
RP12	CRB1	Crumbs homolog 1	den Hollander et al. (1999)

Continued

TABLE 37.2 Disorders of the eye—cont'd

Name	Gene	Gene product	Reference
RP13	PRPF8	Pre-mRNA-processing factor 8	McKie et al. (2001)
RP14	TULP1	Tubby-related protein 1	Hagstrom et al. (1998)
RP17	CA4	Carbonic anhydrase IV	Rebello et al. (2004)
RP18	PRPF3	Pre-mRNA-processing factor 3	Chakarova et al. (2002)
RP19	ABCA4	Retina-specific ATP-binding cassette transporter	Rozet et al. (1999)
RP20	RPE65	Retinoid isomerohydrolase	Gu et al. (1997)
RP25	EYS	Eyes-shut homolog	Abd El-Aziz et al. (2008)
RP26	CERKL	Ceramide kinase-like	Tuson et al. (2004)
RP27	NRL	Neural retina-specific leucine zipper protein	Bessant et al. (1999)
RP30	FSCN2	Fascin 2	Wada et al. (2001)
RP31	TOPORS	E3 ubiquitin–protein ligase Topors	Chakarova et al. (2007)
RP33	SNRNP200	Small nuclear ribonucleoprotein 200 kDa	Zhao et al. (2009)
RP35	SEMA4A	Semaphorin-4A	Abid et al. (2006)
RP36	PRCD	Progressive rod–cone degeneration, dog, homolog	Zangerl et al. (2006)
RP37	NR2E3	Photoreceptor-specific nuclear receptor	Coppieters et al. (2007)
RP38	MERTK	MER tyrosine kinase	Gal et al. (2000)
RP39	USH2A	Usherin	Rivolta et al. (2000)
RP40	PDE6B	Rod cGMP-specific cyclic phosphodiesterase, beta subunit	McLaughlin et al. (1993)
RP41	PROM1	Prominin 1	Maw et al. (2000)
RP42	KLHL7	Kelch-like protein 7	Friedman et al. (2009)
RP43	PDE6A	Rod cGMP-specific cyclic phosphodiesterase alpha subunit	Huang et al. (1995)
RP44	RGR	Retinal G-protein coupled receptor	Morimura et al. (1999)
RP45	CNGB1	Cyclic nucleotide-gated channel beta 1	Bareil et al. (2001)
RP46	IDH3B	Isocitrate dehydrogenase 3 beta subunit	Hartong et al. (2008)
RP47	SAG	S-antigen; S-arrestin	Nakazawa et al. (1998)
RP48	GUCA1B	Guanylate cyclase activator 1B	Sato et al. (2005)
RP49	CNGA1	Cyclic nucleotide gated channel alpha 1	Dryja et al. (1995)
RP50	BEST1	Bestrophin 1	Davidson et al. (2009)
Juvenile, AR	SPATA7	Spermatogenesis associated 7	Wang et al. (2009)
Newfoundland rod–cone	RLBP1	Retinaldehyde-binding protein 1	Eichers et al. (2002)
Cone–rod dystrophy			
CORD2	CRX	Cone–rod homeobox protein	Freund et al. (1997)
CORD3	ABCA4	Retina-specific ATP-binding cassette transporter Rim)	(Cremers et al. (1998)
CORD5	PITPNM3	Phosphatidylinositol transfer protein, membrane-associated 3	Kohn et al. (2007)
CORD6	GUCY2D	Retinal guanylyl cyclase 1	Kelsell et al. (1998)
CORD7	RIMS1	Protein-regulating synaptic membrane exocytosis 1	Johnson et al. (2003)
CORD9	ADAM9	A disintegrin and metalloproteinase domain 9	Parry et al. (2009)

