Review Article

Ocular findings and genomics of X-linked recessive disorders: A review

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Advent of new sequencing technologies and modern diagnostic procedures has opened the door for a deeper understanding of disorders about which little was known previously. Discovery of novel genes, new genetic variants in previously known genes and better techniques of functional validation has immensely contributed to unraveling the molecular basis of genetic disorders. Availability of knockout animal models like the zebrafish and gene editing tools like CRISPR-Cas9 has elucidated the function of many new genes and helped us to better understand the functional consequences of various gene defects. This has also led to better diagnosis and therapeutic interventions. In this context, a good body of research work has been done on X-linked recessive disorders with ocular findings. This review will focus on ocular and genetic findings of these rare disorders. To our knowledge, this is the first comprehensive review encompassing ocular and genomic spectrum of X-linked recessive disorders.

Key words: Genomics, ocular findings, X-linked recessive

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X-linked disorders have the causative genetic defect in the X chromosome. Males have one X and one Y chromosome. In males, if a gene at a particular locus on the X chromosome is defective, there will be no other copy to compensate this damage. In this case, the disease phenotype may be apparent and the inheritance pattern will be X-linked recessive. In females, both X chromosomes should have the defect at a particular locus (very rare), leading to X-linked recessive disease phenotype. However, females with a single defective gene will act as carriers passing the mutated gene copy to their children. Affected individuals are generally males, and females very rarely manifest the symptoms and usually act as carriers. With advances in disease diagnostics and sequencing technologies (like whole genome or exome sequencing), the genetic basis of a large number of diseases has been deciphered. This also holds true for rare, X-linked recessive disorders wherein a good number of genes have been associated with a particular disease. In this review, we will try to cover the genetics of rare, X-linked disorders that have associated ocular defects. Attempt will also be made to come up with the latest ocular findings in these defects. This review will be beneficial for clinicians and basic researchers working in the field of ocular genetics and rare disorders. Various rare, X-linked diseases, their genomics and latest ocular findings are discussed below.

Åland Island Eye Disease

Genetics and pathobiology

Åland Island eye disease [AIED] (OMIM # 300600) is an X-linked recessive retinal disorder with males having a variety of ocular defects. AIED is an X-linked disorder and results from mutations in the *CACNA1F* gene (OMIM # 300110) at Xp11.23 locus.[1,2] Genetic locus for AIED is shared with incomplete congenital stationary night blindness (CSNB2A).[1] *CACNA1F* encodes a multi-pass transmembrane protein that functions as an alpha-1 subunit of the voltage-dependent calcium channel.[3–7] Table 1 enlists the latest genetic variants found to be associated with X-linked disorders having ocular findings.

Ocular features and lab investigations

AIED is characterized by fundus hypopigmentation being pronounced in the posterior pole and peripapillary region, nystagmus, protan color vision defect, astigmatism, progressive myopia, decreased visual acuity and defective dark adaptation.[8–9] Nystagmus and color vision defects may be observed in mildly affected females. In a recent study, Mahmood *et al*.[1] reported reduced vision, high myopia, jerk nystagmus, and hypopigmented fundi with visible choroidal vasculature. Mildly hypo-plastic optic nerve in both eyes and peripapillary atrophy was also present.[1] AIED is different from albinism, as there is no misrouting of the optic nerves.[8-9] Defects in photopic function and scotopic

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Table 1: Some recent variants found to be associated with X-linked disorders by WES

