Understanding Retinal Dystrophies: Genetics and Clinical Features

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Abstract

Retinal dystrophies include a wide range of inherited disorders that primarily affect the retina, resulting in progressive vision loss due to the regeneration of photoreceptors and the retinal pigment epithelium. This chapter offers a comprehensive examination of various major retinal dystrophies, including both syndromic and non-syndromic forms, with an emphasis on their genetic and molecular bases, underlying pathophysiological mechanism, and varied clinicals manifestations.These conditions follow inheritance patterns that can be autosomal dominant, autosomal recessive, or X-linked. Prominent among these conditions are Sorsby Fundus Dystrophy, Doyne Honeycomb Retinal Dystrophy, Occult Macular Dystrophy, and North Carolina Macular Dystrophy, which are characterized by macular involvement and progressive degeneration of retinal tissues. Butterfly-shaped Pigment Dystrophy, Fundus Pulverulentus, Pseudo-Stargardt Pattern Dystrophy, and Sjögren's Reticular Pattern Dystrophy, contribute to the diversity of presentations. Other notable retinal dystrophies include Retinitis Pigmentosa, Stargardt Disease, Leber Congenital Amaurosis, and Best Vitelliform Macular Dystrophy, each presenting distinct genetic mutations and clinicals features. Genetic mutations in a wide array of genes, play crucial roles in the pathogenesis of these diseases, leading to abnormal deposits, choroidal neovascularization, and progressive retinal degeneration. Understanding the genetic mechanism and clinical course of retinal dystrophies is vital for advancing diagnostic accuracy, prognostic prediction and the development of effective treatments strategies.

Keywords: Syndromic IRDs, Non-Syndromic IRDs, Clinical Symptoms, Genetics

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Introduction

Inherited Retinal Dystrophies

These are among the leading causes of permanent vision loss and blindness in children and young (Bunce et al., 2010). Diagnosis can be challenging due to overlapping clinical symptoms and genetics heterogeneity across different IRDs (Hull et al., 2014). Different IRD are categorized based on factors like age of onset, inheritance pattern, site of retinal dysfunction (e.g., rod dominant, cone dominant and generalized retinal degeneration), rate of disease advancement , and links with syndromes (Holtan et al., 2020). The greater part of IRD cases is non-syndromic, affecting only the eyes, but over 80 syndromic forms have been documented. More than 280 genes have been associated with different types of IRDs (https://sph.uth.edu/retnet/), leading to enhanced understanding and knowledge of their genetic causes. Some IRD loci have been mapped to specific chromosomal areas, though the responsible genes are still unidentified. These genes encode a broad spectrum of proteins, including structural proteins and transmembrane proteins, retinoid cycle proteins, and proteins implicated in phototransduction, exhibiting various patterns of inheritance (Tatour & Ben-Yosef, 2020).

Retinitis Pigmentosa

Affecting 1 in 5000 individuals globally, Retinitis pigmentosa marks as the most prevalent inherited retinal dystrophy that is predominantly bilateral, progressing with diverse clinical manifestations (Verbakel et al., 2018). It can be syndromic or non-syndromic (Weller et al., 2014) with nyctalopia often being the first symptom. As RP progresses, the visual field narrows, causing tunnel vision or blindness, along with reduced color discrimination, visual acuity, and photopsia, potentially leading to visual hallucinations in severe cases (Bittner et al., 2011; O'Hare et al., 2015). RP is a genetically heterogeneous condition involving mutations in over 80 genes critical for retinal functions like photoreceptor structure, phototransduction, visual cycle, and ciliary Approximately 3100 mutations have been identified, with inheritance including autosomal recessive (5-20%), autosomal dominant (15-25%), X-linked recessive (5-15%), and sporadic cases (40-50%) (Fahim et al., 2023). Common mutated genes include: *USH2A, ABCA4, CERKL, CRB1, EYS, PDE6A, PDE6B*, RPE65, *RP1*, and *SAG* in autosomal recessive *RP; RHO, RP1, CRX, GUCA1B, IMPDH1, KLHL7,* NR2E3*, PRPF8, PRPF3, PRPF31, PRPH2, SEMA4A, SNRNP200,* and *TOPORS* in autosomal dominant RP and *RPGR*, *RP2,* and *OFD1* in X-linked RP.