TABLE 37.2 Disorders of the eye—cont'd

Name	Gene	Gene product	Reference
CORD10	SEMA4A	Semaphorin-4A	Abid et al. (2006)
CORD12	PROM1	Prominin 1	Yang et al. (2008)
CORD13	RPGRIP1	Retinitis pigmentosa GTPase regulator-interacting protein	Hameed et al. (2003)
CORD14	GUCA1A	Guanylate cyclase activator 1A	Payne et al. (1998)
CORD15	CDHR1	Cadherin-related family member 1; photoreceptor cadherin	
CORDX1	RPGR	Retinitis pigmentosa GTPase regulator	Demirci et al. (2002)
CORDX3	CACNA1F	Voltage-dependent L-type Ca^{2+} channel, alpha-1 F; Cav1.4	Jalkanen et al. (2006)
Early-onset severe	LRAT	Lecithin retinol acyltransferase	Thompson et al. (2001)
Stargardt disease			
STGD1	ABCA4 CNGB3	Retina-specific ATP-binding cassette transporter Cyclic nucleotide-gated cation channel beta-3	Allikmets et al. (1997) (Nishiguchi et al., 2005)
STGD3	ELOVL4	Elongation of very long chain fatty acids protein 4	Zhang et al. (2001)
STGD4	PROM1	Prominin 1	Yang et al. (2008)
Leber congenital amaurosis			
LCA1	GUCY2D	Retinal guanylate cyclase	Perrault et al. (1996)
LCA2	RPE65	Retinoid isomerohydrolase	Marlhens et al. (1997)
LCA3	SPATA7	Spermatogenesis-associated protein 7	Wang et al. (2009)
LCA4	AIPL1	Aryl–hydrocarbon-interacting protein-like 1	Sohocki et al. (2000)
LCA6	RPGRIP1	Retinitis pigmentosa GTPase regulator-interacting protein	Dryja et al. (2001)
LCA7	CRX	Cone–rod homeobox protein	Freund et al. (1997)
LCA8	CRB1	Crumbs homolog 1	Abouzeid et al. (2006)
LCA10	CEP290	Centrosomal protein of 290 kD	den Hollander et al. (2006)
LCA11	IMPDH1	Inosine-5′-monophosphate dehydrogenase 1	Bowne et al. (2006)
LCA12	RD3	Retinal degeneration 3	Friedman et al. (2006)
LCA13	RDH12	Retinol dehydrogenase 12	Janecke et al. (2004)
LCA15	TULP1	Tubby-like protein 1	Hagstrom et al. (1998)
LCA16	KCNJ13	K channel, inward rectifier, Kir7.1	Sergouniotis et al. (2011)
Night blindness			
CSNBAD1	RHO	Rhodopsin	Dryja et al. (1993)
CSNBAD2	PDE6B	Rod cGMP-specific cyclic phosphodiesterase beta subunit	Gal et al. (1994)
CSNBAD3	GNAT1	G protein, alpha transducing 1 (transducin, alpha subunit)	Dryja et al. (1996)
CSNB1A	NYX	Nyctalopin	Bech-Hansen et al. (2000)
CSNB1B	GRM6	Metabotropic glutamate receptor 6	Dryja et al. (2005)

Continued

TABLE 37.2 Disorders of the eye—cont'd

Name	Gene	Gene product	Reference
CSNB1C	TRPM1	Transient receptor potential cation channel subfamily M member 1	Bellone et al. (2008) Li et al. (2009)
CSNB1D	SLC24A1	Sodium/potassium/calcium exchanger	Riazuddin et al. (2010)
CSNB2A	CACNA1F	Voltage-dependent L-type Ca^{2+} channel, alpha-1 F; Cav1.4	Bech-Hansen et al. (1998) Strom et al. (1998)
CSNB2B	CABP4	Calcium-binding protein-4	Zeitz et al. (2006)
Oguchi disease 1	SAG	S-arrestin	Fuchs et al. (1995)
Oguchi disease 2	GRK1	Rhodopsin kinase	Yamamoto et al. (1997)
Joubert syndrome			
JBTS5	CEP290	Centrosomal protein of 290 kD	Sayer et al. (2006) Valente et al. (2006)
JBTS7	RPGRIP1L	Retinitis pigmentosa GTPase regulator-interacting protein	Delous et al. (2007)
JBTS8	ARL13B	ADP-ribosylation factor-like protein 13B	Cantagrel et al. (2008)
JBTS9	CC2D2A	Coiled-coil and C2 domain-containing protein 2A	Gorden et al. (2008) Noor et al. (2008)
JBTS10	CXORF5	Oral–facial–digital syndrome 1	Coene et al. (2009)
Peters' anomaly	PAX6	Paired box 6 protein Pax-6	Hanson et al. (1994) Mirzayans et al. (1995)
	PITX2	Pituitary homeobox 2	Doward et al. (1999)
	CYP1B1	Cytochrome P450 1B1	Stoilov et al. (1998)
	FOXC1	Forkhead box protein C1	Honkanen et al. (2003)
Axenfeld–Rieger syndrome	PITX2	Pituitary homeobox 2	Semina et al. (1996)
Iridogoniodysgenesis			
IRID1	FOXC1	Forkhead box protein C1	Nishimura et al. (1998)
IRID2	PITX2	Pituitary homeobox 2	Semina et al. (1996)
Posterior embryotoxon	JAG1	Jagged 1	Le Caignec et al. (2002)
Aniridia	PAX6	Paired box 6 protein Pax-6	Jordan et al. (1992)
Anterior segment mesenchymal dysgenesis	PITX3	Pituitary homeobox 3	Semina et al. (1998)
	FOXE3	Forkhead box protein E3	Semina et al. (2001)
Ectopia pupillae	PAX6	Paired box 6 protein Pax-6	Hanson et al. (1999)
Optic nerve hypoplasia	PAX6	Paired box 6 protein Pax-6	Azuma et al. (2003)
Foveal hypoplasia	PAX6	Paired box 6 protein Pax-6	Azuma et al. (1996) Hanson et al. (1999)
Coloboma of the optic nerve (morning glory disc)	PAX6	Paired box 6 protein Pax-6	Azuma et al. (2003)
Krause–Kivlin syndrome			
Cataract–microcornea syndrome	GJA8	Gap–junction alpha-8 protein	Devi and Vijayalakshmi (2006)
Bardet–Biedl syndrome			
	ARL6	ADP-ribosylation factor-like protein 6	Chiang et al. (2004)