Disorder	Gene	X-linked variant found by WES	Reference
Åland Island Eye Disease	*CACNA1F*	c.4294-11C>G	[1]Mehmood *et al*., 2021
Adrenoleukodystrophy, X-Linked	*ABCD1*	c.1991 G>A	[11]Cho *et al*., 2020
	ABCD1	c.1394-2A>G	[16]Foschi *et al*., 2019
	ABCD1	c.1534G>A	[17]Dekker *et al*., 2019
	ABCD1	c.1661G>A	[18]Zhan *et al*., 2013
Ocular Albinism Type 1	*GPR143*	c.333_360+14del42insCTT, c.276G>A, c.793C>T, c.494C>A	[20]Zou *et al*., 2017
	GPR143	c.623C>A	[21]Jung *et al*., 2018
Blue Cone Monochromacy	*OPN1LW*	c.427T>C and c.607T>C	[27]Iarossi *et al*., 2021
	OPN1LW	c.-28144_-25340del-25339_-25012inv328insGTG-25011_*7764del84549	[28]Wang *et al*., 2016
	OPN1LW	deletion of exon 5	[29] Weiss *et al*., 2016
	OPN1LW	c.607C>T	[31]Luo *et al*., 2015
Bornholm Eye Disease	*OPN1LW*	c.607C>T	[32]McClements *et al*., 2010
	OPN1LW	Leu153-Ile171-Ala174-Val178-Ala180	[33]Holmquist *et al*., 2021
Cone-Rod Dystrophies, X-Linked	*RPGR*	ORF15+1343_1344delGG and ORF15+694_708del15	[43]Yang *et al*., 2002
	RPGR	ORF15+A1094C G1095T, ORF15+1176G>T	[44]Ebenezer *et al*., 2005
	CACNA1F	IVS28-1 GCGTC>TGG	[45]Jalkanen *et al*., 2006
Dyskeratosis Congenita	*DKC1*	c.1218_1219insCAG	[51]Trotta *et al*., 2018
	DKC1	c.146C>T	[52]Lim *et al*., 2014
	DKC1	c.1058C>T	[53]Chen., *et al*. 2019
Hunter Syndrome	*IDS*	c.1436_1440AGCCG	[61]Semyachkina *et al*., 2019
	locus - Xq28	c.438T>A	[62]Lonardo *et al*., 2014
	IDS	c.240+1G>A, c.281G>A c.1188G>A, c.610C>T	[63]Chkioua *et al*., 2020
	IDS	c.1870A>C	[66]Nikkel *et al*., 2014
IFAP Syndrome	*MBTPS2*	c.671-9T>G	[70]Wang *et al*., 2014
	MBTPS2	c.1523A>G	[73]Aten *et al*., 2010
Lowe Oculocerebrorenal Syndrome	*OCRL*	Xq25-q26.1	[83]Watanabe *et al*., 2016
	OCRL	c.1423C>T, c.1502T>G, c.2464C>T	[84]Zheng *et al*., 2019
Megalocornea	*CHRDL1*	c.872G>A, c.240T>A, c.1247-1_1247del, c.100G>T, c.297C>A, c.865T>C	[89]Davidson *et al*., 2014
	CHRDL1	c.90_100delAAAACGTAAGT	[92]Mangialavori *et al*., 2015
Microphthalmia, Syndromic 1	*NAA10*	c.43A>G, c.*39A>G, c.*40A>G	[95]Jhonston *et al*., 2019
Myopia 1, X-Linked (MYP1)	*OPN1LW*	c.532A>G and c.538T>G	[101]Li *et al*., 2015
Night Blindness, Congenital Stationary	*NYX*	c.371_377delGCTACCT and c.214A>C	[103]Dai *et al*., 2015
Norrie Disease	*NDP*	c.385G>T	[113]Marakhonov *et al*., 2019

Contd...

Table 1: Contd...