Usher Syndrome (USH)

It is a multifaceted genetic condition characterized by retinitis pigmentosa, bilateral sensorineural hearing loss, and in some cases, vestibular dysfunction. It is the leading cause of syndromic RP, accounting for 10-20% of the cases, and is the most prevalent type of deaf-blindness (Fuster-García et al., 2021). USH is an autosomal recessive disorder , including three subtypes with distinct clinical and genetic features (Figure 1) (Karuntu et al., 2024). In USHI, five genes (*MYO7A, USH1C, CDH23, PCDH15*, and *USH1G*) are involved in a protein network essential for retinal photoreceptors and inner ear function (Reiners et al., 2006). USHIII is primarily linked with USH2A gene mutations, accounting for 50-75% cases (Dreyer et al., 2008). *USHIII* linked to CLRN1, is widely studied in Finnish and Ashkenazi population because of founder mutation (Ness et al., 2003). The *CLRN1* gene encodes clarin-1, localized clari-1, localized in photoreceptor synapses and inner ear cells, with 11 known splice variants contributing to its phenotypic diversity (Västinsalo et al., 2011).

Usher subtype	Causative genes	Sensorineural hearing loss	Retinitis pigmentosa	Vestibular function
Usher 1	*MYO7A, USH1C, CDH23, PCDH15, USH1G, CIB2*	Congenital, severe to profound	Prepubertal onset; average age of diagnosis in second decade; legal blindness in fourth decade	Vestibular hypofunction; motor development may be delayed; infants typically do not walk before 18 months of age
Usher 2	*USH2A, ADGRV1, WHRN*	Congenital, moderate to severe; high frequencies most affected	Onset in second decade; average age of diagnosis in third decade; legal blindness in sixth decade.	Normal vestibular function
Usher 3	*CLRN1*	Post-lingual onset, progressive, variable	Variable onset, typically in second decade	Variable; vestibular abnormalities in ~50% of patients, usually mild

Fig. 1: Usher Syndrome

Alstrom Syndrome

It is rare genetic disorder, manifested by muated *ALMS1* gene, which affect cilliary functions ,intracellular transport , and cell cycle (Hanaki, 2024). This condition affects multiple organ system and is characterized by early-onset version and hearing loss, childhood obesity , type 2 diabtes with severe insulin resisitance, cardiomyopathy, renal dysfunction, and endocrine issues.Additionally complications, such as liver damage and hypogonadism ,vary in the onset,typically appealing from infancy to adolescence . The syndrome accounts for 20% of inherited retinal dystrophies , with a prevalence of 1 in 1000-4000 individuals (Perea-Romero et al., 2021). Alström syndrome is linked to mutation in ALMS1, mainly nonsense mutations, insertions, and deletions with exons 8,9 and 16 being recognized as primary mutation hotspots (Bdier et al., 2020).

Senior- Loken Syndrome (SLS)

It is an autosomal recessive disorder characterized by RP or Leber congenital amaurosis, and nephronophthisis (NPHP), an autosomal recessive kidney disease that is the leading cause of end-stage renal disease (ESRD) in children and adolescents (Wolf & Hildebrandt, 2011). Mutations in 13 genes (*NPHP1-13*) cause NPHP and associated retinal degeneration, with proteins localized in the connecting cilium of photoreceptor cells and kidney primary cilia. Nephronophthisis, the prominent clinical feature, leads to ESRD, typically diagnosed around age 13, with symptoms like polyuria, nocturia, and progressive kidney atrophy seen in ultrasound scans. The majority of genes involved in Senior-Loken syndrome are expressed in the photoreceptor connecting cilium, a structural counterpart of the primary cilium found in most body cells (Ronquillo et al., 2012). Various mutations have been identified causing nephronopthisis, with autosomal recessive inheritance, although transmission can be monogenic or digenic (Lifton et al., 2009). The implicated genes include: *NPH1*, *NPH2*, *NPHP3*, *NPHP4*, *IQCB1* and others. The presence of RP alongside nephronopthisis, referred to as Senior-Loken syndrome, depends on the mutated nephrocystin gene.