TABLE 37.2 Disorders of the eye—cont'd

Name	Gene	Gene product	Reference
	MKKS	McKusick–Kaufman/Bardet–Biedl syndromes putative chaperonin	Katsanis et al. (2000) Slavotinek et al. (2000)
	MKS1	Meckel syndrome type 1 protein	Leitch et al. (2008)
	CEP290	Centrosomal protein of 290 kD	Leitch et al. (2008)
	CCDC28B	Coiled-coil domain containing 28B	Badano et al. (2006)

Compiled in part from OMIM; OMIM gene symbols are used throughout.

disorder can manifest as early as the first decade. Genes encoding a sodium borate cotransporter (SLC4A11) and transforming growth factor, beta-induced (TGFBI) have been implicated in multiple corneal dystrophies; however, relatively few animal models exist, corneal transparency itself is not well understood, and both the normal functions and the pathologies of these gene products are largely unknown (Klintworth, 2009).

Cataract, an opacification of the lens, occurs congenitally in 1–6 of 10,000 births. Worldwide, congenital cataract may account for 15% of childhood blindness, and if left untreated, this peripheral disorder can induce significant central visual deficits such as amblyopia. Inherited congenital cataract in humans is commonly autosomal-dominant and phenotypically variable, as cataracts appear with varying densities, colors, and locations within the lens.

The lens itself consists primarily of lens fiber cells surrounded by an epithelial cell layer on the outer surface; this structure continues to grow throughout life from the inside out, adding new lens fiber cells, formed from the outer epithelial cell layer to the body of the lens underneath the epithelial cell layer. Lens transparency is ensured in part by the loss of all intracellular organelles in lens fiber cells as they differentiate from the epithelial cell layer. In the avascular lens, homeostasis is maintained through a gap–junction coupled network. The cytosolic crystallins form the principal protein component of lens fiber cells, and the inside–out growth process of the lens dictates that the crystallins be extremely stable, as they cannot be replaced during the life of the lens. Furthermore, the crystallins play a role in setting refractive index and maintaining transparency of the lens. The α-crystallins are heat-shock proteins and chaperones, with α-crystallin making up almost half of the total lens protein by weight. Both αA-crystallin and αB-crystallin are found in the developing lens, and β- and γ-crystallins are also present in the adult lens (Andley, 2007; Bassnett, 2009).

Mutations of several of the crystallins, including αA, αB, βA1, βB1, βB2, γC, γD, and γS, have been associated with hereditary congenital cataracts as well as with a developmental cataract that is absent at birth but develops in early childhood. The pathologies of the crystallin mutations are incompletely understood; they may involve several distinct pathways that ultimately affect solubility and transparency of the crystallins. For example, levels of the chaperone *αA*-crystallin may control the ratio of soluble to insoluble *αB* protein, as the loss of *αA*-crystallin in mice leads to higher levels of insoluble *αB*-crystallin and reduced lens transparency (Brady et al., 1997). Additional mutations may alter protein transparency by actions on protein folding or protein solubility, or through effects on crystallin–crystallin interactions.