Disorder	Gene	X-linked variant found by WES	Reference
Nystagmus 1 and 6, Congenital, X-linked	*FRMD7*	c.875T>C	[119]Kohmoto *et al.*, 2015
	FRMD7	c.2036del, c.801C>A c.875T>C	[120]Al Moallem *et al.*, 2015
	FRMD7	c.823-829delACCCTAC	[121]Chen *et al.*, 2019
	GPR143	c.333G>A, c.360+1G>C, c.659-1G>A, c.43_50dupGACGCAGC, c.703G>A	[126]Han *et al.*, 2015
Pelizaeus-Merzbacher Disease	*PLP1*	c.251C>A	[132]Lyahyai *et al.*, 2021
	PLP1	c.453+59_+259del	[133]Yamamoto Shimojima *et al.*, 2017
	PLP1	c.251C>A	[134]Grossi *et al.*, 2011
Retinitis Pigmentosa 2 and 3, X-Linked	*RPGR*	c.1059+1 G>T, c.2002dupC, c.2236_2237del CT, c.2899delG	[138]Jiang *et al.*, 2017
	RPGR	c.3399delG, c.3308_3309delAT, c.3178_3179delGA, c.3104_3105delAG, c.3092delA, c.2625dupA, c.2236_2237delGA, c.1693C>T, c.1070 G>A, c.832 A>G, c.628 G>T, c.679 C>T, and c.389_390delTT,	[140]Mawatari *et al.*, 2019
	RP2	c.665delC	[149]Lim *et al.*, 2016
Spastic Paraplegia 2	*PLP1*	c.88G>C	[150]Noetzli *et al.*, 2013

b-wave amplitude (Schubert-Bornschein type) are revealed in electroretinography (ERG).[8-9] Spectral domain optical coherence tomography (SD-OCT) revealed grade 1 bilateral foveal hypoplasia and retinal nerve fiber layer thinning.[1] Auto-fluorescence of fundus presented a reduced foveal reflex, being normal otherwise.[1] Photopic flash and flicker responses were severely attenuated in both eyes.[3] Isolated rod responses were also severely attenuated bilaterally.[1]

Adrenoleukodystrophy, X-Linked

Genetics and pathobiology

This is an X-linked (X-ALD, OMIM # 300100) disorder caused by mutations in the *ABCD1* gene at Xp28 locus. *ABCD1* (OMIM # 300371) is a transporter of ATP-binding cassette (ABC) superfamily that is active in peroxisomes.[11-12] These transporters are involved in translocation of metabolic products including lipids, sterols and drugs across extra- and intracellular membranes.[13,14] Accumulation of very-long-chain fatty acids (VLCFAs) in plasma and tissues due to impairments in *ABCD1* contributes to the demyelinating pathology and cerebral neuropathy in X-ALD.[15-18]

Ocular features and lab investigations

Visual symptoms common to this disorder include strabismus, hemianopia, loss of acuity, optic atrophy and visual agnosia. Decreased corneal sensation due to neuropathy and ocular apraxia–related gaze abnormalities may be present.[13,14] Thinning of the retinal nerve fiber layer, loss of ganglion cells, inclusions in retinal neurons and optic nerve macrophages may be revealed upon histopathological examination of ocular structures.[13,14] Funduscopy of the affected individual revealed severe optic disc pallor and lack of light perception in both eyes.[19] Retinal ganglion cell thinning and inner plexiform layers possibly due to trans-neuronal retrograde degeneration of ganglion cells has also been reported in SD-OCT.[19]

Ocular Albinism Type 1

Genetics and pathobiology

Mutations in the *GPR143* gene (OMIM # 300808) at Xp22.3. locus lead to Ocular Albinism type 1 (OA1), an X-linked recessive disorder.[20-22] OA1 primarily affects males, with females being rarely affected. *GPR143* encodes a 404 amino acid protein, expressed highly in melanocytes and the retinal pigment epithelium (RPE).[20-26] Mutant protein may cause failure of melanosomes to bud off endoplasmic reticulum (ER) and their likely aggregation, leading to the formation of giant melanosomes.[20-26]

Ocular features and lab investigations

Visual symptoms include ocular hypopigmentation with reduced coloring of the iris and retina. Foveal hypoplasia, photophobia, nystagmus, strabismus and high refractive errors including hypermetropia are also present.[21-25] Concentric macular rings have been identified in some OA1 patients using infrared reflectance images. Magnetic resonance imaging (MRI) may reveal smaller optic chiasm with optic tracts having wider angle in between, reflecting the atypical crossing of nerve fibers.[21-25]

Blue Cone Monochromacy

Genetics

Blue cone monochromacy [BCM] (OMIM # 303700) is a rare, X-linked congenital stationary cone dysfunction syndrome caused by mutations in either the *OPN1LW* (OMIM # 300822) or *OPN1MW* (OMIM # 300821) gene(s).[27-28]