Bardet-Biedl Syndrome

It is a genetic ciliopathy presented by polydactyly, renal malfunction, and hypogonadism, with a prevalence influenced by consanguinity (Karuntu et al., 2024). The most notable feature includes retinal dystrophy, with 90% of affected individuals experiencing rod-cone dystrophy and early macular involvement life's first decade, leading to a progressive loss of night vision, peripheral vision, color discrimination, and visual acuity (Figure 2) (Mockel et al., 2011). Some patients also develop nystagmus, cataracts, and diabetic retinopathy due to associated type 2 diabetes (Meng et al., 2021). Obesity, cognitive impairment, postaxial polydactyly, developmental delay, renal impairment, and hypogonadism are other notable features, while minor features may involve neurodevelopmental, dental, cardiovascular, gastrointestinal, and endocrine abnormalities (Karuntu et al., 2024). BBS the most frequent syndromic RP after the Usher syndrome, inherited in an autosomal recessive

manner and caused by mutations in 26 known BBS genes. Key disease-causing mutations in genes (*BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9,* and *BBS18)* impair the BBSome, an octamer multiprotein complex essential for ciliary signaling and photoreceptor function (Chandra et al., 2022).

Fig. 2: Primary and secondary features of BBS.

Mackel- Gruber Syndrome

It is a rare autosomal recessive disorder compromising the central nervous system, kidneys, and normal development of the hands and feet The incidence ranges from 1 in 1,350 to 1 in 140,000, with a 100% mortality rate (Alexiev et al., 2006). Most affected children are stillborn or die shortly after birth, with common features including orofacial cleft, cardiac malformations, ductal plate deformity of the liver, and partial genital development. Classic malformations associated with MKS include cystic renal dysplasia, occipital encephalocele, central nervous system abnormalities, and postaxial polydactyly. MKS exhibits significant genetic heterogeneity and allelism with other ciliopathies, such as COUCH syndrome, Joubert syndrome, oro-facio-digital syndrome, and Bardet-Biedl syndrome. Mutations in 14 genes have been identified, with notable associations found in *C5orf42*, *CSPP1*, and *CEP55* (Bondeson et al., 2017)**.**

Joubert Syndrome

This rare and phenotypically diverse disorder is marked by developmental abnormalities in the nervous system, including cerebellar vermis aplasia and the " molar tooth " sign observed on brain scans. Retinal dystrophy, typically presented as Leber Congenital Amaurosis (LCA) or early -onset retinitis pigmentosa, is a common extra – neurological feature, affecting 24-30% of patients. Retinal manifestations range from congenital to adolescence, with variations including rod – cone or cone -rod dystrophy (Brooks et al., 2018). System symptoms include developmental delays, ataxia, hypotonia, intellectual disability, and breathing irregularities, with characteristic facial features such as widely spaced eyes and multicystic kidney disease (Bachmann-Gagescu et al., 2020). It is primarily caused by mutations in the *AH1, CC2DA, CEP290*, *CPLANE1*, and *TMEM67* genes, each responsible for 6-9% of cases. Approximately 3% of cases are linked to biallelic pathogenic variants in *INPP5E, CSPP1*, and *TMEM* (Sangermano et al., 2023).

Cohen Syndrome

The disorder is predominantly marked by progressive myopia and pigmentary retinopathy, with patients often developing night blindness and, in some cases, a constricted visual field by age 6, which typically leads to a diagnosis of retinitis pigmentosa a few years later (Nasser et al., 2020).

Additional ophthalmic manifestations, including nystagmus, microphthalmia, strabismus, retinoschisis, and coloboma of the retina or eyelids, are seen less frequently but still contribute to the overall presentation. Beyond ophthalmic manifestations, Cohen syndrome is marked by neurological and developmental abnormalities, craniofacial defects, and hematological and immunological issues. Pathogenic variants in the VPS13B (COH1) gene leading to aberrations in the transportation and cellular sorting of protein at golgi complex (Seifert et al., 2015) cause Cohen syndrome. The absence of the encoded protein causes defective neurite outgrowth and disrupts the normal trafficking of proteins between the inner and outer segments of photoreceptors, which contributes to the loss of function (Uyhazi et al., 2018).

Neuronal Ceroid Lipofuscinosis

It is the most prevalent hereditary neurodegenerative diseases in case of children. The disease is marked by the accumulation of lipofuscin, a toxic protein-lipid aggregate, within lysosomes in the central nervous system, particularly in neurons. These lipofuscin granules, are autofluorescent and can disrupt the cytoskeleton of neurons and intracellular transport, leading to neuronal degeneration and glial cell proliferation. Progressive vision loss, cognitive decline, and seizures, a condition later termed "amaurotic familial idiocy" by Sachs (Simonati & Williams, 2022). Key symptoms of NCLs include progressive visual impairment, dementia, seizures, and motor deficits. Neuronal ceroid lipofuscinoses (NCLs) are triggered by mutations in genes encoding proteins implicated in lysosomal activity, transport, and membrane repair. These genes, include *CLN1* to *CLN14*, and follow an autosomal recessive inheritance pattern (Jalanko & Braulke, 2009).

