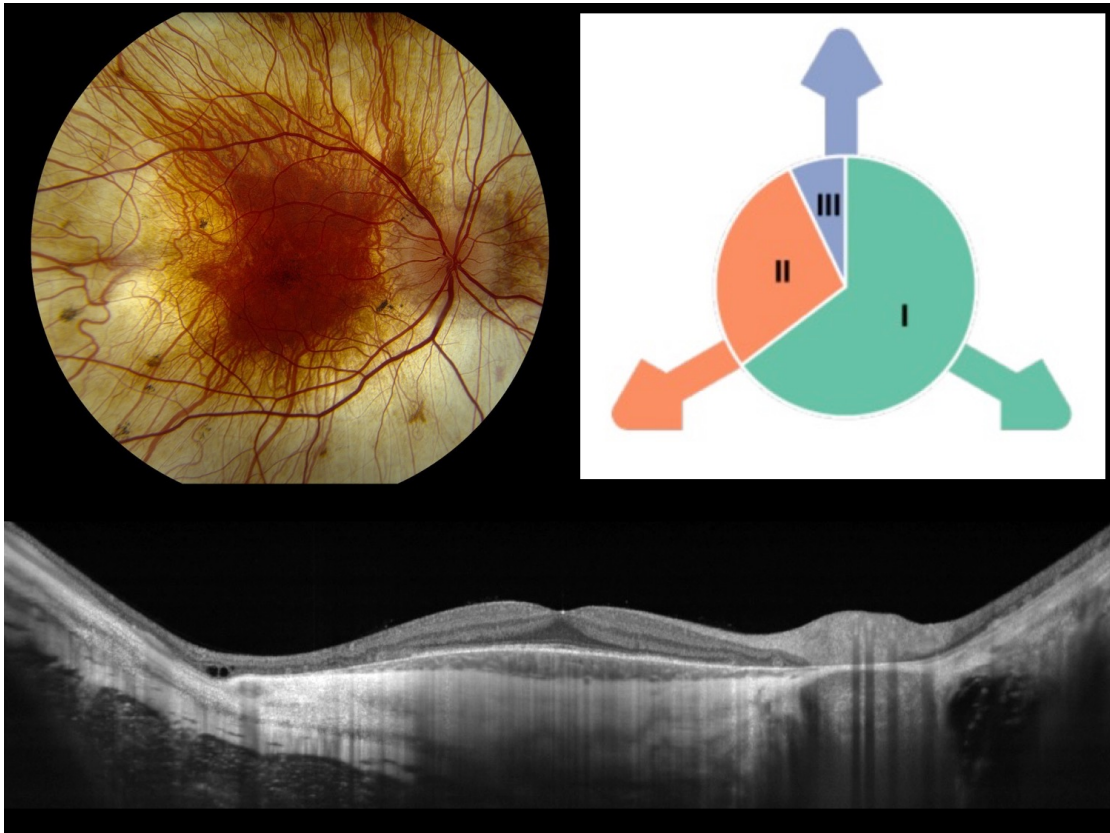


Introduction to the Big 14



a tutorial from
StoneRounds.org

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Editor

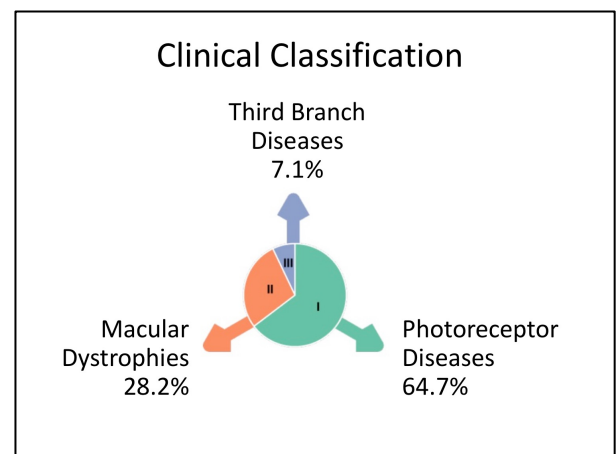
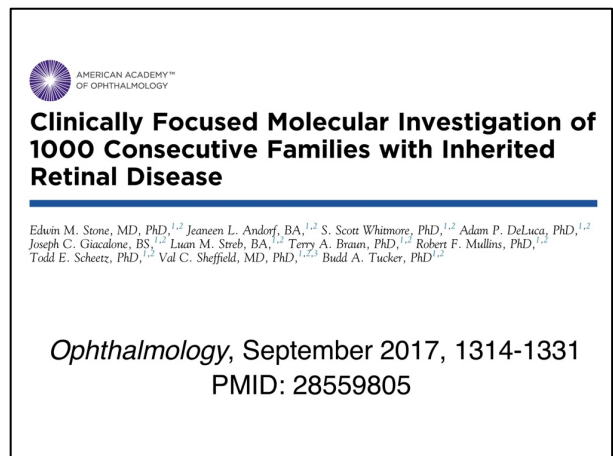
Now that you have a basic understanding of the anatomy and physiology of the retina, it's time to start learning about the inherited retinal diseases themselves. As you do this, you'll need some type of classification system to keep the diseases organized in your mind so that you can call this knowledge up from memory as you see patients, read the literature or work on projects in the laboratory. The system that we use at the University of Iowa is based upon the clinical findings we observed in a cohort of 1000 consecutive families seen in my inherited retinal disease clinic between 2010 and 2016.

The fact that these families came to the clinic from 40 different US states means that they should be reasonably representative of the kinds of inherited disease patients a retina doctor can expect to see anywhere in the US. Also, the fact that these families were added to the cohort consecutively allows us to use this group to estimate the relative frequencies of their diseases in our country.

Sixty-two different clinical diagnoses were used for at least one family in the cohort and it is this diagnostic complexity that makes inherited retinal disease seem so daunting to many people. Fortunately, the diseases are not equally prevalent in the population and if one studies them in the order of their prevalence they will appear much more understandable and approachable.

For example one disease, nonsyndromic retinitis pigmentosa, is responsible for 34 percent of all inherited retinal disease and the second most common condition, autosomal recessive Stargardt disease represents another 18.5 percent. So, by learning about just two diseases, one can knowledgeably contribute to the care or research of over half of all the inherited retinal disease patients seen in the United States.

The Iowa classification system for inherited retinal diseases has three main branches: photoreceptor diseases – typified by retinitis pigmentosa, macular dystrophies – perhaps most typified by Best disease, and a heterogeneous group of other conditions, known as the “third branch” that are unified only by being recognizably distinct from the larger two categories. If you are new to these conditions, it is probably best to spend most of your time focusing on photoreceptor diseases and macular dystrophies because between them they are responsible for almost 93% of all inherited retinal disease and when you are well-grounded in these two branches of the classification scheme, the disorders of the third branch become much easier to understand.



Another thing that is somewhat daunting for many eye doctors is that inherited retinal diseases as a whole are pretty rare, occurring in less than 1 in 2000 people in the general population.

However, despite their rarity, I think that every person who takes care of patients with eye disease should have a good working knowledge of at least the 14 most common inherited eye diseases for at least three reasons: 1) to recognize patients with single gene disorders and get them accurately counseled about the risk that the disease could recur in other family members, 2) to plug them into a tertiary care system that will ultimately be able to treat them, and 3) to get all the inherited eye disease questions right on your board exams.

At the beginning of the 19th century, Goethe said: “We only see what we know.”

A few decades later, Pasteur said: “Chance favors the prepared mind.” Both of these aphorisms really apply to inherited retinal disease because if you don’t keep these diseases in mind and understand that it is very important to your patients for you to recognize them, they will tend to just blend into the background of the much more common non-Mendelian diseases like age-related macular degeneration and central serous retinopathy.

So what clinical features would make you suspect a Mendelian retinal disease?

Mendelian disorders tend to manifest themselves by age 40 – some are even detectable within the first few weeks of life.

They are almost invariably bilateral and the lesions in one eye are often an almost perfect mirror image of the lesions in the other unless there has been a complication like choroidal neovascularization or geographic atrophy that may obscure this symmetry.

Mendelian retinal diseases tend to progress very slowly, over years – not months or weeks.

There are some ophthalmoscopic findings that are almost exclusively seen in inherited retinal disease such as pisciform flecks, vitelliform macular lesions and bone-spicule-like pigmentation. When such findings are present and very symmetrical they are pretty reliable indicators of a single gene disorder.

Perhaps the most compelling historical feature of Mendelian disease is the existence of a similarly affected relative. However, one should be wary of relatives that are more distant than grandparents or first cousins unless they can be examined or have very convincing medical records supporting the diagnosis.