Ocular features and lab investigations

Ocular manifestations may include impaired color vision, pendular nystagmus, myopia, photophobia and low visual acuity. Vision is derived from the preserved blue (*S*) cones and rod photoreceptors while discrimination of colour is severely

impaired from birth.[29-31] Affected individuals with BCM reported color vision impairment, nystagmus, photophobia, night vision difficulty and low vision since early childhood.[27] Myopic pattern with relative pale optic disk, regular vessel caliber and mild RPE mottling were revealed in fundus examination. Absence of foveal depression, thickening of the deep choroidal vessels, ellipsoid layer thinning in the central fovea and fragmentation of the corresponding external limiting membrane were reported in SD-OCT.[27] Absence of functional long wavelength–sensitive and medium wavelength–sensitive retinal cones is a characteristic feature.[27,28]

Bornholm Eye Disease

Genetics

Bornholm eye disease (BED) (OMIM # 300843) is an X-linked disorder mapping to Xq28 locus harboring the *OPN1LW* and *OPN1MW* genes.[32-35]

Ocular features and lab investigations

Affected individuals reported diffuse chorioretinal atrophy, myopic fundi with tilted discs and retinal pigment epithelium with crescent-shaped peripapillary atrophy.[33] Studies have revealed patients being deuteranopic with hypoplasia of the optic nerve head, myopia, visible choroidal vessels in the posterior pole and subnormal flicker function.[32-37] ERG revealed normal rod function while pathologic bilaterally, showing marked decreased function of cones.[34]

Cataracts, Ataxia, Short Stature, and Mental Retardation

Genetics

CASM (OMIM #300619) is an X-linked recessive disorder and maps at Xpter-q13.1 locus, containing the disease and co-segregating with the cataract phenotype in both sexes.[38]

Ocular features and lab investigations

It is often characterized by muscle hypotonia, mild-to-moderate mental retardation, postural tremor and weakness in males.[38] Ocular findings include cataracts in both sexes with opacification being more extensive in males.[38] Affected females reported blurred vision, pulverulent and punctate lens opacities with posterior subcapsular sclerosis. Anterior chamber, iris, pupils and cornea were normal.[38]

Color Blindness, Red-Green, Partial

Red-green color vision defects (OMIM # 303900) have variable phenotypes being inherited in recessive X-linked pattern.[39–41] Dichromatic color vision is produced by red and green cones whose pigments are generated from contiguous gene regions on the X chromosome encoding *OPN1MW* (green pigment) and *OPN1LW* (red pigment) produce.[39-41] The Xq28 locus on X chromosome resides in the *OPN1LW* and *OPN1MW* genes in a cluster with a head-to-tail configuration.[39-41]

Cone–Rod Dystrophies, X-Linked

Genetics and pathobiology

Genetically, X-linked cone dystrophy (OMIM # 304020) is a heterogeneous disorder, linked to loci on Xp11.4–Xp21.1.[42] Cone–rod dystrophy, X-Linked, 1 (CORDX1) has been mapped to a region harboring *RPGR* (OMIM # 312610) gene mutations.[43,44] *RPGR* encodes a protein with characteristics of the highly conserved guanine nucleotide exchange factors and localizing to the outer segment of rod photoreceptors being essential for their viability.[43,44] Mutation in the *CACNA1F* gene cause additional forms of X-linked cone–rod dystrophy including CORDX2 (OMIM # 300085) and CORDX3 (OMIM # 300476).[45,46]

Ocular features and lab investigations

X-linked cone–rod dystrophy is a group of related eye disorders presenting with loss of color vision, photophobia and progressive vision loss.[42] Ocular findings include photophobia, decreased visual acuity, abnormal color vision, decreased photopic electroretinographic responses, myopia, full peripheral visual fields, central visual field scotomas, peripheral vision loss, night blindness and granularity of macular retinal pigment epithelium.[42-46] Affected individuals had moderate-to-high myopia with variable astigmatism, decreased visual acuity, myopic optic discs, chorioretinal thinning and peripapillary atrophy.[44]