Leber Congenital Amaurosis

It is a rare autosomal recessive genetic disorder, that typically manifests in early childhood with symptoms like congenital nystagmus, slow pupillary light response, eye-poking behavior (oculo-digital sign), and difficulty tracking light or objects (Coussa et al., 2017). By the second year of life, two clinical types of LCA emerge; a severe, non-progressive cone-rod dystrophy with intense photophobia, hyperopia, and severely reduced visual acuity, and a progressive rod-cone dystrophy, where rod cells are affected first, followed by cone cells (Figure 3). It is a genetically diverse retinal disorder, with mutations in over 38 genes responsible for around 75% of cases. Most mutations are autosomal recessive, except for *CRX* and *IMPDH1* mutations, that affect retinal processes like the phototransduction, the retinoid cycle , ciliary function, photoreceptor morphogenesis, and guanine production (Huang et al., 2021).

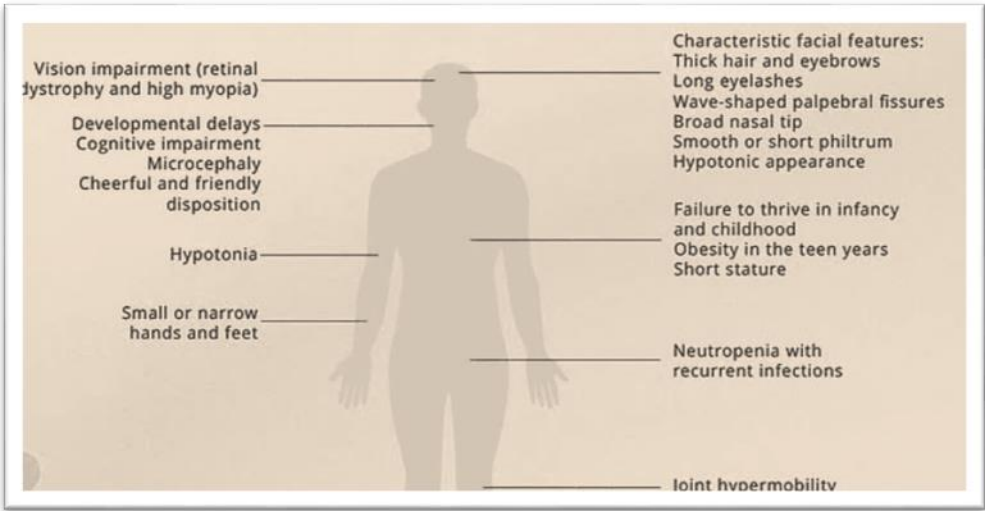

Fig. 3: Clinical symptoms of Cohen syndrome

Congenital Stationary Night Blindness

It is a non-degenerative inherited retinal condition categorized by congenital nyctalopia, along with symptoms like myopia, nystagmus, strabismus, and occasionally photophobia (Almutairi et al., 2021) . It involves photoreceptor dysfunction and can be inherited in either autosomal dominant or recessive forms. Fundus Albipunctatus presents scattered white dots on the retina, while Oguchi disease is noted for a golden-yellow retinal coloration that reverses after dark adaptation CSBN is a genetically diverse disorder with mutations in at least 17 genes affecting phototransduction, signal transmission, and retinoid recycling. Key genes include *GNAT1, PDE6B, RHO, GRM6, TRPM1, GPR179, NYX, RDH5, RPE65, CACNA1F, CABP4, CACNA2D4*. Inheritance patterns are X-linked (*NYX, CACNA1F*), autosomal dominant (*RHO, GNAT1*), or autosomal recessive (*GRM6, TRPM1*) (Zeitz et al., 2015).

Stationary Cone Dystrophies

It is a stable, inherited retinal disorder affecting the cones. It is congenital and does not worsen over time like progressive cone dystrophy, with normal rod function preserved. CDS typically presents at birth or early infancy, causing vision loss, light sensitivity, nystagmus, and varying degrees of color vision impairment. The symptoms become more noticeable as the foveal cone cells degrade, affecting about 5% of the retina's photoreceptor cells (Michaelides et al., 2004). Several genes are associated with five forms of cone dysfunction disorders, Bornholm eye disease, blue-cone monochromatism, oligocone trichromacy, complete and partial achromatopsia, and Bradyopsia (Schornack et al., 2007).