Connexins expressed in the lens, Cx46 (GJA3) and Cx50 (GJA8), allow gap–junction coupling of both lens fiber cells and lens epithelial cells. Although it is still not precisely understood how gap–junction coupling maintains transparency, gap–junction coupling provides a circulation system for the avascular lens, promoting homeostasis among the anuclear lens fiber cells and promoting crystalline solubility, and mutations of Cx46 and Cx50 are associated with congenital cataract. In mice, knockouts for Cx46 and for Cx50 exhibit different cataract phenotypes; nevertheless, it appears that Cx50 and Cx46 are functionally redundant and that the number of gap junctions is more critical than the specific connexin components for preserving transparency (White, 2002).

37.4.2 Disorders of the Retina

37.4.2.1 Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a disorder of retinal vascularization that first appeared in high-income countries in the 1940s, when advances in neonatal care led to increased survival rates for premature infants. Today, global incidence of this disorder describes an inverse U-shape as a function of economic context. Low-income countries typically have high infant mortality rates, which are associated with very low ROP incidence because premature infants do not survive. High-income countries also have low rates of ROP, and it is middle-income countries with variable quality in neonatal care that have the highest rates of ROP. Oxygen exposure

was identified as a risk factor early on, but the survival of increasingly smaller infants in the developed world has kept ROP incidence high. Although genetic factors may play a role in developing ROP, the primary risk factors remain oxygen exposure, degree of prematurity, and low birth weight. By current estimates, a majority (68%) of premature infants born in first-world countries and weighing 1250 g or less at birth will develop ROP (Good et al., 2005).

Two phases of ROP are seen, the first characterized by a loss of vascularization and the second by a pathological angiogenesis. In normal development, the retinal vasculature develops radially, reaching the peripheral extent of the retina at about 36 weeks gestation. Thus, in premature infants, an avascular area, with extent determined by gestational age at birth, surrounds the central vascularized retina. At birth, retinal vascularization slows, possibly in response to the relatively hyperoxic environment outside the uterus. During the first phase of ROP, the avascularized retina, unable to meet metabolic demand, becomes hypoxic until about 32 weeks gestational age. The second phase begins at 32–34 weeks gestation and involves neovascularization in response to hypoxia. In more extreme cases, the pathological blood vessel growth can pull the retina away from the RPE, leading to retinal detachment and blindness; prevention consists of careful monitoring and laser photocoagulation to prevent retinal detachment. Less extreme forms of ROP that resolve spontaneously are associated with abnormally thick retinae with broad, shallow foveal pits, and with altered rod photoreceptor development. Vascular endothelial growth factor (VEGF), which can be regulated by hypoxia, plays a critical role in vascularization of the retina. The proximal cause of the first phase of ROP may be hyperoxic downregulation of VEGF-induced vascular growth, whereas the second stage is likely caused by hypoxic upregulation of VGEF to stimulate angiogenesis. VEGF activity requires insulin-like growth factor (IGF-1), in a permissive or added manner. Thus, the loss of maternally supplied IGF-1 at birth in premature infants may abolish VEGF activity (Smith, 2008). Potential preventative treatments for ROP include supplemental IGF-1 in the preterm infant and the development of small-molecule antagonists to VEGF receptors.

The primary ROP risk factors of gestational age and oxygen exposure can be potentiated by genetic background; in particular, several mutations in the Wnt–beta-catenin pathway affect development of retinal vasculature and may also increase risk for developing ROP. These include the Norrie disease protein norrin, the canonical Wnt receptor *Frizzled-4* (*Fz4*; gene FZD4), and the Wnt coreceptor Lrp5. Norrin, normally produced in the Muller glia, is a high-affinity ligand for the canonical Wnt receptor *Fz4* at retinal epithelial cells. Additional inherited pathologies of retinal vascularization that are associated with this group of proteins include X-linked familial exudative vitreoretinopathy (FEVR), Coats' disease, and persistent fetal vasculature syndrome (PFVS).

37.4.2.2 *Retinitis Pigmentosa*

Retinitis pigmentosa occurs frequently in isolation; the term refers to a large group of genetically heterogeneous degenerative disorders with a prevalence of 2–3 in 10,000. The disease may be inherited in X-linked, autosomal-dominant, or autosomal-recessive mode, and age of onset is variable after the first year. Diagnosis typically occurs in young adulthood, but early-onset forms may manifest in the first 5 years. This disorder is essentially a rod–cone dystrophy, in that rod photoreceptors degenerate before cone photoreceptors, resulting in a loss of peripheral and night vision.