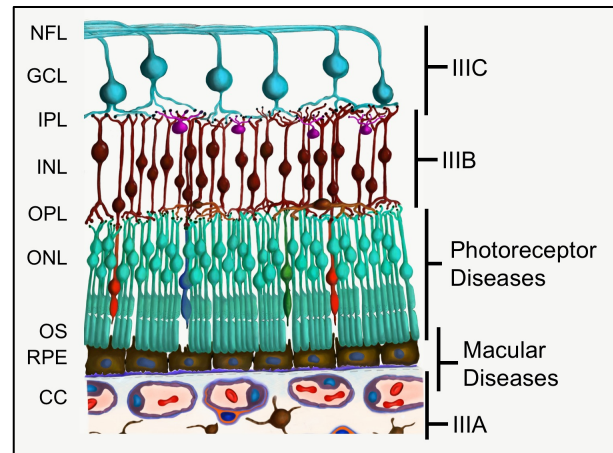
Between 15 and 20% of patients with an inherited retinal disease will have manifestations outside the eye. Because these manifestations are often recognized before the eye disease, their connection to the patients’ eye condition is frequently overlooked.

Once you have decided that a patient may have an inherited retinal disease, the next step is to decide whether the condition is a photoreceptor disease, a macular dystrophy, or one of the disorders of the “third branch”.

The most fundamental way that these categories differ from one another is the anatomical level at which the initial pathological changes occur.

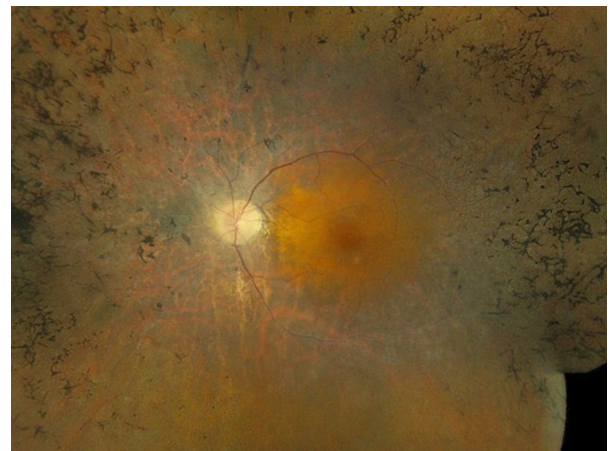
The initial anatomical changes in photoreceptor diseases occur in the photoreceptor layer while the initial abnormalities in the macular dystrophies occur in a very thin anatomical zone ranging from the tips of the photoreceptor outer segments to the very beginning of the choriocapillaris. The initial anatomical changes associated with the diseases of the third branch tend to be either deeper or more superficial than the photoreceptor and macular diseases.

Let's look at a couple of patients to get a feel for these classification principles.

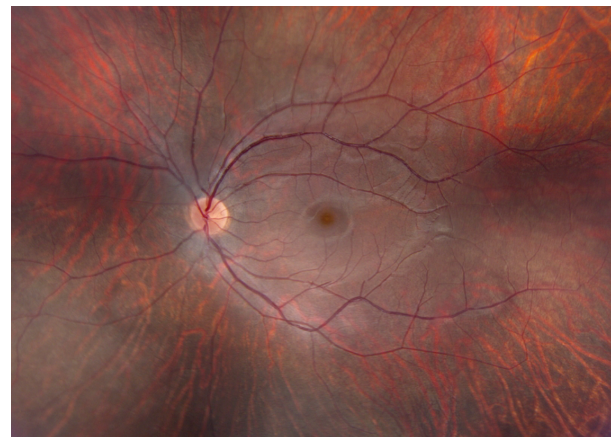


Retinitis Pigmentosa

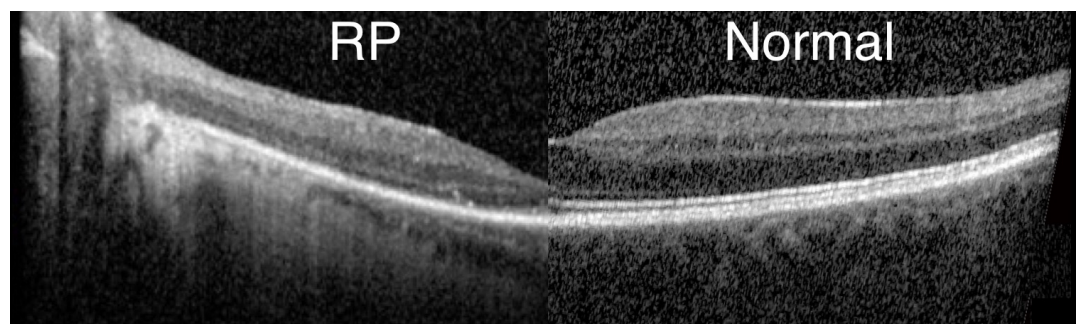
Here is a color photograph of the left eye of a 65 year old man with 20/20 acuity. He has poor night vision and quite constricted peripheral vision. The most striking retinal finding is the lacy black intra-retinal pigment in the periphery. Also, the retinal vasculature is so narrowed that it is almost invisible in most areas. Finally, the optic nerve head is a bit more pale than normal. These three findings in the presence of good central vision are very suggestive of the rod-selective photoreceptor cell death that is characteristic of retinitis pigmentosa.



Here, for comparison is a normal retina with no intra-retinal pigment, a normal vascular caliber and normal color of the optic nerve head.



Below is the optical coherence tomogram of the RP patient and for comparison, a normal OCT. The inner retina from the nerve fiber layer to the outer plexiform layer is not terribly different between these two individuals. What is very different is that the normal individual has a very prominent outer nuclear layer and ellipsoid zone, both of which are characteristic of intact photoreceptors.



To summarize, the main features of nonsyndromic retinitis pigmentosa are: night blindness, constricted visual fields, bone spicule like pigmentation, narrowed arterioles, disk pallor and loss of the outer nuclear layer and ellipsoid zone on OCT. The most common gene associated with autosomal recessive retinitis pigmentosa is *USH2A* and this patient has two disease-causing mutations in this gene.

Best Disease

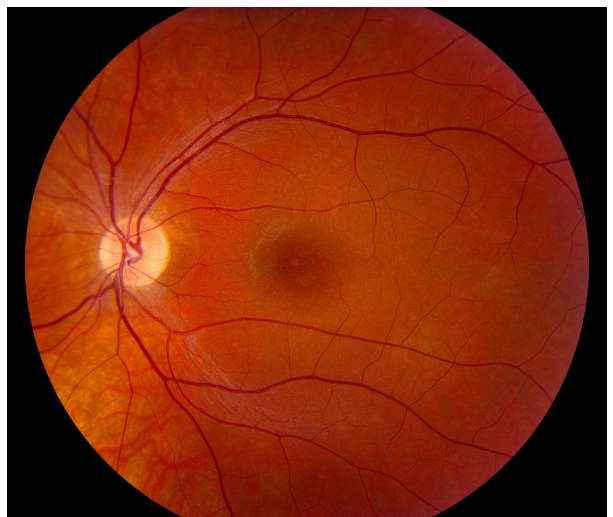
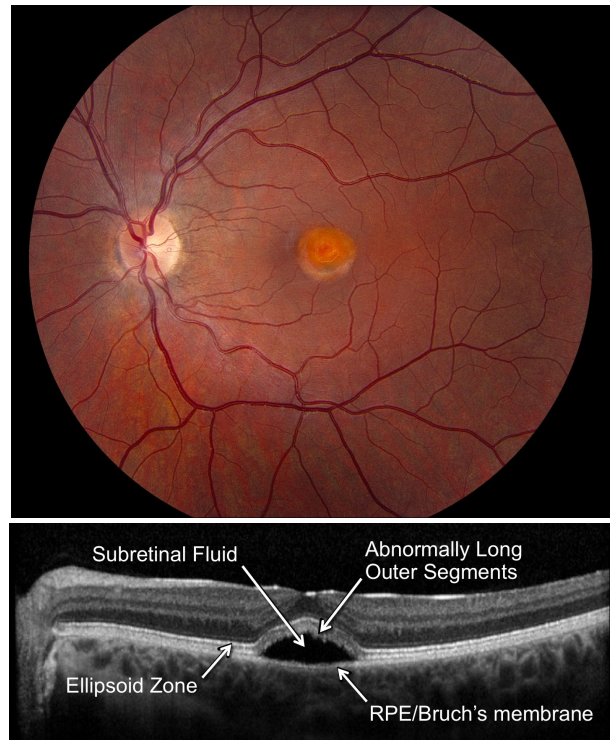
Let's contrast the clinical features of RP with the findings in this 17 year old male who has normal night vision, normal peripheral vision and 20/20 central acuity. There is no abnormal pigment in the periphery, the disk is a normal color and the retinal vessels have a normal course and caliber. In fact, the only abnormality in this retinal photograph is a vitelliform lesion about one disk area in size centered right on the fovea. He also has a family history of adult onset loss of visual acuity in his mother and a number of his maternal relatives.

