INHERITED RETINAL DEGENERATIONS

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CHAPTER CONTENTS

AIMS

This unit aims to outline the diagnosis and management of inherited retinal degenerations via developing:

- A protocol for assessing the signs of inherited retinal degenerations
- A framework for making a differential diagnosis of the inherited retinal degenerations
- Management guidelines for the inherited retinal degenerations

LEARNING OBJECTIVES

At the end of these lectures and readings the student will be able to:
1. Understand the diversity of presentations of inherited and acquired retinal degenerations
2. Appreciate the complex nature of the aetiology of inherited and acquired retinal degenerations
3. Develop a plan for clinical investigation of these conditions
4. Understand that the treatment options are complex and are often still in early phase of development

BACKGROUND

This unit reviews the following areas:

1. Brief review of gross and cellular anatomy of the retina/choroid complex
2. How to clinically assess retina/choroid structure and function
3. Inherited retinal degenerations (e.g. retinitis pigmentosa, achromatopsia, juvenile macular degenerations); including review of genetic terms
4. Acquired retinal degenerations / retinopathies (e.g. AMD, autoimmune retinopathies)

NB: diabetic and hypertensive retinopathies can be considered as acquired retinopathies

Retinal dystrophies and degenerations include:

- Various disorders in which visual loss is due to photoreceptor degeneration or dysfunction * rod or cone dominated conditions
- Conditions with changed visual function and degeneration are generally associated with:
  - Patchy atrophy and associated pigmentary changes
  - Neuronal loss
  - Net loss of tissue volume
  - Astrocyte proliferation
  - Cyst development
- Many with a genetic component (inherited)
- Environmental conditions (ageing, drug-induced)
- Some that are relatively ‘stationary’

ANATOMY OF THE RETINA AND CHOROID

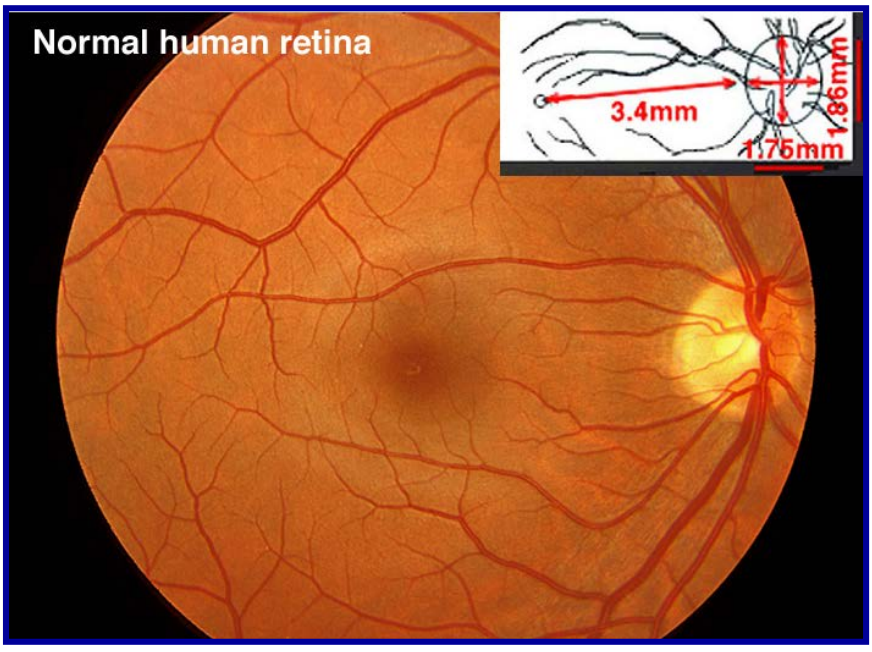

Figure 1: *The normal retinal appearance*

The thickness of the retina varies from the central region to the periphery (Figure 2). At the fovea the retina is approximately 150 microns (µm) thick and increases to about 300 µm at the foveal rim. In the periphery of the retina, the ora serrata is approximately 80 µm in thickness.