Over 10% of retinitis pigmentosa patients have the most severe, X-linked form (XLRP), which is associated with mutations in retinitis pigmentosa 2 (RP2) or in retinitis pigmentosa GTPase regulator (RPGR). RP2 is a membrane-associated protein that is found throughout the retina and in the RPE. RP2 shares sequence homology with tubulin-specific cofactor C, a GTPase activator for tubulin, and regulates the GTP-bound form of the microtubule-associated protein ADP ribosylation factor-like 3 (Arl3). RP2 and Arl3 are localized to the connecting cilium between inner and outer photoreceptor segments, where they mediate trafficking of vesicles from the Golgi (Evans et al., 2010).

RPGR interacts with the delta subunit of rod cyclic phosphodiesterase (PDE), which mediates transport of certain proteins to photoreceptor outer segments, and retinitis pigmentosa alleles of RPGR exhibit reduced binding to PDE/delta. RPGR also interacts with a protein localized to the connecting cilia of photoreceptors: PPGR-interacting protein 1 (RPGRIP1), and its expression overlaps that of usherin.

The photopigment of the photoreceptor outer segment consists of a transmembrane opsin (in cones) or rhodopsin (in rods) G-protein-coupled receptor and a covalently attached small organic moiety, 11-*cis*-retinal, that determines the photoreceptor's wavelength sensitivity. Absorption of a photon isomerizes the 11-*cis*-retinal, causing a conformational change in the opsin that leads to activation of the membrane-bound G protein transducin. Transducin activation turns on a cGMP PDE that hydrolyzes cGMP, causing the normally open cGMP-gated cation channels in the outer segment plasma membrane to close. Closure of the cation channel hyperpolarizes the photoreceptor and leads to a decrease in tonic neurotransmitter release at the photoreceptor–bipolar cell synapse. Inactivation of opsin is accomplished in part by S-arrestin, while 11-*cis*-retinal is regenerated through the retinoid cycle. Well over 100 mutant

rhodopsin (RHO) alleles, some with mouse models, can cause retinitis pigmentosa. These alleles may cause protein misfolding that prevents formation of a functional photopigment, interfere with trafficking to the outer segment, affect activation of transducin, and/or initiate the formation of stable rhodopsin that is constitutively active in the dark. Protein misfolding can underlie certain forms of retinitis pigmentosa, though the mechanism of degeneration is unknown. Mutations of S-arrestin (SAG) are also associated with retinitis pigmentosa, probably due to constitutive rhodopsin activation. The cyclic nucleotide channels in photoreceptor outer segment membrane are heteromeric tetramers composed of A (CNGA1) and B (CNGB1) subunits; each subunit has been linked to retinitis pigmentosa (Wright et al., 2010).

The RPE plays a critical role in retinal health, phagocytosing about 10% of the photoreceptor outer segments daily and performing many of the steps necessary in the retinoid cycle in which 11-*cis*-retinal is regenerated from the all-*trans*-retinal product of photoisomerization in the outer segments, and mutations affecting the retinoid cycle are associated with many retinal disorders. One such mutation in retinitis pigmentosa affects the retinoid isomerase RPE65, which is normally expressed in RPE and in cone photoreceptors and is necessary for the isomerization of all-*trans*-retinyl to 11-*cis*-retinal. Loss of RPE65 results in a gradual disorganization of the outer segments and a slow degeneration of photoreceptors, loss of the rod ERG and of rhodopsin, and an accumulation in the RPE of all-*trans*-retinyl esters. The rhodopsin homology RGR (retinal G-protein-coupled receptor) is another RPE protein involved in the retinoid cycle that has been implicated in retinitis pigmentosa. The retina-specific ATP-binding cassette transporter ABCA4 gene encoding the photoreceptor Rim protein also functions in the retinoid cycle, though it is expressed in the disk membrane of photoreceptor outer segments, where it is involved in active transport of retinoids from the lumen of the disk to the cytoplasm. The all-*trans*-retinal product of photoactivation is a precursor for potentially toxic diretinal compounds. Loss of ABCA4 activity allows accumulation of diretinal compounds that are then incorporated in the RPE during outer segment phagocytosis. Finally, mutations of the anion channel bestrophin 1 (BEST1), which is also expressed in RPE cells, lead to a retinitis pigmentosa of unknown pathology.