Optical coherence tomography of this lesion reveals all of the abnormalities to lie between the ellipsoid zone and the retinal pigment epithelium. The abnormal material that has accumulated in this ordinarily very small space consists of some subretinal fluid and some extraordinarily long photoreceptor outer segments. These are classic findings of autosomal dominant Best disease. The reasons that this patient can still see normally are that: 1) all of the abnormalities are beneath the photoreceptors; 2) the Mueller cells are capable of performing the visual cycle for the cone photoreceptors so it doesn't matter that they are so far away from the RPE; and, 3) the ionic composition of the subretinal fluid is very similar to the normal interphotoreceptor matrix. The most common cause of this phenotype are missense mutations in *BEST1*.

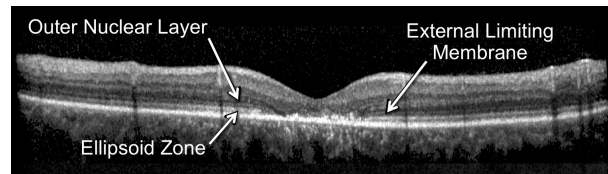
To summarize the features of Best disease, this patient has good visual acuity but a family history of reduced acuity suggestive of autosomal dominant inheritance. The retina outside the arcades is normal and the macula exhibits a yellow egg-yolk-like lesion centered on the fovea. The OCT shows the abnormal material to lie between the photoreceptors and the retinal pigment epithelium – the typical location for the initial pathological changes in the Macular Dystrophy branch of our classification scheme.

Autosomal Dominant Cone Dystrophy

The next patient is a 32 year old man with 20/150 visual acuity. He had relatively normal acuity as a young child but gradually lost vision after age 10. He is photophobic and cannot recognize any of the Ishihara pseudo-isochromatic plates. Two of his siblings as well as his mother and his maternal grandfather are all



similarly affected. Optical coherence tomography shows an area of outer retinal thinning about one disk diameter in size, centered on the fovea. In the abnormal area, there is a complete loss of the outer nuclear layer, the ellipsoid zone and the external limiting membrane. These OCT features are all components of photoreceptors, and their loss suggests that this disease belongs in category I – photoreceptor disease. The area of greatest loss corresponds to the anatomical fovea which is the part of the retina with the highest density of cone photoreceptors. This, coupled with the patient's reduced acuity, poor color vision and photophobia are all suggestive of a cone-selective disease. The most common gene associated with autosomal dominant cone dystrophy is *GUCA1A* and a mutation in this gene is indeed the cause of the photoreceptor loss in this patient. To summarize the key features of autosomal dominant cone dystrophy, they are: a fairly normal fundus appearance except for the central two millimeters or so, reduced acuity, poor color vision, photophobia, loss of foveal photoreceptors on OCT, and an autosomal dominant family history. An ERG was not needed for the diagnosis in this case but had it been performed the photopic responses would have been selectively reduced.



Pattern Dystrophy

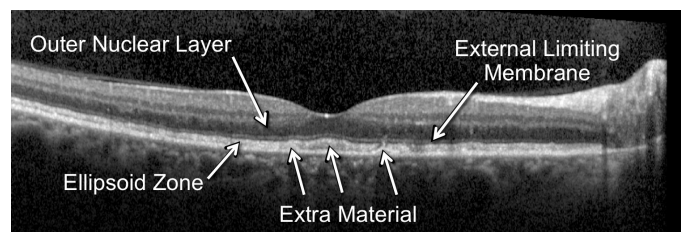
This is a fundus photograph of the right eye of a 63 year old woman with 20/25 vision. She has many similarly affected relatives including one of her parents. Some yellow flecks were first observed in her retina in her 20's and there is now an extensive network of reticular yellow deposits throughout the posterior pole. The retinal vasculature and optic nerve look very normal.



The optical coherence tomography findings in this patient are much more subtle than the previous three patients.

The outer nuclear layer and external limiting membrane are intact – which argues against a photoreceptor problem.

The ellipsoid zone is mottled and there seems to be some extra material between the ellipsoid and the RPE in some areas.



Yellow deposits in this anatomical location are a common characteristic of Mendelian macular dystrophies. Branching yellow subretinal deposits in a patient with good acuity and an autosomal dominant inheritance pattern are most consistent with the diagnosis of pattern dystrophy – and this condition is most commonly caused by mutations in the gene *PRPH2* – sometimes also called *RDS*.

Iowa Classification System

Before we talk about any more diseases, I'd like to tell you a bit more about the structure of the Iowa classification system so you will have some hooks and cubby holes in your brain to help you retain and organize some of the facts I am going to tell you about the other diseases. As I've already told you, we divide all inherited retinal diseases into three main branches:

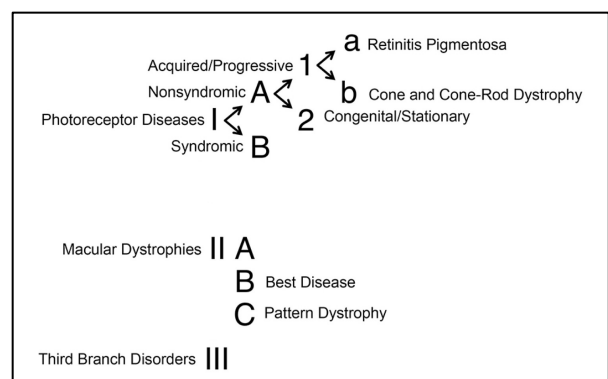
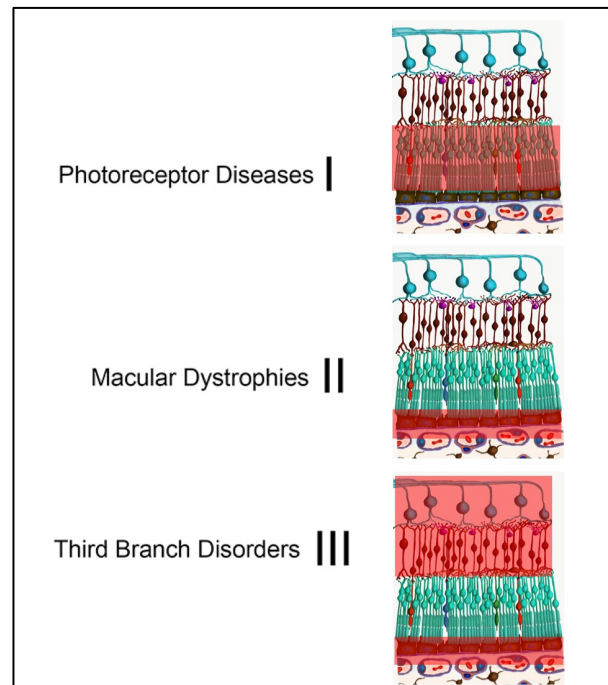
photoreceptor diseases, macular dystrophies and a miscellaneous group we call the third branch. These three main groups are defined in large part by the anatomical location of the earliest signs of pathology.

Photoreceptor diseases begin in the photoreceptor layer; macular dystrophies begin at the interface between the photoreceptors and retinal pigment epithelium; and, the diseases of the third branch start either deeper or more superficial than the other two groups.

There are only three macular dystrophies in the Big 14 and I have already shown you two of them: Best disease and pattern dystrophy.

Photoreceptor diseases comprise almost 65% of all inherited retinal diseases and are more clinically and genetically heterogeneous than the macular diseases. They can be subdivided into four large groups by the answers to three pretty straightforward questions: 1) does the disease affect tissues outside the eye or not; 2) does the disease first manifest itself after the fourth birthday or not; and, 3) does the disease initially affect rod photoreceptors more or less than cone photoreceptors.

We can also look at the photoreceptor diseases numerically using the same three questions. You start off with almost 65% of all inherited retinal disease initially manifesting in the photoreceptor layer. About a fourth of these or 15.4% of all inherited retinal disease is syndromic. If we divide the larger non-syndromic group according to whether the disease is congenital or acquired we see that about a fifth of it, or 10.6% of all inherited retinal disease is congenital and nonsyndromic. If we again divide the largest category, this time according to photoreceptor type, we see that only about 4.5% of all inherited retinal disease is a cone or cone-rod dystrophy. To further narrow the pre-test hypothesis of the very large RP group one can consider the inheritance pattern of their disease.



Congenital	10.6%	34.2%	Retinitis Pigmentosa
		4.5%	Cone and Cone-Rod Dystrophies
Syndromic		15.4%	

We have now learned about the two main types of nonsyndromic acquired photoreceptor disease -- retinitis pigmentosa and cone dystrophy -- and two of the most common types of macular dystrophy, Best disease and pattern dystrophy.

Stargardt Disease

Now I'd like to briefly introduce you to one of the most important and challenging inherited eye diseases you will encounter in your career: Stargardt disease. Sir William Osler said: "To know syphilis is to know medicine." I think what he meant by this was that syphilis affects so many organ systems and does so in so many different ways that if you fully understand all of its nuances you will be in a good position to really understand all of the nuances of medicine.