Progressive Cone Dystrophies

These include a category of retinal conditions in which the cone photoreceptor cells gradually lose their function, causing decline in vision; sharpness and deterioration of color vision. Clinical signs may include visual field problems, like ring-shaped scotomas, central scotomas, peripheral vision loss, and general sensitivity loss, alongside light sensitivity and uncontrolled eye movements (nystagmus) as noteworthy characteristics (Krauss & Heckenlively, 1982). Progressive cone dystrophies has been documented with autosomal dominant, autosomal recessive, and X-linked recessive inheritance patterns linked to several mutated genes, such as *GUCA1A, RPGR, CNGB3, CNGA3, COD2, RCD1,* and *RCD2* (Michaelides et al., 2006).

Achromatopsia

Complete achromatopsia, or rod monochromatism, is an uncommon and rare, non-progressive retinal disorder marked by the lack of functional cone photoreceptors. It presents with early-onset symptoms like pendular nystagmus, photophobia, and low visual acuity, often accompanied by hypermetropic refractive error (Sharpe & Gegenfurtner, 1999). Visual acuity typically remains at 6/60, and affected individuals have no color vision. Achromatopsia is caused by mutations in *CNGB3* (40-50%), *CNGA3* (25%), *GNAT2* (<2%), PDE6C (<2%), and *PDE6H*. The phototransduction cascade activates *GNAT2*, which interacts with *PDE6C* and *PDE6H*, leading to membrane polarization through CNGA3 and CNGB3 channels (Genead et al., 2011)

Stargardt Disease (STGD1)

It the most common inherited macular disorder, inherited in an autosomal recessive pattern (Britten-Jones et al., 2023). It is caused by

autosomal recessive mutations in the *ABCA4* gene. Clinically, progressive central vision loss starting in childhood or early adulthood, although later onset and foveal sparing cases have been reported in this disease (Moore et al., 2015). The mutated *ABCA4* gene encodes a protein crucial for removing phototransduction byproducts from photoreceptors and preventing their accumulation in the retinal pigment epithelium.

Bestrophinopathies

It is caused by mutations in the BEST1 gene, encompasses a range of autosomal dominant and recessive disorders, including Best disease, Adult vitelliform macular degeneration (AVMD), and Autosomal recessive bestrophinopathy (ARB), which primarily affect the macular region and mostly appear in the first 20 years of life (Shah et al., 2020). These conditions mainly affect the retinal pigment epithelium, where the BEST protein functions as an ion channel crucial for retinal maintenance. Besrophinopathy can also resemble retinitis pigmentosa, complicating diagnosis due to overlapping clinicals features (Brodsky et al., 2019).

Best Vitelliform Macular Dystrophy (BVMD)

It is also known as BEST disease, with onset varying from the first to the sixth decade of life, progressing through distinct stages, starting with an asymptomatic carrier phase pre -vitelliform , material, and finally reaching the cicatricial stage with chorioretinal atrophy and subretinal scarring. The underlying cause is dysfunction of the retinal pigment epithelium, leading to abnormal ionic transport and the accumulation of subretinal fluid and vitelliform material, consists of waste products from photoreceptor outer segments and pigmented cells laden with lipofuscin (Boon et al., 2009). BVMD a type of bestrophinopathy, is caused by autosomal dominant mutations in the *BEST1* gene, which encodes the bestrophin-1 protein, that functions as a calcium-activated chloride channel in RPE cells and modulates voltage-gated calcium channels (Gómez et al., 2013). Additionally, *PRPH2* variants have been associated with *BVMD*, and other genes, such as *C1QTNF5, EFEMP1, FSCN2, GUCA1B, HMCN1, IMPG1, RP1L1,* and *TIMP3*, contributing to autosomal dominant macular dystrophies.

Adult-onset Foveomacular Vitelliform Dystrophy (AOFVD)

It typically presents as bilateral, symmetrical, grayish-yellow lesions in the macula, usually between ages 30Y and 50Y, with a suggested autosomal dominant inheritance pattern. It causes slow, progressive central vision loss, but may worsen rapidly if subfoveal choroidal neovascularization (CNV) develops (Gass, 1974). The disease progresses through the previtelliform stage, to the vitelliform stage, then the pseudohypopyon stage, and the vitelliruptive stage. The exact cause remains unclear, though leakage from perifoveal and subfoveal capillaries has been found to take part in the formation of vitelliform lesions in he disease. More recent studies point to lipofuscin accumulation as the primary factor behind retinal dysfunction (Dubovy et al., 2000).