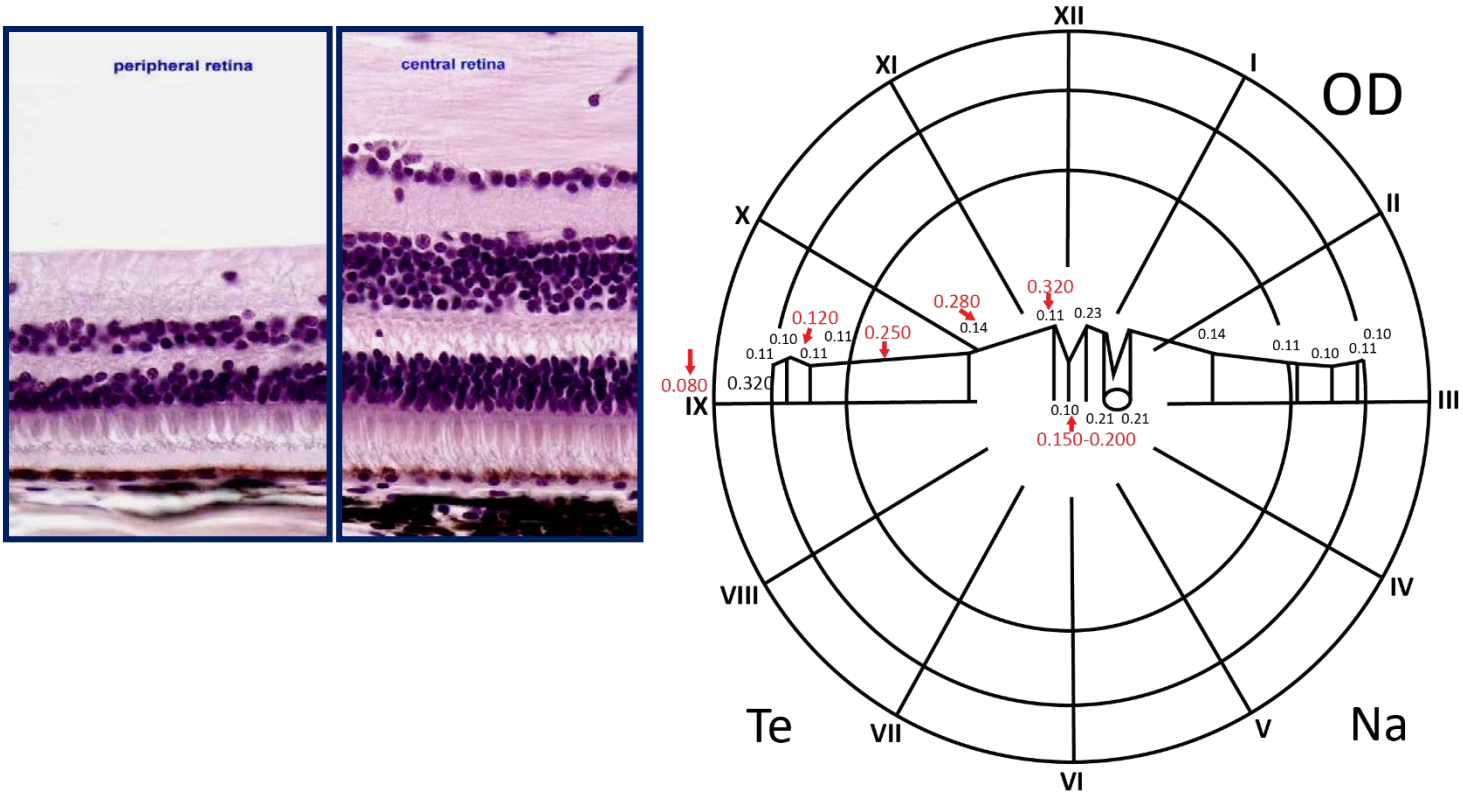

Figure 2: *Variation in retinal thickness*

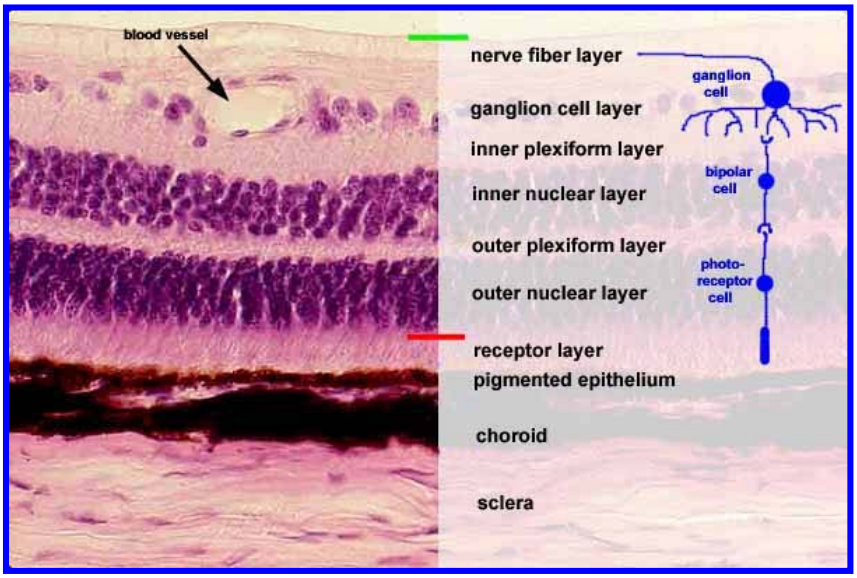

Figure 3: *The layers of the retina*

The choroid/choriocapillaris and the retinal pigment epithelium (RPE) are important for the health of the retina.
The main features of the choroidal blood supply are:

- It develops earlier than retinal blood supply
- The choriocapillaris supplies the outer 1/3 of the retina and importantly supplies the RPE and the retinal photoreceptors

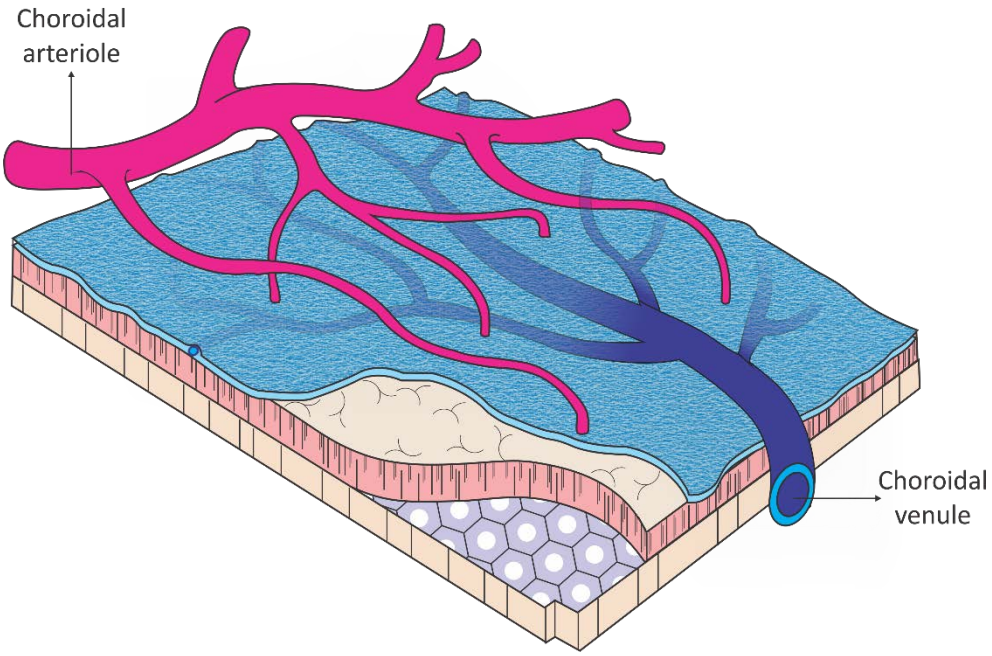

Figure 4: *Blood circulation in the choroid*

There are important differences to note when comparing the choroidal and retinal blood supplies

- Rate of blood flow; autoregulation
- Cell junctions ('tight' vs. 'leaky')
- Response to various growth factors

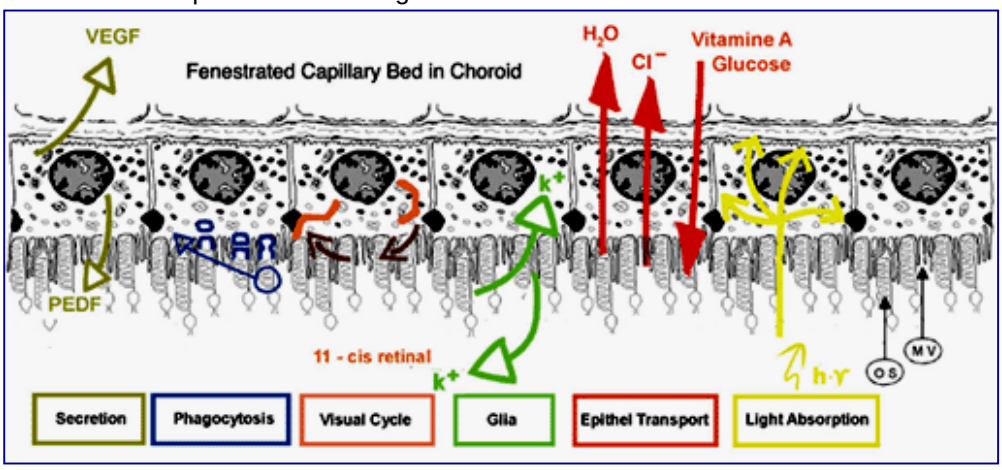

Figure 5: *Important features of the choroid*

EXAMINING THE POSTERIOR EYE

A large number of tests are available to assess the structure, health and integrity of the posterior eye including:

- Visual acuity assessment
- Pupil reactions
- Intraocular pressure (IOP) measurement
- Gonioscopy
- Visual fields (central and peripheral)
- Amsler chart
- Color vision perception
- Slit-lamp fundoscopy / ophthalmoscopy
- Dark adaptation

- OCT and HRT assessment (high definition approaches, etc.)
- Electrophysiology (ERG, VEP, EOG)
- Autofluorescence and angiography (fluorescein, ICG)
- Ultrasound (B-scan)

Assessment of the dark adaptation response is shown in Figure 6. The photopic response involves the cones. The mesopic response involves the cones and rods. The scotopic response involves the rods.

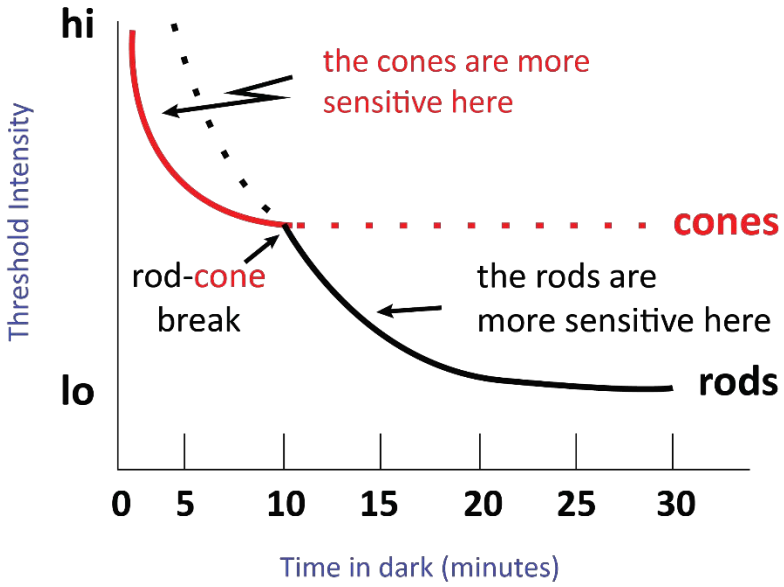

Figure 6: *Dark adaptation response curve*

In conditions that affect the retina such as age-related macular degeneration (AMD), the dark adaptation response curve is significantly changed (Figure 7).