Dyskeratosis Congenita (DKC) and Hoyeraal–Hreidarsson Syndrome (HHS)

Genetics and pathobiology

DKC (OMIM #305000) is a rare defective telomere maintenance multisystem disorder caused by mutations in *DKC1* (OMIM # 300126) gene (Xq28).[47-53] Oral leukoplakia, dysplastic nails and lacy reticular pigmentation of the upper chest and/or neck are a classic triad of DKC.[47-53] *DKC1* encoded protein functions in telomerase stabilization or maintenance and may have roles in DNA damage response, nucleo-cytoplasmic shuttling and cell adhesion.[51,53] Clinically severe variant of DKC with early onset in utero, multisystem involvement and *DKC1* gene mutations refers to Hoyeraal–Hreidarsson syndrome (HHS).[54,55]

Ocular features and lab investigations

Ocular features in DKC include cicatrizing conjunctivitis, lid margin keratinization, blepharitis, trichiasis, absence of lacrimal puncta, entropion or ectropion, symblepharon and sparse eyelashes.[47-54] Keratinization of the corneal epithelial surface and vascularization may also be present. A prominently involved part of the generalized muco-cutaneous disease include conjunctiva and eyelids.[47-54] Ocular findings in HHS include distortion of lid margin, corneal and conjunctival scarring.[56-58] HHS, being more severe disease, may lead to infants death before the muco-cutaneous manifestations appear.[47-49] In a study by Allingham, individual with HHS presented vitreous opacity without retinal detachment or mass.[57] Temporal periphery with sclerotic retinal vessels, preretinal heme infero-temporally and bilateral proliferative retinopathy were reported.[57]

Hunter Syndrome (MPS II)

Genetics and pathobiology

Hunter syndrome (MPS II) (OMIM # 309900) is a genetic X-linked recessive disorder mapping to *IDS* (OMIM # 300823) gene at the chromosomal region Xq28 and spanning 44 kb with nine exons.[59-66] The gene encodes a member of the sulfatase family of proteins with 550 amino acid polypeptide and is involved in the lysosomal degradation of dermatan and sulfate.[60]

Ocular features and lab investigations

Ocular findings may include pigmentary retinopathy with variable severity, corneal clouding as early as six months of age, elevated disc with swollen appearance and secondary optic atrophy in long standing cases.[59,61,65-68] In a study by Semyachkina *et al*., the affected individual reported astigmatism of both eyes with high degree of myopia, and slit-lamp examination revealed discrete corneal lesions.[61] Exophthalmos, hypertelorism, peripheral pigment epithelial changes, bilateral uveal effusions and radial parafoveal folds may also be present.[65]

IFAP (BRESHECK) Syndrome and Keratosis Follicularis Spinulosa Decalvans, X-Linked

Genetics and pathobiology

The IFAP/BRESHECK (OMIM # 308205) syndrome is a multiple anomaly disorder having variable severity and mapping to *MBTPS2* (OMIM # 300294) gene (Xp22.12-p22.11).[69-72] IFAP is classically characterized by triad of photophobia, ichthyosis follicularis and atrichia.[69] Mutations in the *MBTPS2* gene may lead to impaired cholesterol homeostasis and response to endoplasmic reticulum stress.[69-72] Keratosis follicularis spinulosa decalvans (KFSD), an inherited and rare skin condition, maps to Xp22.1 and is in many cases caused by mutations in the *SAT1* (OMIM # 313020) gene.[73,74] KFSD is a form of ichthyoses where the skin tends to be rough and thick with scaly appearance.[73-76]

Ocular features and lab investigations

Ocular findings in IFAP/BRESHECK syndrome may include sparse or completely absent eyelashes and eyebrow hair, keratitis with secondary photophobia often leading to corneal vascularization and scarring.[69-72] Affected individuals had severe photophobia, corneal vascularization and loss of vision.[77] The mother was a carrier having tortuous retinal vessels.[77] Abnormal findings in five patients in the form of corneal xerosis, vascularization, keratitis, opacity, and meibomitis.[78] Ocular findings in KFSD may include alopecia of the eyelashes and eyebrows. Blepharitis/conjunctivitis, photophobia and corneal dystrophy are characteristic ancillary findings.[79-81]