Autosomal Recessive Bestrophenopathy (ARB)

It is a rare genetic retinal disorder menifested by mutations in the *BEST1* gene, similar to Best vitelliform macular dystrophy (Best disease), unlike its inheritance pattern. To develop ARB, two mutated copies of the gene, either in a homozygous or compound heterozygous state must be inherited (Burgess et al., 2008). ARB typically presents in childhood or adolescence, with onset ranging from 3 to 25 years. Clinical features include variable visual loss, hyperopia, angle-closure glaucoma, yellowish subretinal deposits, macular cysts, subretinal fluid. Fundus autofluorescence reveals multiple white flecks in the posterior retina, and some cases exhibit subretinal deposits or RPE atrophy with scars (Figure 4). Additional symptoms include metamorphopsia, photophobia, night blindness, floaters, intraretinal fluid, hypermetropia, and increased risk of angle-closure glaucoma (Casalino et al., 2021).

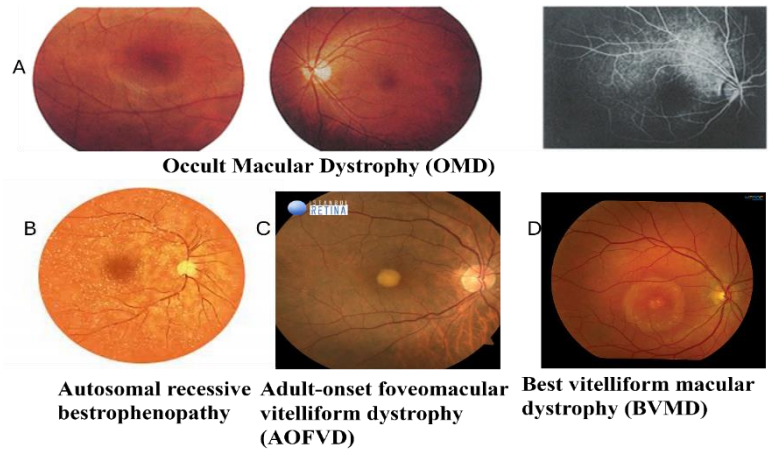

Fig. 4: Fundus images of some diseases.

X-linked Retinoschisis (XLRS)

It is a rare inherited retinal disorder primarily affecting males and is the most notable form of juvenile-onset macular degeneration due to its X-linked recessive inheritance pattern (Rahman et al., 2020). It is characterized by retinal layer splitting (schisis), particularly in the macula and peripheral retina. XLRS typically manifests in first or second decade of life, with symptoms like reduced visual acuity, strabismus, anisometropia, and unexplained visual loss. The hallmark feature is macular schisis, often presenting as "spoke-wheel" folds, though this may progress to nonspecific macular atrophy in older individuals. XLRS is linked to mutations in the *RS1* gene, which encodes retinoschisin, a protein essential for retinal cell adhesion. Pathogenic variants in *RS1* disrupt the protein's subunit assembly, causing retinal layer splitting and progressive vision loss due to retinal dysfunction (De Silva et al., 2021).

Sorsby Fundus Dystrophy (SFD)

It is a rare inherited retinal disorder characterized by progressive vision loss, primarily due to subretinal deposits, retinal atrophy, and macular degermation. Inherited in an autosomal dominant pattern,(Georgiou et al., 2024). Symptoms typically begin in the fourth or fifth

decade of life.

Early signs include yellowish grey, drusen-like deposits in Bruch's membrane (BM). As the disease progresses, macular involvement leads to visual distortions like metamorphopsia. Over time, these deposits affect the central macula, causing gradual atrophic degeneration, resulting in central vision loss. Peripheral involvement typically occurs by the fifth decade. Choroidal neovascularization (CNV) often complicates the disease, leading to significant visual acuity loss (Mohla et al., 2016). SFD is linked to missense variants in the *TIMP*3 gene, that normally inhibits matrix metalloproteinases, and its mutations disrupt extracellular matrix remodeling, impairing the function of BM, the choroid, and RPE.