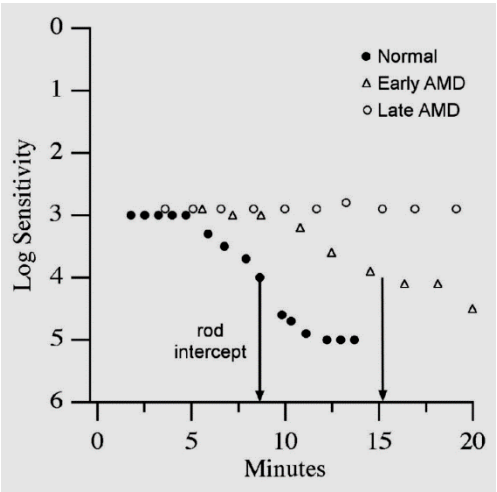

Figure 7: *The dark adaptation response in AMD*

ELECTROPHYSIOLOGICAL TESTS

Electrophysiological tests such as ERG / mfERG and visually evoked potentials (VEP) are valuable for assessing the retina.

- They help establish a diagnosis (specific criteria for certain diseases e.g. cone dystrophy, CSNB)
- They help in finding where the “problem” is in the visual pathway (ERG vs. VEP)
- The ERG records the electrical response evoked from the entire retina by a brief flash of light (Figure 8)
    - It consists of an “a” wave (photoreceptor response) and “b” wave (Müller and bipolar cells)
    - The a-wave reflects the general physiological health of the photoreceptors (outer retina)

    - The b-wave reflects photoreceptor to bipolar cell transmission (inner retinal layers)
    - It is important to consider the oscillatory potentials
        - Latency time and amplitude of response
- The multifocal ERG records central retinal function
- The EOG records the standing electrical potential generated by the retinal pigment epithelium (RPE)

The test results must not be looked at independently from other tests (e.g. visual acuity, fluorescein angiography, OCT) and the overall clinical examination.

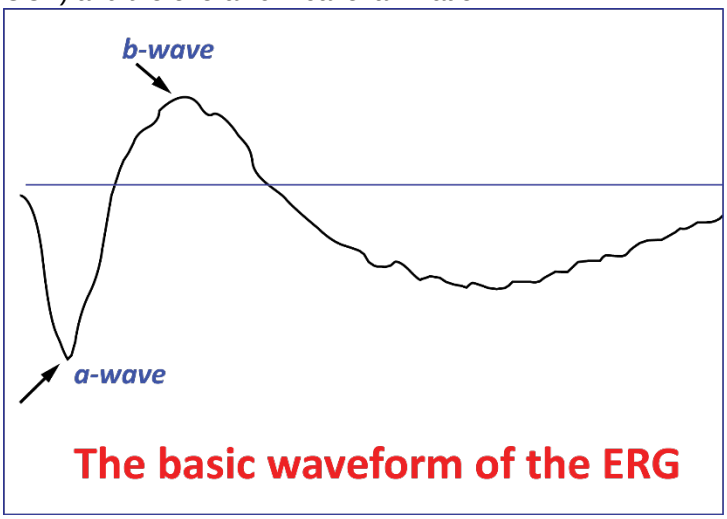

Figure 8: *The electroretinogram waveform*

CLINICAL EXAMPLES

A normal response is shown in Figure 9.

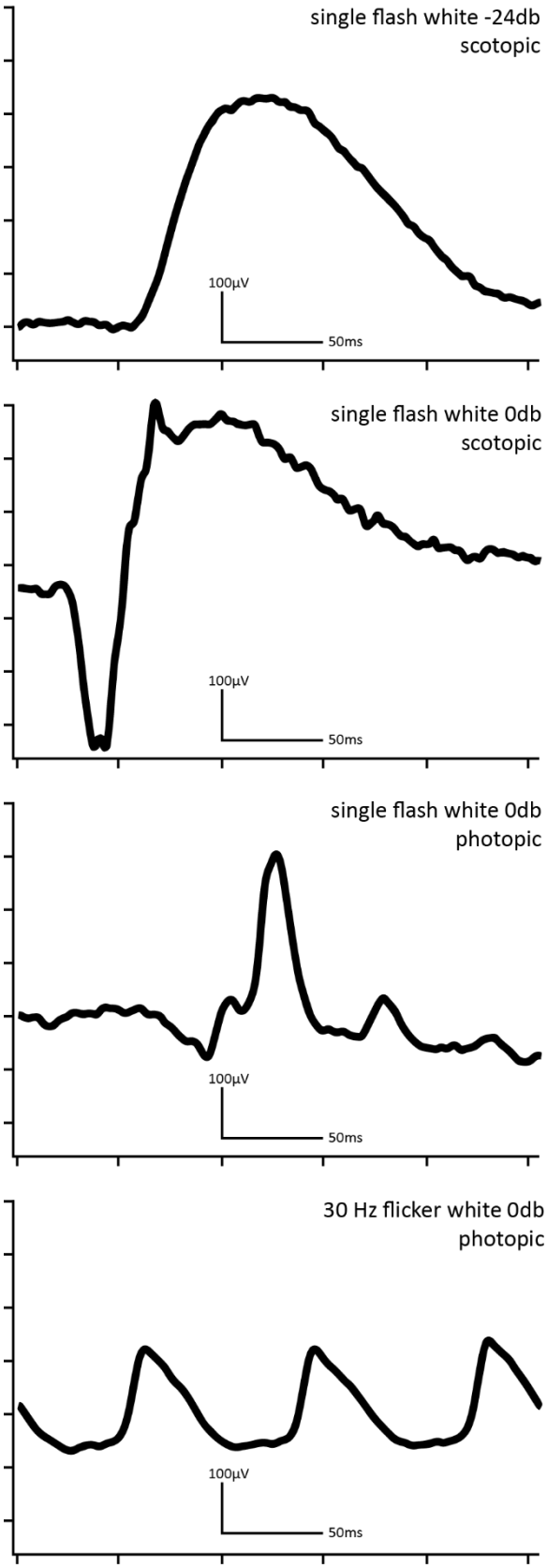

Figure 9: *The ERG waveform for a normal retina*

CONE DYSTROPHY

The key findings in cone dystrophy include:

- Decreased 30Hz flicker and photopic flash response
- OCT indicates photoreceptor loss at the central retina

- Central scotoma is present
- VA is reduced

AUTOFLUORESCENCE (AF)

In **normal AF images**, the macula, optic disc and vessels appear dark. The foveolar region AF is physiologically decreased due to reduced lipofuscin A and a blockade that occurs due to the macular pigments (i.e. lutein and zeaxanthin).
Fundus autofluorescence: usually excited at 488 nm and the emitted light is detected at greater than 500 nm.

DIAGNOSIS AND INVESTIGATIONS

It is necessary to obtain information to assist with the diagnosis of the condition.