Lowe Oculocerebrorenal Syndrome

Genetics and pathobiology

Lowe oculocerebrorenal syndrome (OMIM # 309000) is an X-linked rare disorder caused by mutations in the *OCRL* (OMIM # 300535) gene and affects the eyes, central nervous system and kidneys.[82,83]*OCRL* contains 24 exons encoding inositol-5-phosphatase protein family member, OCRL1, involved in regulating membrane trafficking.[83,84]

Ocular features and lab investigations

Ocular findings may include abnormal lens development probably due to abnormal migration of lens epithelium in fetuses, leading to opacification of varying degree in affected individuals. Neonates may present with miosis, leukocoria, microphthalmos and a shallow anterior chamber. Half of the affected males or more may present with early onset glaucoma that may be difficult to control. Corneal and conjunctival keloids may be found in about one-fourth of patients.[82-86] Peripheral cortical opacities that appear in a radial configuration on slit-lamp examinations may be the characteristics of adult carrier females.[82-86] Bilateral cataracts (observed at birth), strabismus, elevated intraocular pressure, corneal edema with Haab's striae, iris stroma with ectropion uvea and peripheral staphyloma of ciliary body have also been reported.[86] Loss of axons, optic nerve head cupping and optic nerve atrophy can be present.[86]

Megalocornea

Genetics and pathobiology

Megalocornea (OMIM # 309300) is an inherited eye disorder caused in many cases by mutations in the *CHRDL1* (OMIM # 300350) (Xq23) gene, with affected individuals having bilaterally enlarged corneal diameter without increased intraocular pressure.[87-92] The encoded protein is expressed in the retina, corneal development, anterior segment and may play a role in regulation of retinal angiogenesis in response to hypoxia and topographic retinotectal projection.[87-92]

Ocular features and lab investigations

Ocular findings may include enlarged corneal diameter at birth that may be between 13.0 and 16.5 mm, early arcus with eventual crocodile shagreen pattern in the cornea, deep anterior chamber, iridodonesis, iris thinning and presenile cataracts. Mild cone system dysfunction may be revealed in the ERG of some patients.[88-94]

Microphthalmia, Syndromic 1

Genetics and pathobiology

Lenz microphthalmia syndrome (OMIM # 309800) is a rare X-linked disorder mapping to Xq27-q28, which includes *NAA10* (OMIM # 300013).[95,96] Encoded protein, *N*-terminal acetyltransferase, functions as the catalytic subunit of amino-terminal acetyltransferase *A* complex.[95,96] Protein has role in *N*-alpha-acetylation, post-translational protein modifications essential for normal cell function.[95,96]

Ocular features and lab investigations

Ocular findings in lenz microphthalmia may include abnormally small (microphthalmia) or absent (anophthalmia) eyballs, leading to vision loss or blindness. Nystagmus, cataract, coloboma, glaucoma, ocular cysts have also been reported. Bilateral colobomas involving the choroid, optic disc, iris and ciliary body is often present.[95-99]

Myopia 1, X-Linked (MYP1)

Genetics

Myopia (nearsightedness; OMIM # 309800), a refractive error of the eye, has been mapped to Xq28 locus.[100-102] Studies have also confirmed the involvement of a unique *OPN1LW* haplotype in syndromic and nonsyndromic X-linked high myopia.[101,102]

Ocular features and lab investigations

Ratnamala *et al*. described two large multi-generation Asian Indian pedigrees with affected males having variable degree of myopia ranging from −6 to −23 D (mean, −8.48 D).[100] Age of onset was between ages 4 and 12 years. Color vision defect or night blindness was absent. Affected individuals had myopic fundus changes, mild-to-moderate reduced cone responses, high myopia and mild protanomaly.[101]