Doyne Honeycomb Retinal Dystrophy (DHRD)

It is also known as Malattia Leventinese or EFEMP1-associated autosomal dominant drusen, succeeded in an autosomal dominant pattern is a uncommon genetic eye disorder. Symptoms usually begin in the second to fourth decade of life, with significant vision loss occurring in the advanced stages. The drusen deposits in this condition often exhibit a radiating or honeycomb-like pattern, typical to this disease, and are commonly found adjacent to the optic nerve head (Michaelides et al., 2006). Visual impairment results from varying degrees of central atrophy or complications such as choroidal neovascularization (CNV) (Cusumano et al., 2023). Symptoms include blurred or distorted central vision (metamorphopsia), decreased visual acuity, difficulty seeing in low light, and trouble with fine visual tasks like reading. It resulted by mutation in the EFEMP1 gene, which encodes fibulin-3, an extracellular matrix protein, leading to the accumulation of membranous debris beneath the retinal pigment epithelium, associated with complement activation and RPE atrophy, as seen in mouse model of ADD (Hulleman, 2016).

Occult Macular Dystrophy (OMD)

It is a rare inherited retinal disorder that primarily affects macula, leading to progressive central vision loss, typically manifesting between late childhood and early adulthood (age 20-40).

Despite normal fundus and fluorescein angiograms, patients may have trouble with tasks requiring detailed vision and may develop symptoms like metamorphopsia. As the disease progresses, subtle retinal changes, including macular atrophy and retinal pigment epithelium abnormalities may appear. Autosomal dominant is the primary hereditary pattern, with mutations in *RP1L1,* though some cases are sporadic, lacking these mutations (Nakamura et al., 2019).

North Carolina Macular Dystrophy (NCMD)

It is a rare autosomal dominant disorder affecting macula, resulting in loss of vision that is progressive in nature and typically starts in childhood or adolescence, with potential stabilization in 20s or 30s. Symptoms include blurred or distorted central vision, with visual distortions like wavy lines. Drusen-like yellow deposits often form in the macula are hallmark of macular dystrophies. Although rare, choroidal neovascularization can develop and affect visual acuity. NCMD results by mutated *PRDM13* gene, specifically at MCDR1 locus. PRDM13 is a transcription factor that regulates genes involved in retinal cell development, and mutations or altered expression of this gene disrupt normal retinal function (Small et al., 1993).

Butterfly-shaped Pigment Dystrophy

Butterfly-shaped pigment dystrophy of the fovea is an autosomal dominant ocular condition characterized by the bilateral accumulation of yellowish or pigmented deposits at the RPE, forming a distinctive butterfly-shaped pattern (Figure 5). The deposits are typically centered in the macula and can lead to gradual vision loss, particularly in central vision. Over time, the abnormal pigmentation expands, contributing to a decline in visual function (Tanner et al., 2021). Genetic causes vary by subtype. The condition is associated with Pattern Dystrophy of the (RPE), often caused by mutations in genes like *PRPH2, BEST1, CTNNA1,* and *PYGM*. *PRPH2* encoding peripherin-2, a structural protein critical for photoreceptor outer segment morphology (Wickham et al., 2009).