For reasons that are analogous to Osler's, I frequently say that "to know Stargardt disease is to know molecular ophthalmology." For example:

Stargardt disease can first present to an ophthalmologist between age 5 and greater than 50 years;

there are at least 4 genes that can cause a Stargardt-like phenotype: *ABCA4*, *PRPH2*, *ELOVL4* and *PROM1*; (*ABCA4* is by far the most important of these and depending on the severity of the mutations, abnormalities in *ABCA4* can cause disease ranging in phenotype from pattern dystrophy to retinitis pigmentosa);

some of the disease causing mutations in these genes lie outside the coding sequences making genetic testing challenging; and,

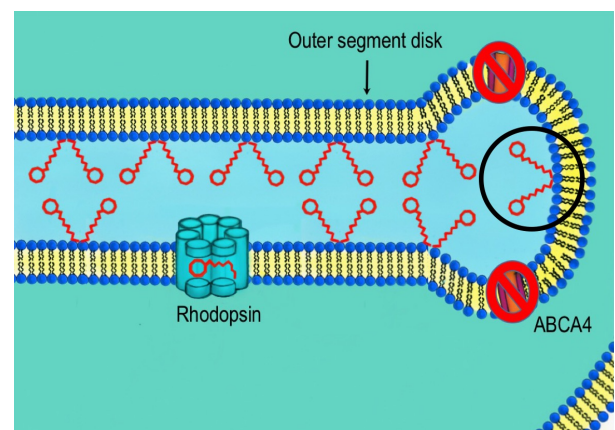
modifying genes can increase or decrease the injury to the fovea and the retinal pigment epithelium.

Because of all this complexity, we have created a separate tutorial devoted entirely to the nuances of Stargardt disease. But for today, we will focus only on the extreme phenotypic heterogeneity of *ABCA4* mutations and the way we have chosen to deal with this in our classification scheme.

You will recall from our anatomy and physiology tutorial that the function of the *ABCA4* protein in photoreceptors is to flip the visual cycle intermediate N-retinylidene-phosphatidyl-ethanolamine from the inner to the outer leaflet of the disk membrane. Failure to do this at the normal rate results in the irreversible formation of a toxic molecule known as A2PE.

If the *ABCA4* genotype is relatively mild, the normal shedding of disk membranes rids the photoreceptors of the accumulated A2PE. Most of it ends up in the retinal pigment epithelium causing a pattern-dystrophy-like phenotype.

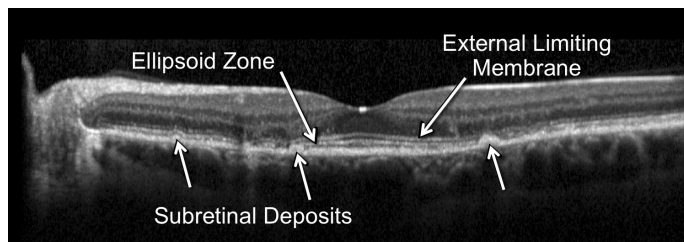
Because the cone outer segments turn over more slowly than rods, moderate *ABCA4* genotypes selectively injure cone photoreceptors causing a cone or cone-rod dystrophy phenotype.



Very severe *ABCA4* genotypes injure both photoreceptor types and cause a clinical appearance resembling retinitis pigmentosa.

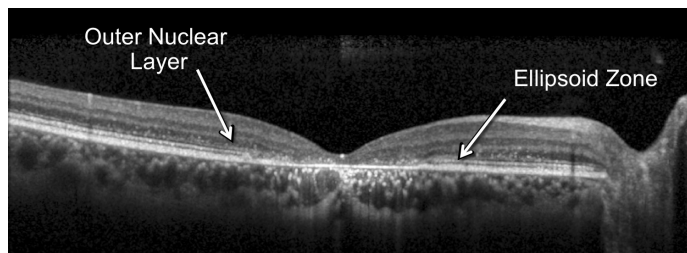
Looking at this on our classification diagram, *ABCA4*-associated autosomal recessive Stargardt disease lies right at the border of photoreceptor diseases and macular dystrophies and can exhibit features of either one depending on the severity of the genotype.

Let's look at a few patients to solidify these concepts. This is a 38 year old woman with 20/20 vision. Fundus examination reveals a branching pattern of greenish yellow deposits throughout the posterior pole. Both of her parents have good vision. Optical coherence tomography shows an

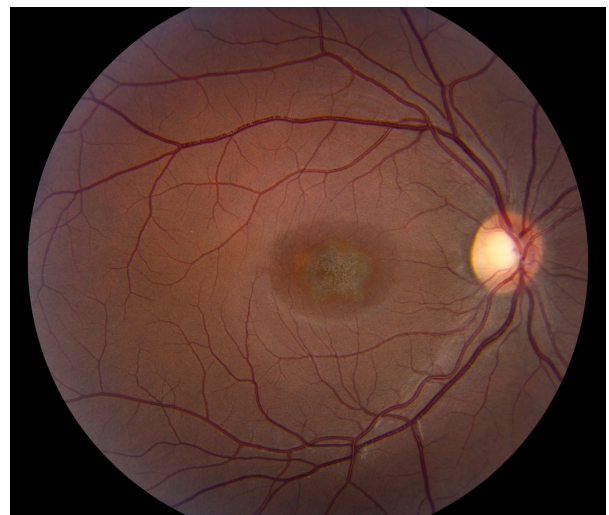
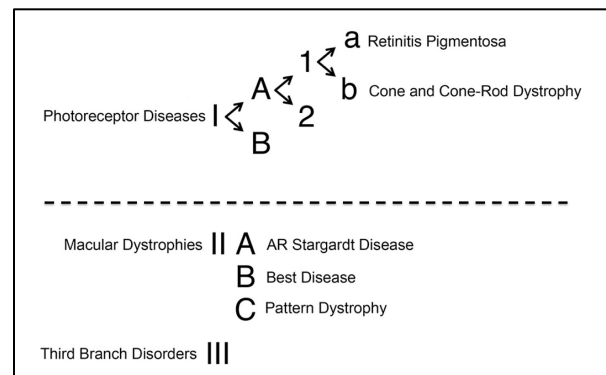


intact ellipsoid zone in the fovea consistent with her normal acuity and some small collections of abnormal material that seem to lie within or beneath the retinal pigment epithelium. The late age of presentation and excellent acuity would both suggest *PRPH2*-associated pattern dystrophy and it is only the lack of a family history that raises the possibility of a mild autosomal recessive *ABCA4* genotype which it did turn out to be.

This is a 19 year old woman with 20/160 acuity. Fundus examination reveals a normal disk and vessels but there is an atrophic macular lesion with a shiny base centered on fixation. There are no yellow flecks. Both of her parents have normal acuity. Optical coherence tomography shows a

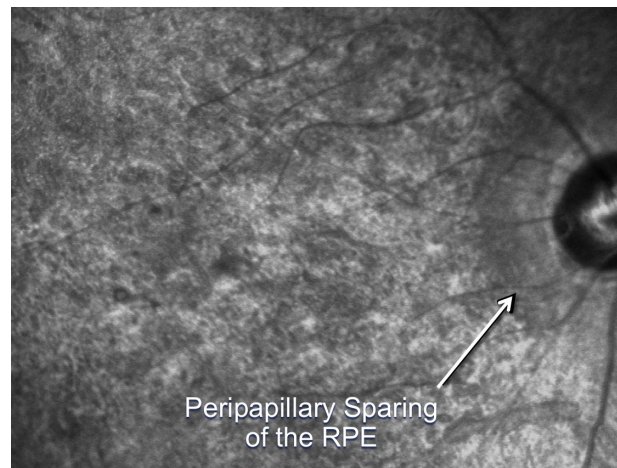
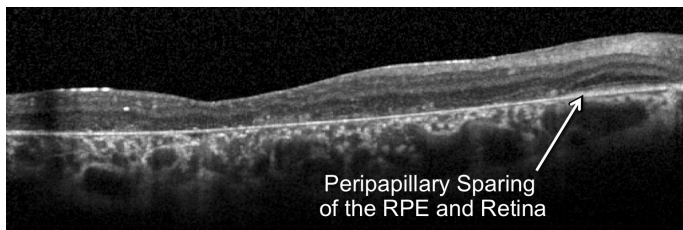
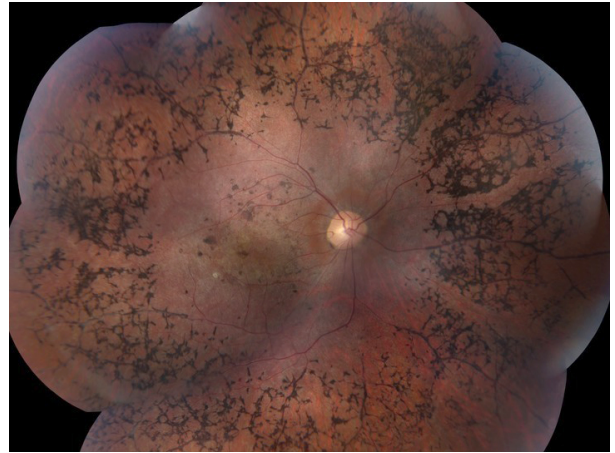


loss of the outer nuclear layer and ellipsoid zone in the fovea indicating a selective loss of foveal cone photoreceptors. Although one could not be faulted for using the descriptive diagnosis "cone dystrophy" in this patient, the most common molecular cause of autosomal recessive cone dystrophy is *ABCA4*. Thus, I place patients like this in category IIA, recognizing that they are just part of the *ABCA4* spectrum.