The tubby-related protein TULP1 is expressed in the photoreceptor inner segments where it can bind dynamin, a critical endocytosis protein. In mouse, loss of Tulp1 results in the loss of ribbon synapses at photoreceptor terminals, the mislocalization of the visual pigment rhodopsin to the inner segment, and photoreceptor degeneration. The transcription factor neural retina leucine zipper (NRL) is expressed primarily in rod photoreceptors. The retinae of mice lacking *Nrl* develop with no rod photoreceptors and with more short-wavelength cones than normal, a phenotype similar to that seen in humans with retinitis pigmentosa caused by mutations of NRL (Mears et al., 2001).

Retinitis pigmentosa is distinguished from other retinal dystrophies in that cone photoreceptor death follows the main phase of rod photoreceptor death, and little is currently known about the events that initiate cone photoreceptor death. Several models of retinitis pigmentosa share a common metabolic pathway for cone death, however, suggesting that in diverse cases the late loss of foveal vision may be caused by cell starvation.

37.4.2.3 Cone–Rod Dystrophy

Cone–rod dystrophy is distinguished from retinitis pigmentosa by the order in which photoreceptors are lost. The cone–rod dystrophies are less prevalent than retinitis pigmentosa, but can be severe because the loss of high-acuity, color vision precedes night blindness and the loss of peripheral vision. The transcription factor cone–rod homeobox (CRX) is a member of the orthodenticle family that is expressed primarily in photoreceptor inner segments. Crx transactivates photoreceptor-specific genes including rhodopsin and arrestin, and was the earliest gene identified in cone–rod dystrophy. Additional causes of cone–rod dystrophy are similar to those discussed earlier with retinitis pigmentosa.

37.4.2.4 Leber Congenital Amaurosis

The most severe of the retinal diseases, Leber congenital amaurosis (LCA), underlies about 5% of inherited retinopathies; it includes a heterogeneous group of severe inherited disorders in which nystagmus and retinitis pigmentosa are present, the ERG response is absent, and pupils are amaurotic (i.e., they do not respond to light shining directly in the same eye) (Walia et al., 2010). Identified mutations include the photoreceptor transcription factor Crx, which leads to a failure to form photoreceptor outer segments and the formation of abnormal photoreceptor synapses, and the Crumbs protein (CRB1), a regulator of cell polarity and morphology whose loss leads to dysmorphic Muller glia cells, retinal disorganization, and subsequent degeneration.

Another subgroup of LCA cases results from mutations of visual cycle proteins, either RPE65 or retinol dehydrogenase 12 (RDH12). The role of RDH12 in LCA is still unclear, however, as the Rdh12 deficiency appears to be compensated for in the mouse knockout. Maintenance of the cGMP-gated current in the photoreceptor outer segments requires local cGMP synthesis, and the membrane-bound retinal guanylate cyclase GUC2D has been associated with LCA. *In vitro* results suggest that a GUC2D mutation commonly found in LCA impairs cyclase activity and causes the constitutive closure of the cGMP-gated channels.

37.4.2.5 Stargardt's Disease

Stargardt's disease, an autosomal-recessive juvenile-onset macular dystrophy, presents with loss of central vision and progressive atrophy of the RPE at the fovea. Known causes include mutations of ABCA4 and of the cyclic-nucleotide-gated channel, discussed earlier under retinitis pigmentosa.

37.4.2.6 Night Blindness

The inherited night blindnesses typically cause myopia, reduced visual acuity, and nystagmus in addition to reduced vision in dim light (nyctalopia). Complete congenital stationary night blindness (cCSNB), or type 1 CSNB, is a nonprogressive X-linked or autosomal-recessive disorder that affects the photoreceptor–bipolar cell synapse and can be seen on electroretinogram (ERG). Different forms of cCSNB have been linked with mutations to genes encoding a leucine-rich proteoglycan, nyctalopin (NYX), the metabotropic glutamate receptor mGluR6 (GRM6), and the transient receptor potential channel melastatin (TRPM1). In addition to numerous transgenic mouse models for night blindness, naturally occurring animal models exist in the Nob mouse ("no b-wave," a Nyx mutant) and certain colorations of appaloosa horse (Trpm1 mutant).