- Symptoms and history
- Current complaint
    - Is it chronic?
- Both family and medical history
- Note geographical background, relationship of parents
- Rate of onset of symptoms
- Other considerations
    - Reports from GP and other specialists, pathology reports, imaging, etc.
    - Hereditary nature of diseases
        - Consider referral for genetic testing in some cases, counselling, etc.

INHERITED DEGENERATIONS

Groups of non-inflammatory, genetic disorders including dystrophies, can lead to alterations in structure and function of the retina (photoreceptors, RPE, etc.), choroid/choriocapillaris and vitreous, with associated clinical sequelae. Many dystrophies are autosomal dominant with variable phenotypes. They are rare and tend to manifest between childhood and later decades with variable progression. The presentation is generally bilateral but may be asymmetric.

GENETICS TERMINOLOGY

The autosome involves the 22 non-sex chromosomes.

Autosomal dominant (AD)
- One copy of an abnormal gene required for the phenotype (disease or trait) to develop

Autosomal recessive (AR)
- Two copies of an abnormal gene required for the phenotype (disease or trait) to develop (1 copy = carrier)

X-linked recessive
- A mutation in a gene on the X chromosome causes the phenotype to be expressed in one of two ways:
    - In males (only one X chromosome)
    - In females homozygous for the gene mutation (gene mutation on each X chromosome)

Polygenic inheritance
- A single characteristic that is controlled by more than two genes (many genes; also called multifactorial inheritance)

Oligogenic inheritance
- A single characteristic that is controlled by two genes (or at least less than polygenic)

Mitochondrial inheritance
- Inheritance of a trait encoded in the mitochondrial genome; genes are inherited entirely from the maternal side, segregate randomly at meiosis or mitosis, and are variably expressed

Carrier females

- One copy of a mutation, do not usually express phenotype, but varying degrees of clinical expression in carrier females occur; some cells will express one X allele and some will express the other (see also Lyonisation)

Reduced penetrance

- Dominantly inherited abnormal gene present but clinical evidence not always apparent; probability of getting disease when mutation is present

Variable expressivity

- Range of signs and symptoms that can occur in different people with the same genetic condition
- NB: probably related to combinations of other genetic, environmental and lifestyle factors

Lyonisation

- Dr Mary Lyon (Nature, 1961) proposed that in every somatic cell of a female, only one X-chromosome is functional
  - Lyon's hypothesis thus predicts that females will have two somatic cell populations: one with normal activity and one with mutant activity
  - X-chromosome to be inactivated during development is random
  - Lyonisation results in variable manifestations of a disorder ranging from asymptomatic to severe symptoms; degree is not inherited

An example of a rare X-linked recessive condition is choroideremia in which there is degeneration of the choriocapillaris, loss of the RPE and photoreceptor degeneration.

It is important to know the following about female carriers:

- Female carriers of X-linked conditions may display considerable diversity of phenotype because of random nature of X-inactivation (e.g. RP, choroideremia)
- An example of a mild presentation may be fundus changes in pre-equatorial region
- In other presentations there may be abnormal retinal reflex, pigmentary changes, altered ERG, visual field loss, reduced photopigment content, etc.
- Different proportions of expressed mutant X-gene results in a spectrum of affected individuals; result in mild to severe presentations

INHERITED RETINAL DYSTROPHIES

Pattern of dystrophic changes and degree of anatomical involvement usually determines the associated symptoms and the functional consequences.
A general classification of inherited retinal dystrophies includes:

- Choroidal dystrophies
- Retinal pigment dystrophies (including retinitis pigmentosa and others)
- Macular and 'pattern' dystrophies
- Vitreoretinopathies and others

CHOROIDAL DYSTROPHIES

Choroidal dystrophies are progressive, hereditary disorders characterized by clinically apparent RPE and choroidal atrophy.

They can be classified as those with:

A. Regional fundus involvement
   - Initial or predominant site of degeneration (e.g. macular, peripapillary, paramacular or combination)
   - Severity of involvement (e.g. choriocapillaris or larger choroidal vessels)
B. Diffuse fundus involvement

There is a very long list of choroidal dystrophies that includes:

- Choroideremia

- Gyrate atrophy
- Central areolar choroidal dystrophy
- Diffuse choroidal atrophy
- Helicoid peripapillary chorioretinal dystrophy
- Pigmented paravenous retinochoroidal atrophy
- Progressive bifocal chorioretinal atrophy
    - A rare, autosomal dominant congenital chorioretinal dystrophy
    - Two distinct foci of atrophy, a temporal focus that is present at birth and a nasal focus that appears early in life
    - Retinal detachment is an additional complication of the disease

CHOROIDEREMIA

Choroideremia is an X-linked recessive disease where there is progressive atrophy of the choroid, RPE and photoreceptors toward the posterior pole.
Only a small island of intact retina and choroid remains in the fovea and the white sclera becomes visible. Angiogram reveals RPE loss (large choroidal vessels are visible) and loss of choriocapillaris, except at the fovea.

- X chromosome (Xq21.2) encodes Rab escort protein-1 (REP-1) of Rab geranylgeranyl transferase, a two-component enzyme (components REP-1 and REP-2) that modifies Rab proteins
- > 140 mutations in CHM gene found to cause choroideremia. Nearly all result in abnormally small, nonfunctional REP-1 protein
- Lack of normal REP-1 disrupts ability of Rab proteins to aid in intracellular trafficking; immobility of proteins and organelles within the cell with the result that the cell dies prematurely
- When REP-1 is absent or non-functional, the REP-2 can perform protein escort duties of REP-1 but there is very little REP-2 protein in the retina

Ocular signs
Female carriers may be asymptomatic (mild patchy peripheral RPE atrophy and mottling).
Clinical features, including rate of progression, can show both inter- and intra- family variability. The ocular signs include:

- Impairment of night vision with progression over time
- Usually noted in the first decade of life but the onset may be delayed
- Present with large scalloped areas of peripheral retinal degeneration (hypopigmentation, mottling)
- Nyctalopia in the first decade
- Absent scotopic ERG
- Mid-peripheral patches of RPE atrophy and field loss
- In the intermediate stages, atrophy of the RPE and the choriocapillaris become more diffuse
- Intermediate and large choroidal vessels become more atrophic, exposing the underlying sclera
- Macula is initially spared relatively often; visible as a remaining island of choriocapillaris in the midst of the surrounding white sclera
- The macula is relatively well preserved until late stages of the disease.

GYRATE ATROPHY

Gyrate atrophy is a slowly progressive chorioretinal dystrophy that usually presents in the first decade of life. It is associated with axial myopia, decreased peripheral vision, nyctalopia and crystalline lens changes.
It is a metabolic disorder associated with hyperornithinemia (defect in ornithine aminotransferase (OAT). The enzyme depends on a cofactor, pyridoxal phosphate (vitamin B6).
The OAT gene mapped to 10q26, with greater than 60 mutations identified.
The condition is characterized by discrete areas of chorioretinal atrophy in the mid-peripheral retina with the fovea spared until late in the disease progression. There are well-demarcated, scalloped areas of atrophy. The visual field loss usually follows the areas of atrophy.
There is a sharp demarcation from the more posterior retina.
Attenuated retinal vessels are common.

Prognosis
The progressive nature of gyrate atrophy means that the prognosis is poor. Changes are usually observed by the 4th to 6th decade of life and include e.g.

- Myopia
- Cataract
- Macular oedema

Possible treatment
One treatment modality is to reduce the dietary arginine levels (substrate for ornithine).
The intake of vitamin B6 activates residual enzyme activity.

RETINAL PIGMENTARY DYSTROPHIES

Retinitis pigmentosa (RP) and related rod-cone dystrophies are a diverse set of hereditary disorders generally leading to progressive visual dysfunction because of the photoreceptor cell death.
The prevalence is 1:3000 to 1:5000.