Night Blindness, Congenital Stationary

Genetics and pathobiology

Congenital stationary night blindness (CSNB), a genetically and clinically heterogeneous non-progressive retinal disorder, mainly affects photoreceptors, RPE or bipolar cells. X-linked CSNB may be caused by mutations in the *NYX* (OMIM # 300278) and *CACNA1F* (OMIM # 300110) genes.[103-111] *NYX* gene mutations may be responsible for nearly half of the X-linked CSNB, leading to the complete form or CSNB1A. The product of this gene is a 476-amino-acid polypeptide expressed in the eye during all stages of postnatal retinal development and belonging to a small leucine-rich proteoglycan family of proteins.[103-111] *CACNA1F* gene mutations may explain more than half of the X-linked CSNB and result in CSNB2A.[103-111] *CACNA1F* encodes an alpha-1 subunit of the voltage-dependent calcium channel which is a multipass transmembrane protein mediating the influx of calcium ions into the cell.[111]

Ocular features and lab investigations

Ocular findings in CSNB1A include severe night blindness, mild-to-severe myopia and completely absent rod function. Affected individuals had early childhood night blindness, variable degrees of myopia and decreased visual acuity.[103] Latent nystagmus and dissociated vertical deviation combined with extropia was also reported.[103] In CSNB2A, myopia may range from mild to severe with residual rod function being diminished. Cone function might be impacted to some degree and mild dyschromatopsia may be an associated finding.[103-111] Based on ERG, individuals with X-linked CSNB are the Schubert–Bornschein type with scotopic b-wave amplitudes being reduced in response to bright flashes after dark adaptation.[103-111]

Norrie Disease

Genetics and pathobiology

Norrie disease (OMIM # 310600) is an X-linked disorder resulting from mutations in the *NDP* (OMIM # 300658) gene (Xp11.4), leading to blindness in male infants at birth or soon after birth.[112-117] *NDP* comprises of three exons spanning 28 kb and encodes the norrin protein.[112-117] Norrin may play an important role in cell proliferation, adhesion, migration and may participate in Wnt signaling.[112-117]

Ocular features and lab investigations

Ocular findings include leukocoria, iris atrophy, microphthalmos, synechiae, cataracts and sclerocornea.[112-117] Affected individuals had bilateral retinal folds with retinal detachment and macular traction.[115] Hemorrhagic necrosis of an undifferentiated glial mass was revealed in histology.[114] Absence of the ganglion cells and dysplasia of neuroretina layers were also reported.[114] Progressive hearing loss, mild-to-moderate intellectual disability (often with psychosis), and developmental delays in motor skills are other abnormalities associated with this disease.[112-117]

Nystagmus 1 and 6, Congenital, X-Linked

Genetics and pathobiology

Numerous ocular and systemic disorders may have congenital nystagmus as one of the features. However, isolated idiopathic congenital nystagmus represents a diverse group of abnormal eye movements usually identified in the first six months of life, when other ocular abnormalities are absent. Nystagmus 1, Congenital, X-linked is caused by mutations in the *FRMD7* (OMIM # 300628) gene.[118-125] *FRMD7* contains 12 exons and encodes a 714-amino-acid polypeptide known to be expressed in areas of the brain that control eye movement and in the retina.[121] Nystagmus 6, Congenital, X-linked is attribute to mutations in the *GPR143* (Xp22.2) gene.[126-128]

Ocular features and lab investigations

Ocular findings include typical horizontal (to-and-fro) eye movements with reports of vertical and rotary eye movements.[118-128] Decrease in nystagmus amplitude and increase in frequency of the nystagmus are observed as the patient grows older. Strabismus and amblyopia may often develop.[118-125] Affected individuals had horizontal oscillations of both eyes, head nodding, mild myopia and constant horizontal eye movement.[119]

Optic Atrophy 2, X-Linked

Optic atrophy 2 is an X-linked recessive disorder mapping to Xp11.4–p11.21. Katz *et al*. reported six affected males with decreased visual acuity from early childhood and significant optic nerve pallor affecting a three-generation family from Idaho.[129] In males, the visual acuities ranged from 20/30 to 20/100, while carrier females were clinically unaffected. No other neurological abnormalities were observed in any family members. Variably defective color vision and central scotomas may also be present.[129-130]