In the normal retina at rest, glutamate tonically released from the photoreceptor activates the retina-specific Group III metabotropic glutamate receptor mGluR6, which is expressed specifically on the dendrites of an ON bipolar cell, to cause the closure of a nonspecific cation channel. The reduction in glutamate release with light stimulation causes the mGluR6-coupled cation channels to open, depolarizing the ON bipolar cell. Though the function of nyctalopin is unknown, it is expressed in close proximity to mGluR6 in dendrites of rod bipolar cells, TRPM1 is likely regulated by mGluR6 activity, and loss of *Trpm* causes an abnormal ERG characteristic of ON bipolar dysfunction; in fact, depolarizing bipolar cells from Nob mouse retina show no response to glutamate application. Thus, the cCSNB defect appears to be localized to a site on the ON bipolar cell postsynaptic membrane where nyctalopin, mGluR6, and TRPM1 are likely functionally linked.

Congenital stationary night blindness type-2 (CSNB2) is an X-linked disorder caused by a presynaptic channelopathy at the rod–bipolar synapse. CSNB2 is caused by mutations that affect the α1 subunit of the retinal L-type calcium channel $Ca_v1.4$ ($Ca_v1.4\alpha1$; gene CACNA1F) or the calmodulin-like calcium-binding protein-4 (CABP4), which modulates $Ca_v1.4$ function. The $Ca_v1.4$ channel inactivates slowly in response to depolarization and it lacks calcium-dependent inactivation; both qualities contribute to the photoreceptor's ability to release glutamate tonically, and both the α1 subunit and CABP4 are necessary for transmitter release at the photoreceptor–bipolar synapse.

37.5 DISORDERS OF CHEMICAL SENSATION

Recognized disorders or chemical sensation usually present after infection or after use of certain drugs, and developmental disorders of the chemical senses are rare.

37.5.1 Taste

One well-studied taste 'disorder' is the inability to taste the synthetic compound phenylthiocarbamide (PTC). PTC and 6-n-propylthiouracil (PROP) are members of a class of thiourea compounds that are perceived bimodally, a large number of individuals tasting these compounds as very bitter, and somewhat fewer individuals failing to taste them at all; PTC nontasters exist in nearly every population tested. Bitter tastes are transduced by receptors in the Taste Receptor 2 (TAS2R) family of 7-transmembrane, G-protein-coupled receptors, which are coexpressed with the G protein α subunit gustducin in a subset of taste receptor cells within the taste buds. The TAS2R38 gene is not highly conserved across species, and like other members of the TAS2R gene family, the human PTC (TAS2R38) gene shows broad allelic heterogeneity. Though the lack of PTC conservation across species and the broad distribution of non-tasting PTC alleles might suggest that PTC sensing is less a disorder than an interesting genetic oddity, the PTC-sensing phenotype may confer certain benefits. It has been suggested, for example, that PTC tasters might enjoy an evolutionary advantage by avoiding bitter-tasting toxic compounds, and also that a genetically encoded ability to taste bitter compounds could be protective against nicotine and alcohol consumption that might otherwise lead to addiction. Indeed, specific single-nucleotide polymorphisms in TAS2R38 are associated with a higher incidence of nicotine use in certain populations (Mangold et al., 2008). Interestingly, TAS2R38 and several other bitter-taste receptors are also expressed in ciliated cells of the airway epithelium. When stimulated with bitter compounds, these cells show an increase in ciliary beating (Shah et al., 2009), a response that may play a role in protecting the lungs from exposure to noxious compounds. Variability is not restricted to the bitter receptors, and altered taste perception of sucrose correlates with single-nucleotide polymorphisms in the promoter region of the TAS1R3 gene. Taste anomalies or deficits are exhibited by many of the knockout mice for gustducin, various members of

the TAS1R (sweet) and TAS2R (bitter) families, the taste tissue-specific phospholipase Cβ2 (Plcb2), and the TRP channel Trpm5, and several human taste preferences correlate with polymorphisms in various TAS2Rs (Hayes et al., 2011). Whether or not genetic variability in taste should be considered a disorder is unclear; nevertheless, the broad variability of genetically encoded taste perception offers opportunities for further study.