This is a 17 year old woman with 20/200 acuity. She had completely normal vision until about age 9. Her parents have normal acuity. Fundus examination shows extensive bone spicule like pigmentation and narrowed arterioles suggestive of extensive photoreceptor injury. However, there are also a few other findings that suggest a more specific diagnosis. First, it is unusual for retinitis pigmentosa to cause 20/200 acuity before age 20 and one should always consider *ABCA4* disease when the macula is affected in the first two decades of life. The nummular dark pigment overlying the macular atrophy is also characteristic of severe *ABCA4* genotypes.

A subtle but very meaningful finding is the ring of sparing of the retinal pigment epithelium surrounding the optic disk. This is a bit easier to see on the infra-red image of the same eye. It can



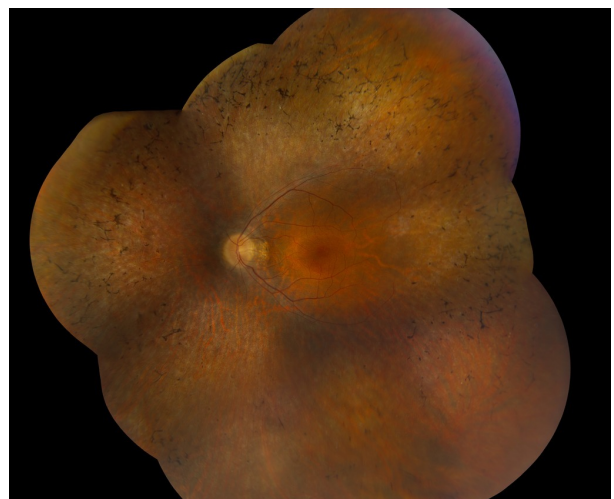
also be seen on the optical coherence tomogram although one has to be pretty disciplined to notice it when there is this much injury to the outer retina in the macula. So, although the phenotype of this individual does indeed have features suggestive of retinitis pigmentosa, there is enough other evidence to suggest *ABCA4* disease in this patient.

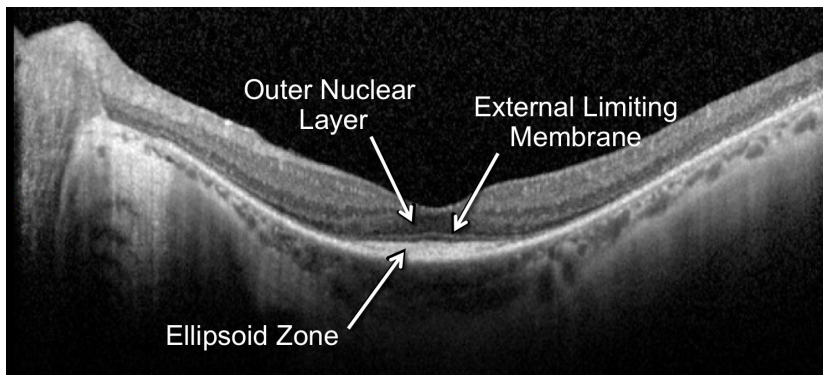
When one groups all of these *ABCA4* phenotypes into category IIA as we did in the 1000 consecutive families study, this one clinical entity is responsible for 18.5% of all inherited retinal disease.

Usher Syndrome

Let's look at another patient and see where they would best fit on our growing diagnostic tree. This is a 49 year old woman with 20/20 acuity. Examination of her fundus reveals narrowed arterioles, bone-spicule like pigmentation and a relatively normal macula.

Optical coherence tomography reveals the outer nuclear layer, external limiting membrane and ellipsoid zone to be preserved in central 2 millimeters or so of the macula but very



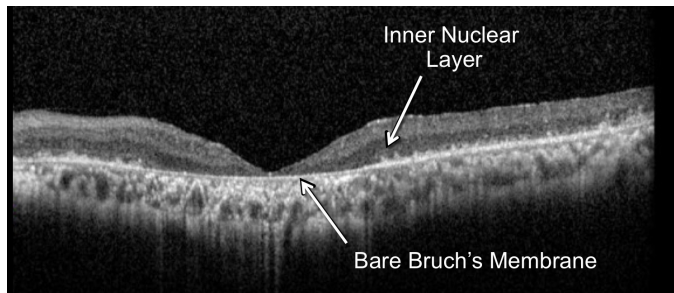


attenuated elsewhere. All of these things suggest the diagnosis of the rod selective photoreceptor disease retinitis pigmentosa. However, in addition to her eye findings, the patient's speech is abnormal and she has worn hearing aids in both ears since her hearing loss was first detected in early childhood.

The combination of retinitis pigmentosa and congenital hearing loss suggests the diagnosis of Usher syndrome. The fact that the patient has effective speech using only hearing aids is suggestive of Type 2 Usher Syndrome. Mutations in *USH2A* are the most common molecular cause of this condition. Usher syndrome is the most common form of syndromic photoreceptor disease and is the final diagnosis in 8.1% of all patients with an inherited retinal condition.

Bardet Biedl Syndrome

This 47 year old woman also has narrowed arterioles and bone spicule like pigmentation; but in addition to these features of photoreceptor disease, she has 20/500 visual acuity and a relatively large area of macular atrophy suggestive of significant cone involvement.



Her parents have normal vision. Optical coherence tomography reveals photoreceptor loss and in the center of the macula the retinal pigment epithelium is also missing such that the inner nuclear layer is apposed to a bare Bruch's membrane. This lady was born with an extra digit on the postaxial side of both hands and both feet and small scars can still be seen where these digits were removed. Her cognitive ability is a bit



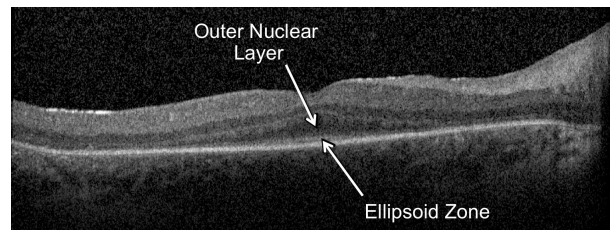
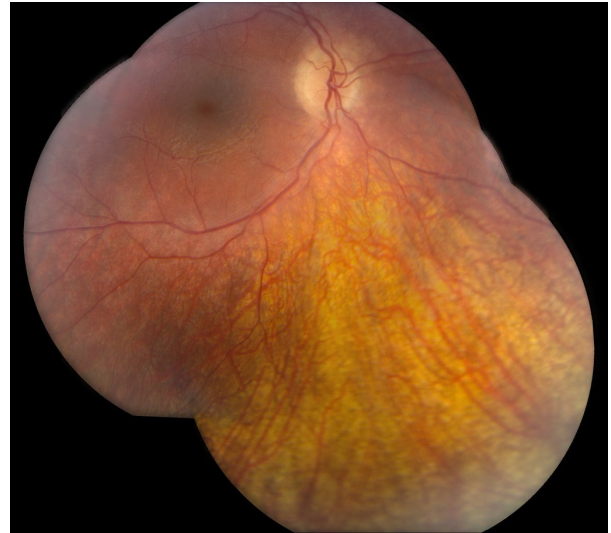
below normal and her body mass index is above normal. She also has type 2 diabetes mellitus. The combination of cone-rod dystrophy, poor visual acuity, reduced cognitive ability, increased BMI and diabetes mellitus are all suggestive of the diagnosis of Bardet Biedl syndrome. Mutations in *BBS1* are the most common cause of this condition.

Bardet Biedl syndrome is the second most common cause of syndromic photoreceptor disease. It and Usher syndrome are the only two syndromic conditions in the Big 14.

Leber Congenital Amaurosis

This 15 year old male was noted to have abnormal vision at 3 months of age. He had large amplitude nystagmus, did not respond to his parents faces and would not follow any type of toy or light that was put in front of him. His pupils constricted when the room lights were turned off and dilated when they were turned on. Retinoscopy revealed over seven diopters of hyperopia and electroretinography detected no responses under any stimulus conditions. The best acuity ever recorded was bare light perception. Fundus examination reveals a remarkably normal fundus for this degree of visual dysfunction. The optic nerves are pink and the arterioles are only modestly narrowed. His parents have normal vision.