Mutations in the same gene can bring about different visual progression/symptoms.
In the final stages of the disease, conditions are difficult to distinguish apart.

CLASSIFICATION OF RP

Heckenlively et al.(1988) classified RP using the average of data from five studies (n=2406). They found the following:

- Autosomal Recessive: approximately 31% of all cases
- Autosomal Dominant: approximately 16% of all cases
- X-linked: approximately 9% of all cases
- Simplex/Multiplex: approximately 44% of all cases
    - Simplex: No other family member affected
    - Multiplex: Only affected siblings

There are too many simplex cases to be explained by Mendelian inheritance patterns – suggests polygenic and oligogenic inheritance patterns.

Massof et al. (1990) classified RP as follows:

TYPE 1 RP

- Early diffuse and preferential loss of rod sensitivity (difficulty with night vision)
- Later progression and regionalized loss of visual field

TYPE 2 RP

- Regionalized and progressive combined loss of rod and cone sensitivity
- Late difficulty with night vision (in adulthood)

RP AND GENETICS

Molecular identification of causative gene is possible for some cases but any aim to correlate a specific gene with a specific phenotype is rarely possible as most RP mutations give a similar phenotype.
Some unique conditions exist, such as mutations in RDS/peripherin gene, which may cause a peculiar maculopathy in addition to peripheral retinal degeneration.
Over 90 human peripherin/RDS gene mutations have been identified and associated with a variety of retinal dystrophies, with a remarkable inter- and intra-familial variation of the retinal phenotype.
In general, it is not yet possible to predict the specific causative gene from the clinical presentation in RP.

Rod-cone dystrophy

In this condition there is progressive night blindness and tunnel vision. The symptoms become more severe as more rods die off.
There are mid-peripheral ring scotomas during the progressive stages of visual field loss and typically both eyes are affected similarly.

Cone-rod dystrophy
Day-vision problems such as reduced visual acuity, color-vision impairment and photophobia are present in this bilateral condition.
At least some peripheral vision is retained in patients who have cone-rod dystrophy (compared with rod-cone dystrophy)

CLINICAL PRESENTATION IN RP

Common symptoms that occur in RP include:

- Nyctalopia
  - Poor night vision, prolonged dark adaptation
  - Problem driving is at dusk or in rain or fog
  - Patients complain of problems in dimly lit restaurants and theatres
  - Slow adaptation when coming indoors from bright sunlight
  - Dark stairwells can cause difficulty
- Loss of peripheral vision
  - Mid-stage of the disease
  - With visual field constriction the patients may be bumping into objects
  - Eventually develops into “tunnel vision”
- Loss of central vision at the final stage of the disease

The typical presentation in RP is as follows:

- Progressive visual field loss
- Difficulty with dark adaptation (nyctalopia)
- Altered scotopic and photopic ERG
- Reduced visual acuity (late in the disease)
- Posterior subcapsular cataracts
- Posterior vitreous detachment (occasional intermediate uveitis)
- Acquired tritan (blue-yellow) color vision loss
- Arteriolar narrowing
- Fine intraretinal pigmentation with loss of RPE (RP sine pigmento)
- Some may have scattered white dots (retinitis punctata albescens)
- Bone spicule changes increase (variable and later) – intraneuronal
- Tessellated fundus appearance
- Further arteriolar narrowing and waxy white disc
- Maculopathy
  - Atrophic, cellophane (pucker or epiretinal) membrane, cystoid macular oedema
  - Relative preservation of the RPE in the macula may occur

See - Kalloniatis M, Fletcher EL. Retinitis pigmentosa: understanding the clinical presentation, mechanisms and treatment options. Clin Exp Optom. 2004;87:65-80.

VARIATIONS OF RETINITIS PIGMENTOSA

- Sector RP: usually inferior nasal degeneration (possibly due to light exposure)
- Pericentral RP: pigmentary changes emanate from disc and spread along the temporal arcade
- RP with exudative retinopathy lipid deposits

PROGRESSION OF RP

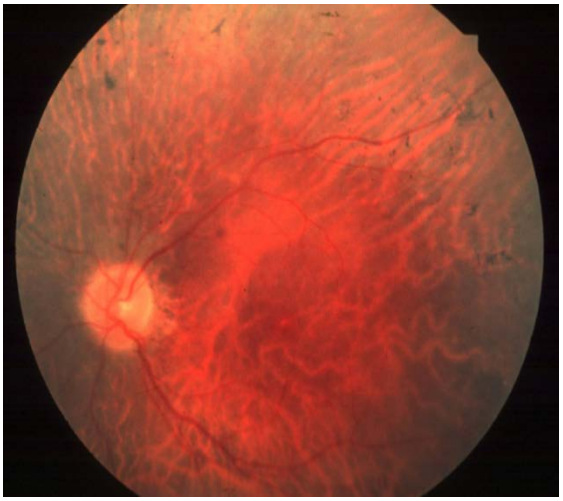

Figure 10: *Fine dust-like pigmentation with arteriolar attenuation*

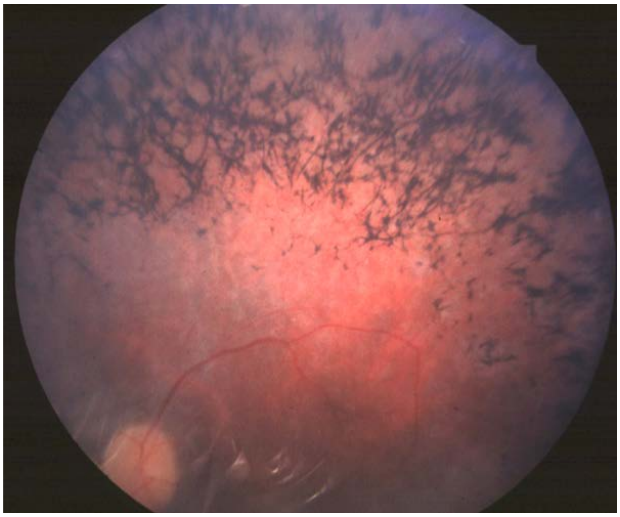

Figure 11: *Perivascular 'bone-spicule' pigmentation, initially seen in the mid-periphery*

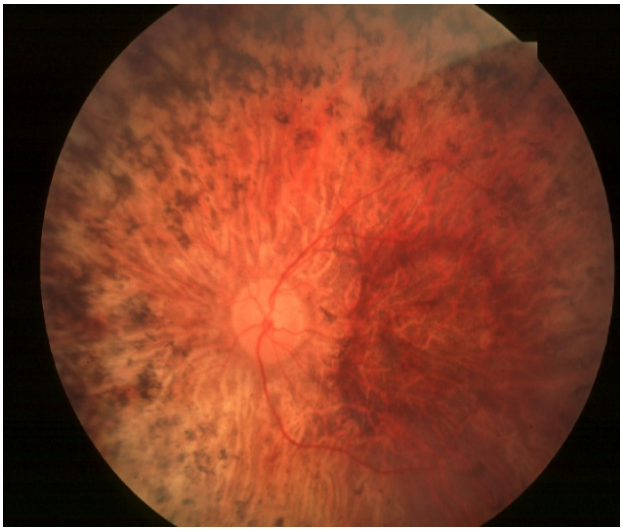

Figure 12: *Anterior and peripheral spread with large choroidal vessels revealed*