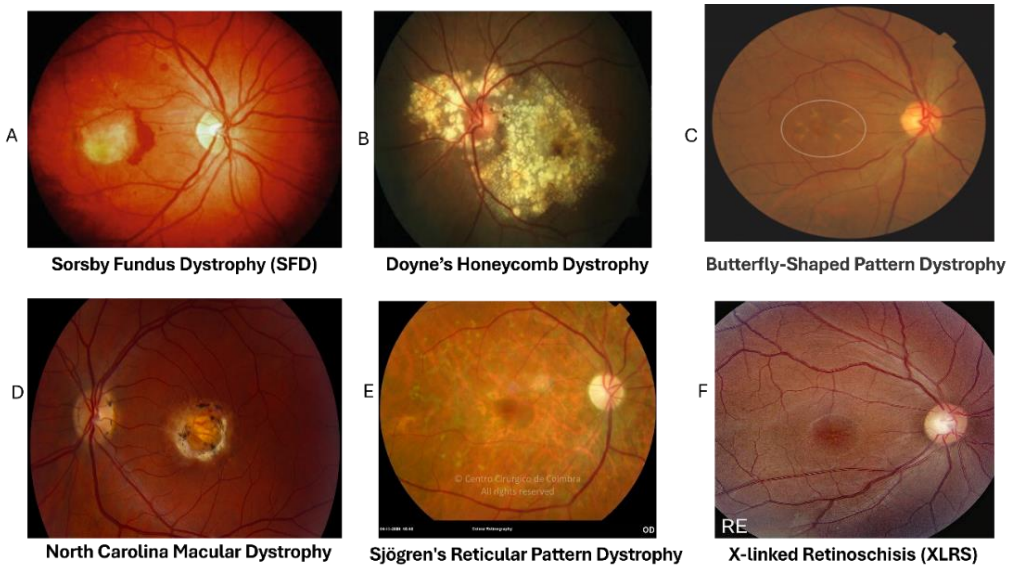

Fig. 5: Fundus showing hallmark features of some IRDs.

Pseudo-stargardt Pattern Dystrophy

It is a macular dystrophy resembling Stargardt disease but with a distinct genetic cause and clinical progression. It features abnormal pigmentation in the macula, often presented with hallmark of "fried-egg" or "sunflower" patterns, similar to Stargardt disease but without the typical *ABCA4* gene mutations (Miere et al., 2021), with symptoms manifesting as progressive central vision loss. Difficulty with tasks like reading/face recognition, and potential visual distortions like metamorphopsia occur mostly (Sodi et al., 2021). It is typically linked to alterations in genes affecting RPE or photoreceptor function, such as *VMD2*, associated with Best disease, or other macular dystrophy-related genes. This autosomal dominant condition is often caused by mutations in the *PRPH2/RDS* gene, which can mimic the presentation of Stargardt disease.

Sjögren's Reticular Pattern Dystrophy

It is a rare, inherited retinal condition, presented by a distinctive net-like (reticular) pattern of pigmentary changes in the retina, primarily affecting RPE and leading to progressive central vision loss and macular degeneration. The reticular pattern, often seen in the parafoveal region, typically appears by infancy and is fully established by 15Y. As the disease progresses, retinal tissue loss and thinning, particularly in the macula, occur. Symptoms include gradual decline in central vision, distorted vision, straight lines appearing wavy, and the development of central scotomas. This dystrophy follows an autosomal dominant pattern, and is associated with mutations in the human retinal degeneration slow (RDS) gene and the peripherin gene (Ahmed & Sierpina DI, 2023).

Fundus Pulverulentus

It is a rare type of pattern dystrophy presented by fine, dust-like pigmentary changes in the retina, particularly at the level of the RPE, and is distinguished by coarse mottled pigmentation in the macula (Tan et al., 2016). Early-onset, or progressive over time, depending on the associated genetic or systemic condition. Associated conditions include RP, where fundus pulverulentus may present as an early or atypical form, Choroideremia, an X-linked retinal dystrophy affecting males, with pigmentary changes resembling pulverulent deposits; Stargardt Disease, where fundus changes may mimic a pulverulent appearance due to flecks of lipofuscin; and Best Vitelliform Macular Dystrophy, which may show pulverulent changes in atypical cases. Systemic syndromes such as Alport Syndrome can present with pulverulent pigment changes in addition to renal and auditory findings, and Bardet-Biedl Syndrome is associated with pigmentary retinopathy, sometimes showing pulverulent-like changes (Ebran et al., 2018). Fundus pulverulent is often linked to autosomal recessive or X-linked genetic mutations, depending on the associated disease. Genes involved include *PRGR, ABCA4, BEST1, USH2A*, and *BBS1/BBS10, COL4A3, COL4A4*, and *COL4A5* (Al-Khuzaei et al., 2021).

Conclusion

In conclusion, retinal dystrophies are a diverse set of inherited disorders that cause severe vision impairment, primarily through the progressive degeneration of the retina. This chapter reports a thorough assessment of the clinical features, genetic origins, and molecular mechanisms that underline various retinal dystrophies, each exhibiting distinct pattern of retinal alterations. The identification of specific genetic mutations has greatly advanced our understanding of the pathophysiology behind retinal degeneration. Despite the challenges, recent advancement in genetic testing, molecular research, and emerging therapeutic approaches offer hope for better management and treatment. Continued research will be critical in uncovering the full range of genetic variations involved, as well as in exploring innovative interventions such as gene therapy and retinal implants. Ultimately, gaining a deeper understanding of these retinal dystrophies will not improve diagnostic accuracy but also open the door to personalized treatments aimed at preserving vision and enhancing the quality of life for those affected.

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