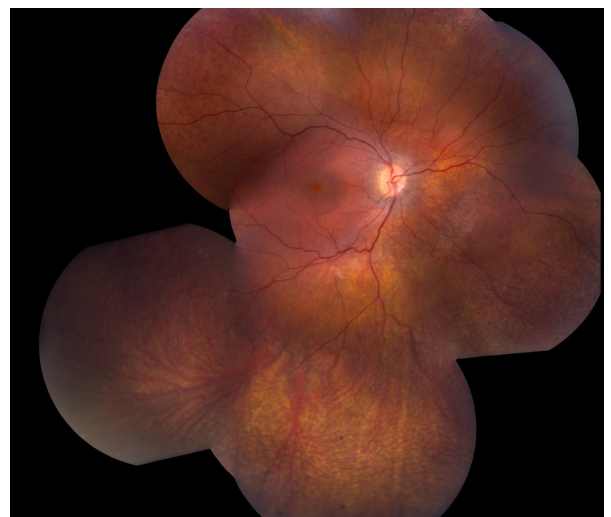
Optical coherence tomography shows preservation of the outer nuclear layer and ellipsoid zone in the fovea but marked outer retinal thinning outside the fovea.



Poor vision noted shortly after birth coupled with a nonrecordable ERG, loss of photoreceptors on OCT, paradoxical pupil responses, high hyperopia and a surprisingly normal fundus appearance are the hallmarks of Leber congenital amaurosis. Mutations in the *CEP290* gene are the most common cause of this condition. Leber congenital amaurosis is the most severe of the congenital photoreceptor disorders.

Severe Early Childhood Onset Retinal Dystrophy (SECORD)

This six year old girl was visually inattentive and had pronounced nystagmus at 4 months of age. An electroretinogram was performed at that time and no responses could be detected under any stimulus conditions. Her parents have normal vision. On our examination, her visual acuity was 20/80. Streak retinoscopy revealed about 5 diopters of hyperopia. Her fundus exam shows only slight arteriolar narrowing and some inferior mottling of the retinal pigment epithelium. The optic nerves are pink.

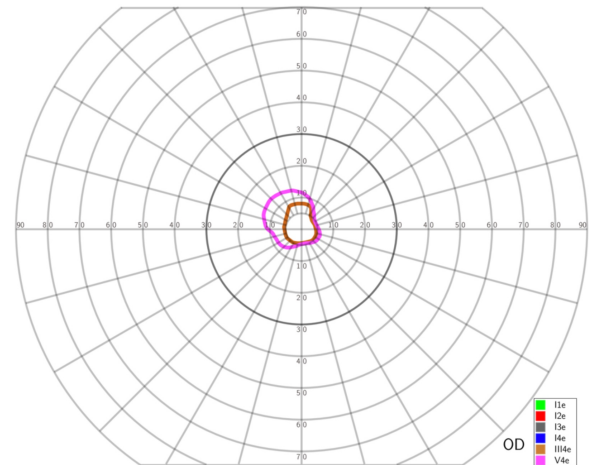
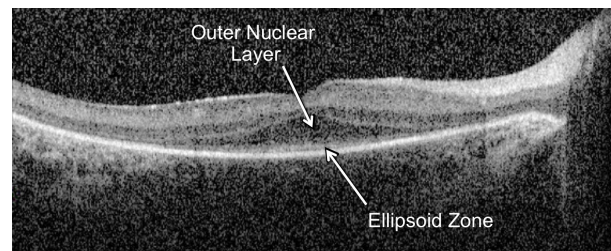


Optical coherence tomography shows some preservation of the outer nuclear layer and ellipsoid zone in the central two millimeters but complete loss of the photoreceptors elsewhere.

Goldmann perimetry reveals the V4e isopter to be constricted to less than 20 degrees which means that despite her pretty good central acuity, she is still “legally blind”.

Nystagmus noted shortly after birth coupled with a nonrecordable ERG, loss of photoreceptors on OCT, high hyperopia and a pretty normal fundus appearance suggest a congenital photoreceptor problem very similar to the Leber congenital amaurosis patient I just showed you.

In fact both of these patients have mutations in *CEP290* and the only difference between them is their visual acuity. For some reason that we don't yet understand, these small collections of foveal cones support 20/80 vision in one patient but don't work at all in the other. Although it is easy for geneticists and eye doctors to see how similar these two patients are, they are so different functionally that it is confusing for patients, families, educators and advocacy groups to use a term that means “congenital blindness” to refer to both of them. For this reason, Dick Weleber introduced the descriptive term “Severe Early Childhood Onset Retinal Dystrophy” for patients with congenital dysfunction of both photoreceptor systems who – like this patient -- have visual acuity that is functionally and educationally useful. SECORD is the second most severe of the congenital photoreceptor disorders.

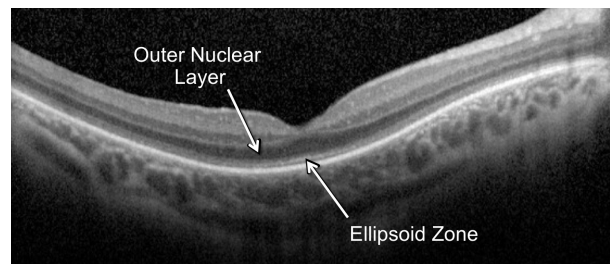


Early Childhood Onset Retinal Dystrophy (ECORD)

This next patient shows that there is an even milder phenotype in the Leber congenital amaurosis spectrum. He is 5 years old and has 20/40 visual acuity. His normally sighted parents noticed that he bumped into things inexplicably shortly after he began to walk. They sought medical attention and he was given hyperopic spectacles of about 4 diopters which seemed to help with his central vision. However, his parents still suspected that his peripheral field was constricted because he would back up to find things. Electroretinography was then performed which revealed reduced scotopic responses and completely extinguished photopic responses. Fundus examination revealed fairly normal optic nerve heads and vessels with some hypopigmentation of the retinal pigment epithelium in the macula giving that region a more orange color than the rest of the fundus. Goldmann perimetry revealed a V4e isopter about 50 degrees in diameter.



Optical coherence tomography shows an outer nuclear layer that is a little thinner than normal and an ellipsoid zone that is a bit less reflective than normal except in the fovea.



The recognition of reduced vision in the second year of life, and an ERG showing reduced responses from both rods and cones suggest that this patient also has a condition that is similar in character to Leber congenital amaurosis. However, since this patient has 20/40 acuity and sufficient visual field that he is not legally blind, even the label “severe” seems unwarranted at present. We use the term “early childhood onset retinal dystrophy” for such patients. Molecular investigation of this patient revealed mutations in the gene *IQCB1* which causes renal failure in some individuals. Fortunately this patient’s renal function tests are normal.

So the first three entities in the nonsyndromic congenital photoreceptor disease group really represent decreasing severity of the same constellation of findings: onset before the first birthday, a fairly normal appearing retina for the degree of retinal dysfunction, and clinical or electrophysiological evidence that both photoreceptor types are involved.

If a patient’s vision is so poor that it cannot be used for education, we use the term Leber congenital amaurosis.

If the patient has educationally usable vision but meets either criterion for legal blindness – acuity poorer than 20/200 in the better eye or a V4e isopter smaller than 20 degrees -- before his tenth birthday, we use the term “severe early childhood onset retinal dystrophy” or SECORD.

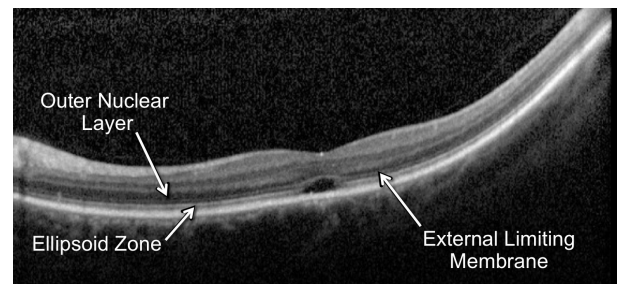
If a patient is not legally blind, we drop the word “severe” and use the term “early childhood onset retinal dystrophy” or ECORD.

Achromatopsia

The next patient is a 47 year old woman who has 20/125 acuity. She has never had acuity better than 20/100. Her normally sighted parents noticed that she did not look at their faces normally or follow toys when she was just 12 weeks of age. Later she had an electroretinogram that revealed normal scotopic responses but extinguished photopic responses. Even as a child, she could not recognize any of the Ishihara plates or name the colors of common objects. She has been photophobic her whole life but could see the same as her friends in very dim environments like playing flashlight tag. Fundus examination reveals a healthy optic nerve and normal retinal vessels. In fact the only abnormality is an elliptical cystic lesion a few hundred microns in diameter.



Optical coherence tomography reveals a small, sharply circumscribed loss of the outer nuclear layer and ellipsoid zone centered on the fovea.