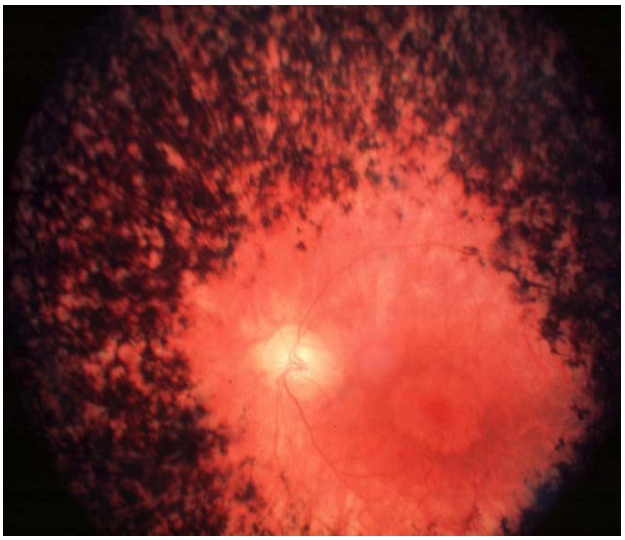

Figure 13: *Optic disc pallor and maculopathy*

CLINICAL PRESENTATION IN RP

With each case of RP, other associated ocular findings may include:

- Maculopathy: cystoid macular oedema, epiretinal membrane formation and/or macular atrophy
- Vitreous degeneration (common)
- Cataract (very common)
- Myopia (common)

In rare circumstances, RP may be associated with keratoconus, optic disc drusen and open angle glaucoma.

The ERG recording in a case of retinitis pigmentosa is shown in Figure 14.

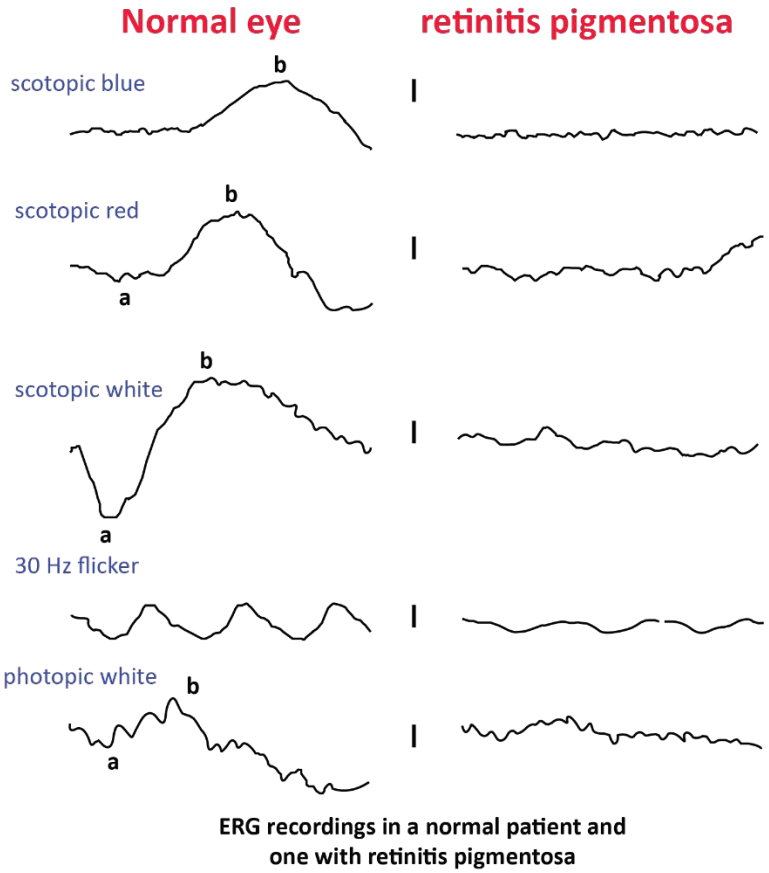

Figure 14: *ERG recordings in a normal patient and one with RP*

RETINITIS PIGMENTOSA: DIFFERENTIAL DIAGNOSIS

Based on the fundus findings it is important to consider the following in any differential diagnosis:

- Acquired retinal degenerations
  - Peripheral reticular pigmentary degeneration
- Cancer-associated retinopathy
- Drug toxicity retinopathy
  - Phenothiazine
  - Chlorpromazine
  - Chloroquine
  - Deferoxamine
- Grouped pigmentation of the retina
  - Bear-track
- Infectious/inflammatory retinopathy
  - Rubella/syphilitic retinopathy
- Choroidal melanoma
- Pigmented paravenous retinochoroidal atrophy
- Retinal detachment resolution
- Traumatic retinopathy

Based on any associated nyctalopia always consider the following:

- Congenital stationary night blindness
- Dystrophies of the choroid and retina
  - Gyrate atrophy, choroideremia
- Vitamin A deficiency

Other important fundus findings can include:

- Cancer-related retinopathies (CAR, MAR)
  - More rapid course
  - But have minimal pigmentary changes
- End-stage chloroquine retinopathy
  - But has no pigmentary changes
- End-stage syphilitic retinitis
  - Mild nyctoplopia present

RP ASSOCIATED WITH OTHER ANOMALIES

Retinitis pigmentosa is associated with a number of syndromes and conditions including:

- Bassen-Kornzweig syndrome: Autosomal recessive disease due to deficiency of beta-lipoprotein – intestinal malabsorption, neurological deficits, including ophthalmoplegia and ptosis; vitamin E instituted early may help neurological deficits
- Refsun disease: Autosomal recessive defect causing defect in phytanic 2-hydroxylase resulting in increased phytanic acid in blood; major neurological deficits and systemic disease
- Usher's syndrome: Autosomal recessive disorder causing deafness and RP
- Kearns-Sayre syndrome: mitochondrial cytopathy causing DNA deletion; atypical RP - course pigmentation central fundus
- Bardet-Biedl syndrome (Laurence-Moon-Bardet-Biedl syndrome): AR, RP associated with mental impairment, obesity, polydactyly and hypogenitalism; bull's eye maculopathy with cone-rod dystrophy

MANAGEMENT OF RP

Management for RP patients:

- Goldmann visual field measurements
- Follow for a minimum of two years in order to estimate the progression
- Estimate visual field progression rate (progression: 8.4 +/- 4.9 years using V/4e target)
- Time of onset of the VF change is a reasonable predictor of remaining duration of functional vision
- Genetic subtype is not a reasonable predictor of progression

- Use the OCT to determine photoreceptor integrity
- Electrophysiology testing (including 30Hz flicker)

There is currently no cure for RP. Pharmacotherapy is suggested for RP management as a means of slowing progression or as a way of reducing the effects of some of the associated conditions.
Pharmacotherapy can include the following:

- High dose vitamin A (15000 IU/day) is reported to slow RP progress by about 2% per year but its use requires careful management (Berson et al.)
- Omega-3 polyunsaturated fatty acid plus antioxidant results in:
    - Less ERG change?
    - Enhanced Vitamin A effect?
    - Increased neuroprotection?
- Calcium-channel blockers (e.g. diltiazem) have been trialled in animal models
- Carbonic anhydrase inhibitors (e.g. acetazolamide, methazolamide) improves the macular oedema in RP

The following may have potential adverse effects when used in RP management:

- Isotretinoin (Accutane)
    - Worsens the ERG response, etc.
- Sildenafil (Viagra)
    - Inhibitor of PDE5 but less so for PDE6
    - Mutations of PDE6 gene result in autosomal recessive RP so therefore it may not be safe for RP patients, including carriers of PDE6B gene mutation
- High-dose vitamin E (400 U/d)
    - May be modestly deleterious in patients with RP

CONGENITAL ACHROMATOPSIA

In this rare condition there is absent or aberrant color discrimination. It is associated with several genes.
Two general forms of the condition are:

A. Blue cone monochromatism (BCM) – These patients are left only with S-cones and rod photoreceptors. Recessive X-linked disease with associated severely impaired color discrimination, low VA, nystagmus, photophobia due to dysfunction of the red/green (L/M) cone photoreceptors. The prevalence is approximately 1/100,000 worldwide.
B. Achromatopsia (ACH) – or rod monochromatism. Is an autosomal recessive condition. In complete presentations the VA is about 6/60. In an incomplete case the VA is about 6/24. There is usually an associated nystagmus. The ERG analysis indicates an absence of cone function with no photopic responses.