Pelizaeus–Merzbacher Disease (PMD)

Genetics and pathobiology

PMD (OMIM # 312080) is caused by mutations in an X-linked gene *PLP1* (OMIM # 300401) (Xq22).[131-137] Nystagmus, spastic quadriplegia, ataxia and developmental delay are characteristic features of PMD.[131] In PMD, myelin is not formed properly in the central nervous system, making it a hypomyelinative leukodystrophy.[131] The *PLP1* gene encodes a transmembrane proteolipid protein that plays an important role in the stabilization, compaction and maintenance of myelin sheaths. Furthermore, the protein is also important for development of oligodendrocyte and axonal survival.[135]

Ocular features and lab investigations

A major ocular feature in this disease is nystagmus appearing early in life. Pendular ocular movements with occasional horizontal and rotatory components may also be observed. The presence of nystagmus is an uncommon finding in other leukodystrophies and may be diagnostically important in PMD.[131-135] Nystagmus usually goes away as the condition worsens, but other movement disorders including spasticity, ataxia, titubation, and dystonia may develop.[131-137]

Retinitis Pigmentosa 2 and 3, X-Linked

Genetics and pathobiology

Retinitis pigmentosa is a group of clinically and genetically heterozygous disorders with X-linked forms being caused by mutations in *RPGR* (OMIM # 312610) (Retinitis Pigmentosa 3, X-Linked) and *RP2* (OMIM # 300757) (Retinitis Pigmentosa 2, X-Linked) genes.[138-140] The retina, a light-sensitive tissue layer at the back of the eye, is affected in these disorders. At least 10 alternatively spliced transcripts of *RPGR* have been

identified, with RPGR^{CONST} and RPGR^{ORF15} being the two major identified RPGR isoforms.[138] *RP2* spans approximately 45 kb on chromosome Xp11.3–11.23 and contains five exons, encoding a protein of 350 amino acids that is ubiquitously expressed. Myristoylation and palmitoylation at its *N*-terminus help this protein localize at the plasma membrane where it functions as a GTPase-activating protein.[138]

Ocular features and lab investigations

Ocular findings in X-linked retinitis pigmentosa 2 and 3 include vision loss, night blindness, pigmentary changes in the retina and field constriction.[138-149] In a study by Jiang *et al*., affected males had night blindness, fundus changes included waxy-pale optic disc, retinal arteries had attenuation, and mid periphery of the retina had bone-spicule pigment deposits.[138] In a study by Mawatari *et al*. affected individuals had reduced visual acuity, night blindness, photophobia, peripheral visual field defect and color vision abnormality.[140]

Spastic Paraplegia 2

Spastic paraplegia type 2 (OMIM # 312920), an X-linked disorder secondary to a mutation in the *PLP1* gene at Xq22.2, is characterized by spasticity and paraplegia.[150-152] Spastic paraplegia type 2 is allelic to the more severe PMD discussed earlier.[131,150] Nystagmus and optic atrophy are ocular findings reported.[150-152]

Conclusion

Ocular findings can be of paramount importance in precise diagnosis of X-linked disorders. This is especially true for X-linked recessive disorders that are rare and may be clinically and genetically heterogeneous. With the availability of databases like ClinVar and Online Mendelian Inheritance in Man (OMIM), it has become easier to access genomic data and look for any casual variant associated with a disease. Combining the ocular findings by using modern instruments and genomic data available in public databases, precise disease diagnoses can be achieved. This review, a compilation of ocular findings and genomics of X-linked recessive disorders, will help clinicians and basic researchers better diagnose and manage these disorders. This is, to our knowledge, one of the very few papers compiled on ocular genetics of X-linked recessive disorders.[153]

Author contributions

R.A.H.K conceived the manuscript. A.S, Y.R.M and R.A.H.K wrote and edited the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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