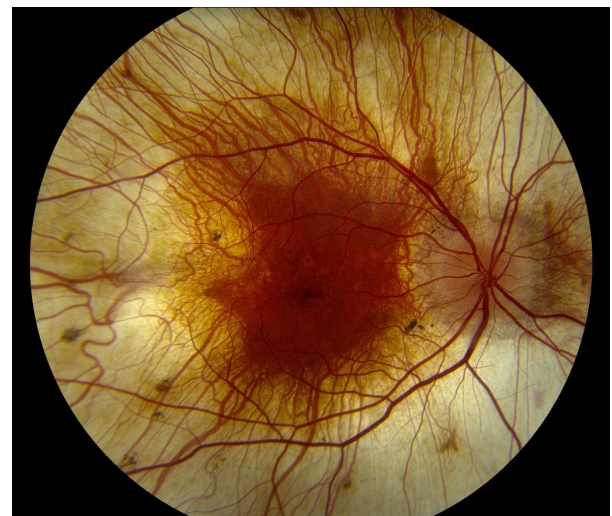


The recognition of vision loss in the first year of life in the presence of a near normal retinal and optic nerve examination suggests a congenital photoreceptor problem. Her reduced acuity, photophobia and completely absent color discrimination in the presence of normal night vision suggest a selective loss of cone function. This constellation of findings suggests the diagnosis of achromatopsia which is usually caused by mutations in one of the genes encoding the two subunits of the cone-specific cyclic nucleotide gated channel. This lady's disease was caused by mutations in CNGA3.

Achromatopsia is the last of the nonsyndromic congenital photoreceptor diseases in the Big 14.

Choroideremia

The next patient is a 19 year old man with 20/20 acuity. He first came to medical attention at age 9 when nummular patches of choroidal atrophy were detected in the periphery of his fundus. His mother and maternal grandmother have completely normal vision but both of them have an unusual "mudspattered" appearance to their retinas. The patient's retinal exam shows essentially bare sclera outside the central 5 millimeters or so. The retinal arterioles are essentially normal in caliber and the optic disks also look quite normal.



Spectral domain optical coherence tomography reveals a loss of the outer nuclear layer, ellipsoid zone, RPE and choriocapillaris in the affected areas.

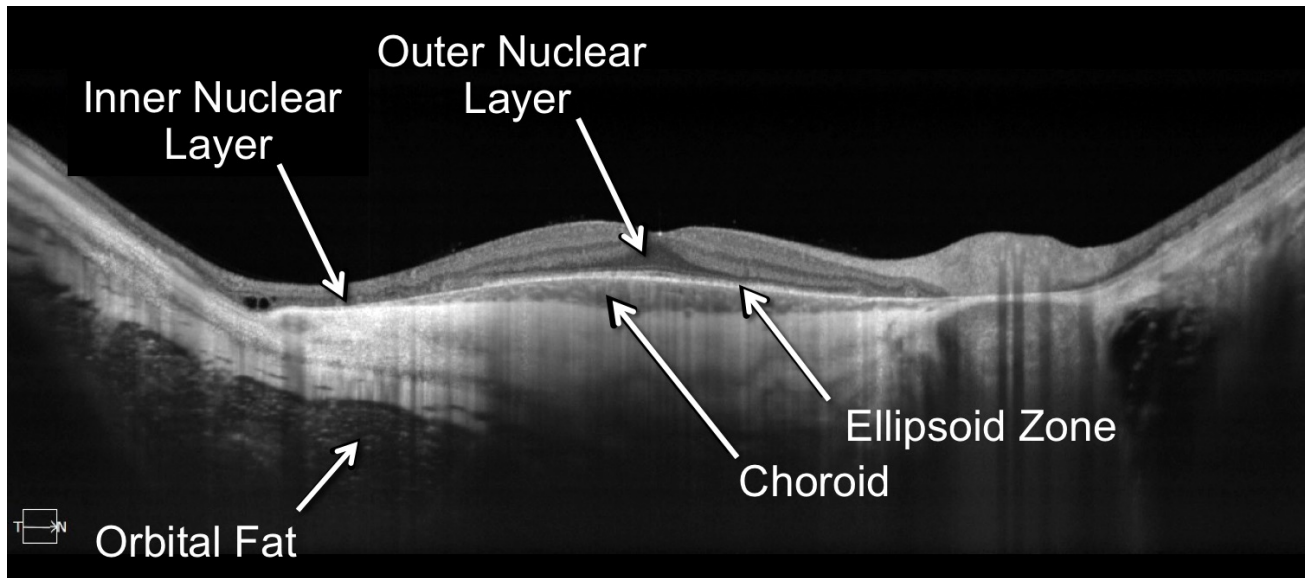


Patient's Normally Sighted Mother

A sixteen millimeter Swept source OCT line scan of the patient (next page) is much more revealing. Here you can still see the normal outer retina and choroidal structures in the macula but it is easier to see the extent of the choroidal loss outside the macula. The inner nuclear layer about 4 millimeters temporal to the fovea is apposed to bare sclera. It is also interesting to see that because of the depth of penetration of the infrared laser in the swept source instrument, you can even see some orbital fat adjacent to the sclera.

The normal retinal arteriolar caliber suggests that the choriocapillaris – the major source of oxygen for the outer retina -- is being lost first and that the photoreceptor loss is secondary.

This, coupled with the mudspattered carrier features in his mother and maternal grandmother suggest the diagnosis of the X-linked disease choroideremia caused by mutations in the gene *CHM*.



Choroidopathies are the most common category of molecularly diagnosable disease in the third branch accounting for about 1.5% of all inherited retinal disease.

More than 85% of the patients in this category have choroideremia.

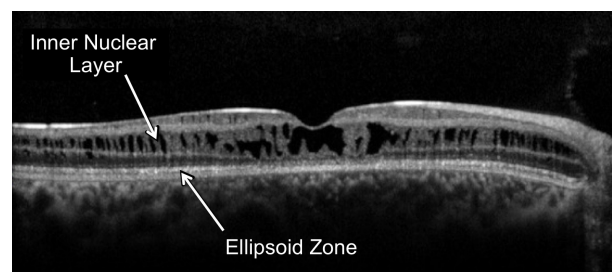
Juvenile X-linked Retinoschisis

This is the right eye of an 11 year old male with 20/60 vision. His parents have normal vision but he has a brother who also has reduced acuity. Fundus examination reveals normal disks and vessels, but there is a stellate arrangement of cysts centered on the fovea.

Optical coherence tomography reveals numerous cystic spaces that are most prominent in the inner nuclear layer. The ellipsoid zone is fairly well preserved despite the extensive cysts.

The presence of cystic spaces in the inner nuclear layer of the macula of a male patient, with relatively good acuity given the degree of retinal abnormality, suggests the diagnosis of X-linked retinoschisis. This disease is caused by hemizygous mutations in the *RS1* gene.

Retinoschisis is the second most common category of molecularly diagnosable disease in the third branch accounting for about 1.4% of all inherited retinal disease and more than 85% of the patients in this category have X-linked retinoschisis.

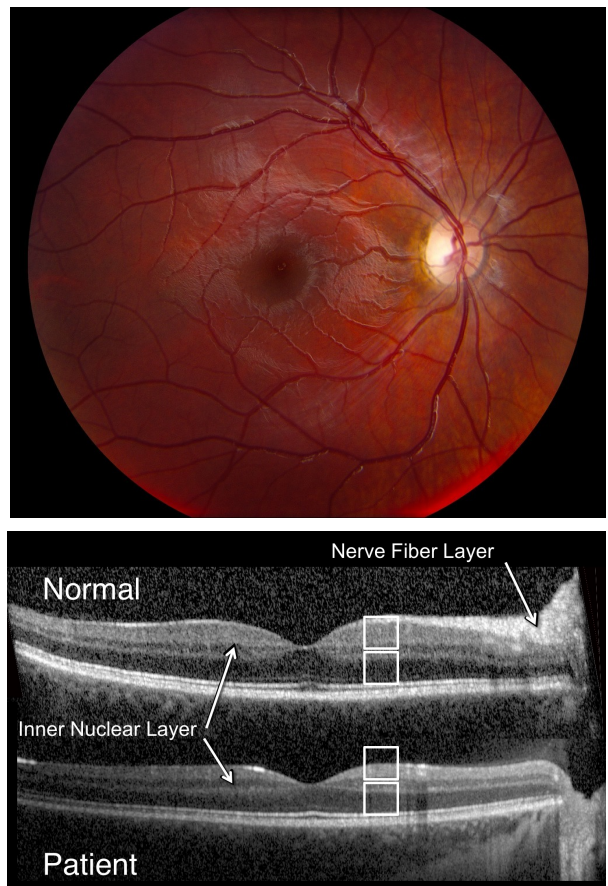


Dominant Optic Atrophy

This is the right eye of an 11 year old male with 20/100 vision. He was first noted to have reduced acuity on a school vision screen at age 7. His parents have normal acuity. Fundus examination reveals normal retinal vessels and a shiny retinal surface that is normal for a patient of this age. The most striking finding is a wedge of temporal pallor on the optic disk.