Patients with ACH and BCM show apparent changes in thickness and structure in the foveal region.

CONE DYSTROPHIES

There are a group of hereditary conditions (autosomal dominant, X-linked, autosomal recessive) that present as cone-rod dystrophies. For example, ABCA4 mutation leads to a spectrum of conditions that include Stargardt's disease and fundus flavimaculatus.
The key findings are:

- Gradual, bilateral impairment of central vision
- May be mild impairment to more severe (6/120)
- Typical progressive red-green defect (against the rule): may progress to achromatopsia
- Normal 'bull's eye' central RPE atrophy and mid-peripheral 'bone spicules'
- Geographic atrophy
- Arteriolar attenuation and associated disc pallor

"BULL'S-EYE MACULOPATHY"

Bull's-eye maculopathy is a term used to describe the characteristic appearance of chloroquine retinopathy. The pathogenesis of the condition is poorly understood.

Signs:

- "Bull's-eye lesions": cone dystrophy and cone-rod dystrophy, rod-cone dystrophy, several macular dystrophy phenotypes (e.g. benign concentric annular macular dystrophy, fenestrated sheen macular dystrophy)
- Characteristic appearance of an annular RPE disturbance with central sparing
    - o May correspond to pattern of RPE lipofuscin accumulation
    - o Initially spared in the center but it usually becomes involved as disease advances

STARGARDT'S MACULAR DYSTROPHY

Stargardt's disease is an autosomal recessive (and some autosomal dominant) condition. Features include:

- Most prevalent inherited macular dystrophy
    - o Approximately 7% of all retinal dystrophies
- The autosomal recessive form affects chromosome 1; ABCR gene (now called ABCA4)
- Stargardt's disease and fundus flavimaculatus are allelic; only about 60% of patients with these diseases have a detected mutation in this gene
- This locus is also involved in age-related macular degeneration and autosomal recessive retinitis pigmentosa

Clinical features

- Discrete yellowish round flecks at level of RPE
    - o The flecks observed are mostly confined to the posterior pole and are present early in life.
- Progress to geographic atrophy in the macula - 'beaten bronze' or 'beaten metal' appearance
- Mutation in ABCR gene leading to abnormality in rod outer segment membrane
- Fluorescein angiography - dark choroid appearance
- No treatment is available

FUNDUS FLAVIMACULATUS

The onset is in adulthood. Characteristic flecks accumulate at the level of RPE and are distributed throughout the fundus. Flecks are hyperfluorescent due to the RPE atrophy. There is an absence of normal background fluorescence (dark choroid).

LEBER'S CONGENITAL AMAUROSIS

This is a group of autosomal recessive inherited blinding diseases with onset during childhood. In these cases there is a severe rod-cone dystrophy.
It presents with blindness at birth or shortly afterwards and is associated with roving eye movements. The rods and cones are both affected and do not develop normally.

Signs:

- Absent or diminished pupil reflexes
- Fundus initially normal but then patches of peripheral chorioretinal atrophy and granularity
- May have optic disc oedema, 'salt & pepper' fundus, diffuse white spots, 'bull's eye' maculopathy
- ERG usually non-recordable even in early cases with normal fundus indicating a severe rod and cone problem

SUMMARY: CLINICAL MANAGEMENT OF RETINAL DYSTROPHY PATIENTS

For cone-rod related dystrophies:

- Threshold visual fields and electrophysiological investigation within and outside the affected area

MACULAR DYSTROPHIES

Macular dystrophies involve a process of premature retinal cell ageing and cell death that is generally confined to the macula. There is no evidence of a clearly demonstrable extrinsic cause, though a heritable, genetically determined enzymatic defect is implicated.

KEY FEATURES

- Yellowish material within or beneath the RPE
- Loss of macular photoreceptors and RPE
- Loss of central vision

ASSOCIATED FEATURES

- Neural retinal / RPE / choroidal atrophy commonly limited to macula
- Pigment clumps in posterior pole, mid-periphery, or far periphery seen rarely
- “Bull's-eye” appearance seen rarely
- Optic atrophy, retinal vascular attenuation, macular oedema, and choroidal neovascularization seen rarely
- Most macular dystrophies share the clinical manifestation of accumulated yellowish material within the macular region
- Course of each disease can be quite different

INHERITANCE

The molecular genetic loci and genes associated with macular dystrophies are shown in Table 1.

Phenotype	Inheritance	Genomic locus	Gene	Mutation in AMD
Stargardt's disease	AR	1p21-p22	ABC4R	No
Dominant drusen	AD	2p16	EFEMP1	No
Pattern dystrophy	AD	6p21.2-cen (+other loci?)	Peripherin/RDS	No
"Macular" dystrophy	AD	6p21.2-cen (+ other loci?)	Peripherin/RDS	No
Adult vitelliform macular dystrophy	AD	6p21.2-cen (+ other loci?)	Peripherin/RDS	No
Stargardt-like fundus dystrophy	AD	6q11-q15, 13q34		
Best's disease	AD	11q13	Bestrophin	No
Sorsby's fundus dystrophy	AD	22q12.1-q13.2	TIMP3	No
X linked retinoschisis				
AR = autosomal recessive, AD = autosomal dominant, XL = X linked.				

Table 1: *Molecular genetic loci and genes associated with macular dystrophies*

BEST’S VITELLIFORM DYSTROPHY

The features of the condition include the following:

- Extremely rare (actual incidence unknown)

- Autosomal dominant with highly variable clinical expression
- Gene for Best's disease chromosome 11q13, mutations in bestrophin (VMD2) gene
- Transmembrane protein of undetermined function, expressed in RPE
- Several mutations within bestrophin gene identified and associated with both Best's and adult vitelliform diseases
- Yellow yolk-like macular lesion in childhood
- Breaks down with scarring and geographical atrophy (GA) later in life
- Both positive and negative for choroidal new vessels
- Potentially visually devastating
- Lipofuscin accumulations within RPE cells, in sub-RPE space throughout the fundus

ADULT VITELLIFORM DYSTROPHY

The features of the condition include the following:

- Individuals show symmetrical, yellowish foveal deposits that resemble lesions of Best's disease but are smaller
- Phenotype can vary from small “yolks” as seen in adults who have widespread, fine, cuticular drusen, to only subtle accumulations of yellowish material in central fovea

- Examples of adult vitelliform degenerations include foveomacular dystrophy (of Gass), and adults who have coalescent, widespread, cuticular drusen that form vitelliform lesions in the macula
- Disorders usually distinguished from Best's disease on basis of normal or only minimally reduced EOG
    - Full-field ERG is normal, but foveal ERG may be reduced
- By definition, adult vitelliform macular dystrophies are presumed to have adult onset, although this has not been well documented

SORSBY’S MACULAR DYSTROPHY

This a rare autosomal dominant disorder, with many clinical similarities to AMD.
The gene for Sorsby's dystrophy codes for tissue inhibitor metalloproteinase – TIMP-3. There are several mutations of TIMP-3 identified in patients with Sorsby's dystrophy.
The gene product is important in regulation and composition of Bruch’s membrane ECM and is critical for wound healing, angiogenesis, etc.
However, no simple association has been found between TIMP-3 mutations and AMD.