37.5.2 Olfaction

37.5.2.1 Kallmann Syndrome

Kallmann syndrome encompasses a heterogeneous group of disorders that include severe hypogonadotropic hypogonadism (impaired or absent function of the testes or ovaries) and hyposmia or anosmia. Diagnosis is typically made when patients fail to enter puberty due to a deficiency of gonadotropin-releasing hormone (GnRH). Olfactory impairment, anosmia or hyposmia, is typically discovered only at this time. The sensory impairment results from the absence or hypoplasia of the olfactory bulbs, which are the principal target of the olfactory epithelium, and of the lateral olfactory tracts. A broad range of additional, variable neurological deficits may also be present. Kallmann syndrome is not precisely a disorder of the olfactory organ, as the deficit is one of axon migration and neurogenesis in central pathways, but is worth mention here as one of very few identified olfactory disorders. Much about this disorder is still unclear, and in fact the genes that have been identified to date represent a minority of all cases (Dode and Hardelin, 2009).

The principal known genes for Kallmann syndrome include KAL1, which shows X-linked inheritance and codes for anosmin-1; KAL2, an autosomal-dominant form associated with mutations of fibroblast growth factor receptor 1 (FGFR1); KAL3 and KAL4, encoding prokineticin receptor-2 (PROKR2) and prokineticin-2 (PROK2); and KAL6, encoding fibroblast growth factor 8 (FGF8). Anosmin-1 is a secreted glycoprotein of embryonic olfactory bulb, tract, and cortex that acts as a chemoattractant and promotes neurite branching of olfactory neurons, possibly signaling through FGFR1, which is co-expressed with anosmin-1 in the olfactory bulbs during development. PROK2 is a secreted ligand for PROKR2, a G protein-coupled membrane receptor necessary for differentiation and migration of neural progenitor cells to the olfactory bulb. It is likely that many of the still unidentified gene products underlying Kallmann syndrome will be proteins that interact with FGFR1 – possibly FGF2 – or with PROKR2.

37.5.2.2 Other Congenital Olfactory Disorders

Hyposmia has also been reported in a few additional syndromic disorders. CHARGE (coloboma, heart disease, atresia choanae, retardation, genital and ear anomalies) syndrome, with an estimated incidence on the order of 10^{-4}, is related to the less severe Kallmann syndrome, type 5. CHARGE syndrome is typically diagnosed in infancy, may be accompanied by deaf–blindness, and nearly always involves olfactory deficits. Over 50% of CHARGE cases are caused by mutations in chromodomain helicase DNA-binding protein 7 (CHD7), and several mouse models of this disorder are associated with *Chd7* mutations. *Chd7* and the transcription factor *Sox2* form a transcriptional network for regulating several target genes in neural stem cells (Engelen et al., 2011).

In both humans and mice, PAX6 mutations and aniridia may be accompanied by olfactory bulb hypoplasia

TABLE 37.3 Disorders of chemical sensation

Name	Gene	Gene product	Reference
PTC non-taster			
PTC	TAS2R38	Taste receptor, type 2, member 38	Kim et al. (2003)
Kallmann syndrome			
KAL1	KAL1	Kallmann syndrome 1 protein; anosmin-1	Franco et al. (1991) Legouis et al. (1991)
KAL2	FGFR1	Fibroblast growth factor 1	Dode et al. (2003)
KAL3	PROKR2	Prokineticin receptor 2	Dode et al. (2006)
KAL4	PROK2	Prokineticin-2	Dode et al. (2006)
KAL5	CHD7	Chromodomain helicase DNA-binding protein 7	Kim et al. (2008)
KAL6	FGF8	Fibroblast growth factor 8	Falardeau et al. (2008)
Aniridia and hyposmia	PAX6	Paired box 6 protein Pax-6	Sisodiya et al. (2001)

OMIM gene symbols are used throughout.

and hyposmia, whereas mutation of SOX 9 (campomelic dysplasia) or SOX10 (Waardenburg syndrome) may be accompanied by a complete absence of the olfactory bulbs. Finally, hyposmia has been reported in some cases of pseudohypoparathyroidism, Bardet–Biedl syndrome, and Leber congenital amaurosis (Table 37.3).

37.6 CONCLUSION

Congenital sensory impairment is widespread. With the success of vaccination, maternal health, and perinatal care programs worldwide, the incidence of congenital sensory impairment has decreased greatly, and inherited disorders are now the most common form of congenital sensory loss. This is both a challenge and a boon: a challenge because these disorders can be quite heterogeneous; a boon because the growth of animal models for specific genetic disorders offers rich opportunities for research into normal and pathological sensory development.

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Relevant Websites

http://hereditaryhearingloss.org/ – Hereditary Hearing Loss Homepage.
http://www.sph.uth.tmc.edu/RetNet/ – Retinal Information Network.