Optical coherence tomography reveals significant thinning of the inner retina but a normal outer retina. Normally, the inner plexiform layer, ganglion cells and nerve fiber layer are about equal in thickness to the outer nuclear layer but in this patient the inner retina is noticeably thinner. Also, the normal thickening of the nerve fiber layer as it approaches the optic nerve head is absent in this patient.

The combination of reduced visual acuity, a wedge of temporal pallor, an otherwise normal fundus appearance and a selective thinning of the inner retina on OCT are all suggestive of dominant optic atrophy which is most commonly caused by heterozygous variations in the gene *OPA1*.



Optic neuropathies are the third most common category of molecularly diagnosable disease in the third branch accounting for about 1.3% of all inherited retinal disease.

More than 85% of the patients in this category have nonsyndromic disease and more than 75% of these patients have autosomal dominant optic neuropathy caused by heterozygous mutations in *OPA1*.

So let's review the structure of the Big 14 inherited retinal diseases one more time.

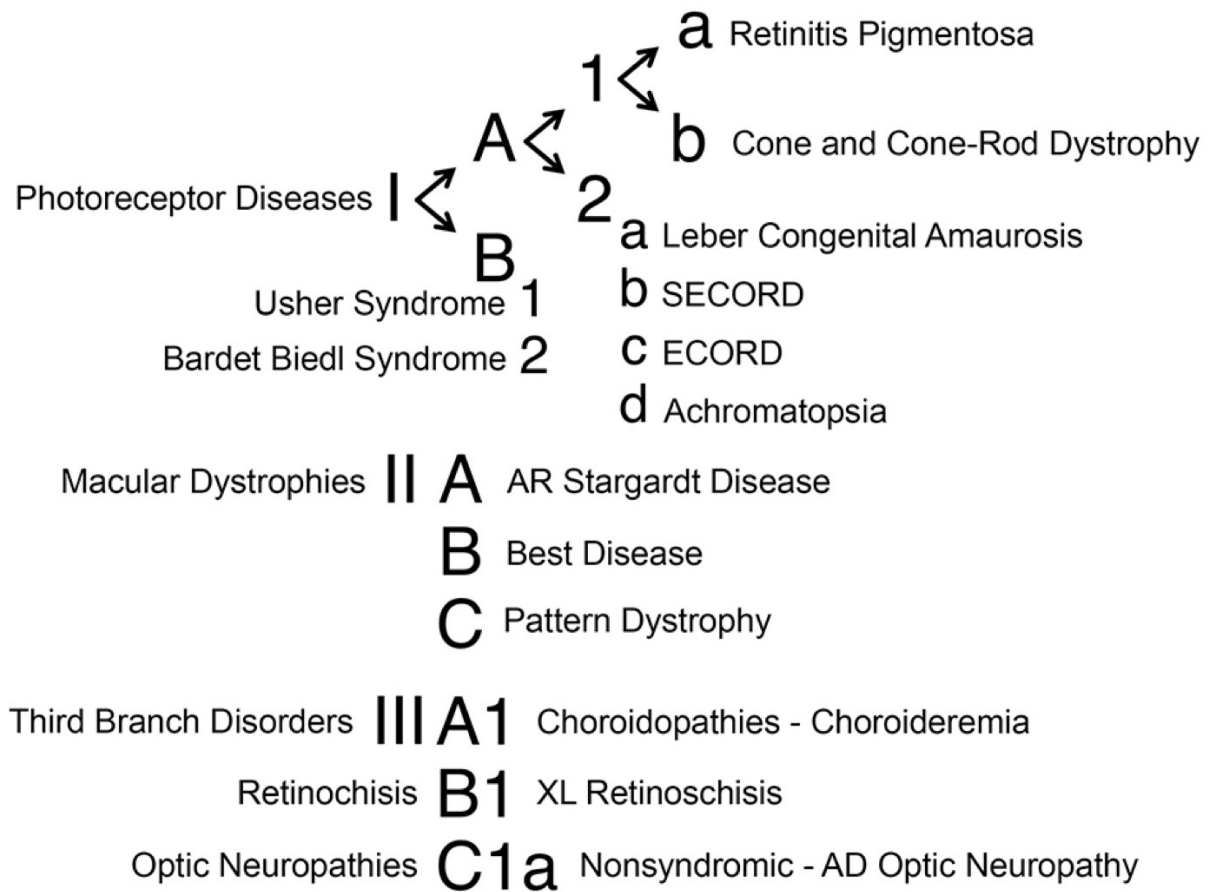
Every first year resident should be able to draw a diagram of the relationships among the Big 14 diseases before they are half way through their first retina rotation. It's pretty easy to do. In fact, most people can do it almost perfectly after watching this tutorial for the first time.

The first big category is photoreceptor disease -- and what we do is divide the largest category three more times with three straightforward questions, always putting the more common division on the top:

Does the patient have syndromic disease or not? Syndromic is less common and goes on the bottom.

Is it congenital or not? Congenital is less common and goes on the bottom.

Is it a rod selective disease or a cone selective disease? Rod selective retinitis pigmentosa is seven times more common than cone and cone-rod dystrophy and goes on the top.



There are two syndromic diseases in the Big 14, Usher syndrome and Bardet Biedl syndrome.

There are 4 congenital and/or stationary diseases in the big 14 and the first three of them are just decreasingly severe versions of combined rod and cone dysfunction at birth --

We use the term Leber Congenital Amaurosis when the vision is so poor it cannot really be used for education.

Children with “severe early childhood onset retinal dystrophy” —or SECORD are legally blind before age 10, and for children who are not legally blind by age 10, we drop the word “severe.”

The remaining congenital stationary condition in the Big 14 is the selective cone dysfunction achromatopsia.

The second major category of inherited retinal diseases are the macular dystrophies and only three of them are common enough to be included in the Big 14: autosomal recessive Stargardt disease, and two dominant conditions, Best disease and pattern dystrophy.


The smallest major category of inherited retinal disease is known as the third branch.

The most common choroidopathy is choroideremia, the most common form of retinoschisis is X-linked and the most common optic neuropathy is dominant optic atrophy.

While you are learning these diseases you may want to carry one of these cards in your wallet.

The one side of the card has a list of syndromic features to think about when you are seeing a complex patient with an inherited retinal disease and the other side shows the relationships among the Big 14 diseases.

You can find a PDF file of this card in the tutorial section of this website.



Syndromic Features to Consider

Deafness, polydactyly, obesity, diabetes, abnormal cognition, developmental delay, seizures, ataxia, dysarthria, other brain abnormalities, hypertension, heart disease, malformation and/or arrhythmias, nocturia, other kidney abnormalities, abnormal dentition, cleft palate, dysmorphic facies, abnormal bruising or bleeding, frequent infections, malabsorption, muscle weakness.

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Big 14 (87%)

I - Photoreceptor Disease

A - Isolated

- 1 - Acquired/Progressive
 - a - Retinitis Pigmentosa
 - b - Cone & C/R Dystrophy
- 2 - Congenital/Stationary
 - a - LCA
 - b - SECORD
 - c - ECORD
 - d - Achromatopsia

B - Syndromic

- 1 - Usher Syndrome
- 2 - Bardet-Biedl Syndrome

II - Macular Diseases

A - AR Stargardt Disease

B - Best Disease

C - Pattern Dystrophy

III - Third Branch Disorders

A1 - Choroideremia

B1 - XL Retinoschisis

C1a - Dominant Optic Atrophy

Inherited Eye Disease History

Today's date:

History taken by:

1. Age of onset:
2. Earliest symptoms (acuity, night blindness, photophobia, color vision with dates):
3. Earliest diagnosis (with date):
4. All previous diagnoses (with dates):
5. Does the patient have rod-selective or cone-selective disease (cite specific examples to support your answer)?
6. Syndromic features? (deafness, polydactyly, obesity, diabetes, abnormal cognition, developmental delay, seizures, ataxia, dysarthria, other brain abnormalities, hypertension, nocturia, other kidney abnormalities, heart abnormalities, abnormal dentition, cleft palate, dysmorphic facies, other skeletal or joint abnormalities, pedal edema, skin abnormalities, hair abnormalities, abnormal bruising or bleeding, frequent infections, malabsorption, muscle weakness, positive serologies (e.g. syphilis, other TORCH, Lyme, ANA, anti-retinal antibodies):
7. Current chronic medications relevant to vision include:
8. Does the patient have any history of cancer or autoimmune disease?:
9. Relevant family history (draw pedigree on a separate sheet):
10. Driving history:
11. Representative refraction (wearing glasses, previous refraction, manifest refraction today, etc.) Include dates and visual acuities:
12. Color vision testing (include date and method):