Progression:

- Yellow-white confluent spots
- Along the vessel arcades and nasal to disc
- Eventual CNV and exudative maculopathy

Early phase:

- Very fine drusen or large confluent plaque of yellowish material may be noted beneath the central RPE
- Around 40 years of age, the patients develop bilateral exudative maculopathy, which leaves heavily pigmented macular scars and areas of geographic atrophy (GA)

Signs:

- ERG and EOG usually normal, but decreased photopic and scotopic ERG amplitudes late in disease
- Patients typically develop bilateral choroidal neovascularization at an early age
- Severe loss of central VA results from extensive macular scarring related to the choroidal neovascular membranes

Treatment:

- Laser treatment has poor results
- Another possibility for gene therapy treatment?

OTHER CONDITIONS

All the conditions below are very rare and mostly autosomal dominant with onset around the 3rd decade of life. The ERG results are mostly normal and the condition is often slowly progressive.

- Dominant cystoid macular oedema (1st to 2nd decades)
- Bietti crystalline dystrophy (crystals in retina, peripheral cornea)
- Alport syndrome (collagen Type IV problems)
- Occult macular dystrophy
- Enhanced S-cone syndrome (AR, enhanced cone ERG)
- Late-onset retinal degeneration (nyctalopia 6th decade)
- Fenestrated sheen maculopathy
- Benign concentric annular macular dystrophy

VITREORETINAL DYSTROPHIES

These are groups of rare, inherited disorders with primary manifestations that include vitreous and retinal degeneration.

- **Main Features:**
  - Premature vitreous syneresis
  - Abnormal acquired retinal pigmentation
  - Retinal degeneration (e.g. schisis)
- **Associated Features:**
  - Autosomal dominant or X-linked recessive inheritance patterns
  - Vitreous degeneration
  - Retinal vascular abnormalities
  - RPE hyperplasia or atrophy
  - Loss of b-wave on ERG
  - Retinal detachment

FAMILIAL EXUDATIVE VITREORETINOPATHY

The pattern of inheritance for this condition is autosomal dominant or, more rarely, X-linked recessive. It typically presents later in childhood.
There is a poor prognosis in most cases of familial exudative vitreoretinopathy.

Signs:

- Vitreous degeneration and peripheral vitreoretinal attachments
- Peripheral vascular tortuosity, telangiectasia
- Fibrovascular proliferation and vitreoretinal traction
- Ridge formation; localized retinal detachments, vascular straightening
- The ERG typically is normal

Fluorescein Angiography:

- Peripheral non-perfusion, vessel straightening
- Fluorescein angiography helps define abnormal retinal vessels in familial exudative vitreoretinopathy

JUVENILE X-LINKED RETINOSCHISIS (XLRS)

Juvenile XLRS is a rare vitreoretinal degeneration affecting males. The retinoschisin protein is involved in cell-cell adhesion and phospholipid binding.
The condition displays relatively uniform clinical characteristics, albeit with intra-familial variation in onset and severity. Note that juvenile XLRS should not to be confused with adult acquired retinoschisis.

Signs:

- Early onset macular degeneration
- Bilateral cystic, foveal changes
    - Cystic-like, stellate maculopathy or foveal schisis is present almost universally and may be only abnormality in approximately 50% of cases
- Mild to severe VA deterioration
- Splitting of retinal layers
    - Inner retina split at level of NFL, typically infero-temporal quadrant, and bilaterally ~40% of patients
    - Inner layer balloons into vitreous cavity; unsupported retinal vessels may lead to recurrent vitreous haemorrhages from associated vitreous traction
- Reduced/loss ERG b-wave
    - ERG affected
    - Fields show absolute scotomas in areas of peripheral schisis
    - Relative central scotoma
    - Secondary retinal detachment can occur

OTHER VITREORETINAL DYSTROPHIES

- Stickler syndrome
    - Autosomal dominant inheritance
    - Commonest cause of retinal detachment in children
    - Associated with:
        - Collagen gene mutations (STL1 – 3)
        - Myopia
        - Vitreous liquefaction and syneresis
        - Orofacial abnormalities
        - Deafness
- Wagner syndrome
    - Autosomal dominant, 5q12-14
    - Optically empty vitreous
- Enhanced S-cone and Goldmann-Favre Syndrome
    - Autosomal recessive
    - Children with nyctalopia and vitreous syneresis

CHERRY-RED SPOT AT MACULA

This is a common feature of central retinal artery occlusion. It is seen in a case of sphingolipidosis which is a very rare disease where there is an accumulation of lipids in various tissues including the retina. The lipids accumulate in the ganglion cell layer (GCL) except in the central macula where there are no ganglion cells (transparency is retained).

Systemic associations:

- Gangliosidosis type (GM) 1
    - A generalized condition
    - Autosomal recessive
    - Death before 2 years of age
    - Progressive neurological disease
    - Cherry-red spot in approximately 50% of cases
- Gangliosidosis type (GM) 2
    - Tay-Sach's disease
    - Autosomal recessive
    - Onset during 1st year
    - Progressive neurological disease
    - Cherry-red spot by 3 months
    - Optic atrophy by 1st year

- Death within 2 – 4 years

- Niemann-Pick disease
  - Three types with varying degrees of central nervous system (CNS) effects
    - Type A – 50% with cherry-red spot
    - Type B – macular cherry-red spot and bull's eye maculopathy

OTHER VITREORETINOPATHIES

- **Dominant neovascular inflammatory vitreoretinopathy**
  - Autosomal dominant
  - 2nd to 3rd decade of life
  - With floaters, uveitis, RPE degeneration, peripheral vascular closure
  - Can get vitreous haemorrhage and associated sequelae
  - ERG has no b-wave
- **Dominant vitreoretinochoroidopathy**
  - Autosomal dominant
  - Seen in adults
  - RPE disturbance between ora serrata and equator associated with vascular changes
  - Later changes include chorioretinal atrophy
- **Snowflake degeneration**
  - Autosomal dominant
  - Extensive areas of 'white-without-pressure' at about 15 years of age
  - Yellow 'flakes' in this region from 15-25 years
  - Vascular sheathing and pigmentation in the area from 25-50 years
  - Increased pigmentation and vascular attenuation
  - Areas of chorioretinal atrophy from age 60 years
  - Also associated with myopia, vitreous degeneration (liquefaction) and retinal tears

BUTTERFLY MACULAR DYSTROPHY

The pattern of inheritance is thought to be autosomal dominant. The condition presents in the 2nd to 3rd decade of life.

Signs:

- Yellow pigment at fovea
  - Pigment at fovea is arranged in a triradiated pattern
- May develop atrophic maculopathy over time
- Peripheral pigment stippling
- ERG normal
- EOG may be abnormal

RETINITIS PUNCTATA ALBESCENS

This condition presents usually before the age of 30 years. The prognosis is poor.

Signs:

- ERG is reduced
- Scattered white dots extending from posterior pole to the periphery
- Subsequent development of 'bone-spicule' pigmentation

NORTH CAROLINA MACULAR DYSTROPHY

This is an autosomal dominant macular degeneration first discovered in large family in North Carolina. It is very rare but has been found worldwide in over 25 families.
It is now known as MCDR1 (macular dystrophy, retinal subtype 1). The chromosome involved is 6q16.

Signs:

- Most striking feature is that about 30% of the affected individuals have a macular coloboma, with well-demarcated atrophy of the RPE and choriocapillaris
- Highly variable phenotypic expression
- Early stage:
    - Yellow-white spots at the periphery and macula
- Progresses to:
    - Confluence of macular lesions
    - Exudative or atrophic maculopathy
- Choroidal neovascularization can occur
- ERG and EOG are normal, as is color vision