Q

- Inheritance?

Stargardt Disease/Fundus Flavimaculatus
Stargardt Disease/Fundus Flavimaculatus

- Inheritance? AR (in most cases; a small % are AD)
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*As hereditary maculopathies go, where does Stargardt rank in terms of prevalence?*
Q/A

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**Huh? how can an AR disease be more prevalent than AD diseases?**
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Huh? how can an AR disease be more prevalent than AD diseases? Because the genes that cause Stargardt are very common in the general population.
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How common is ‘very common’? What percentage of the population is carrying one of the many disease-causing ABCA4 alleles?

Estimates run as high as 10%!
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The ABCA4 gene is mission-critical to the eye, with implications extending far beyond Stargardt/FF. Given this, let’s look at it in some detail…
• Inheritance? AR (in most cases; a small % are AD)
• Gene responsible for most cases? **ABCA4**

*What does ABCA4 stand for?*
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What does ABCA4 stand for?
ATP-Binding Cassette, sub-family A, member 4
Q

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*The ABCA4 gene codes for the ABCA4 protein. (Shocking, I know.) In general terms, what sort of protein is ABCA4? What does it do?*
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ABCA4 is a member of the ATP binding cassette superfamily of transport proteins. (Collectively, they are referred to simply as ABC proteins.)
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ABCA4 is a member of the **ATP binding cassette** superfamily of transporter proteins. (Collectively, they are referred to simply as **ABC transporters**.) They are ubiquitous—found in every phyla of organism from us down to the prokaryotes. Hundreds of different ABC transporters have been identified (is why they’re a ‘superfamily’). To date, nearly 50 different ABC transporters have been identified in humans.
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**OK, but what do they do?**
In a word, they transport—substrates, into (or out of) cells. They are transmembrane channels that use ATP as an energy source to transport substances in or out of a cell against a concentration gradient.
Type I ABC importers

Type II ABC importers

ABC exporters

(Multi-)drug extrusion
Peptide/toxin export
(Glyco-)lipid flipping

Cytoplasm

ModBC-A
Hollenstein et al.,

BtuCD-F
Hvorup et al.,
Science (2007)

Sav1866
Dawson et al.,

Nutrient uptake
(sugars, ions, amino acids)

Nutrient uptake
(vitamin B₁₂, heme, siderophores)
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*For example…?*
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For example…?
Name a substrate, and an ABC transporter is probably involved--most nutrients, vitamins, trace elements, etc coming in; metabolic waste, fats, sterols, and drugs going out.
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‘Drugs going out’—what does that mean?

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‘Drugs going out’—what does that mean?
It means exactly what it says—ABC transporters are how cells rid themselves of therapeutic compounds. For example, bacterial drug resistance is often 2ndry to the development of ABC transporters. Likewise, when a previously effective cancer drug loses efficacy for an individual, it can often be attributed to the appearance in the cancer line of an ABC transporter that effluxes the drug.
Inheritance? AR (in most cases; a small % are AD)

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So what does the ABCA4 transporter have to do with the eye?
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*So what does the ABCA4 transporter have to do with the eye?*

A great deal. This transporter is located exclusively in the retina, specifically in the membrane of the **three words**.
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What role does the ABCA4 transporter play within rod outer segments?
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What role does the ABCA4 transporter play within rod outer segments?
It is responsible for exporting a potentially toxic metabolic byproduct of the visual cycle. When ABCA4 is defective, this byproduct accumulates within the segment. Then, when the outer segments are shed and ‘swallowed’ by the underlying RPE (as part of the normal retinal renewal process), the metabolic byproduct is incorporated into the RPE cell’s wear-and-tear granule.
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And death of the RPE leads to…?
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And death of the RPE leads to…?
Changes in the appearance of the posterior pole, as well as (far more importantly) death of overlying photoreceptors, with subsequent decreased vision.
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The pathophysiology of Stargardt/FF tl;dr
--Defective ABCA4 alleles inherited; defective ABCA4 transporters expressed in rod outer segments
--Defective ABCA4 transporters can’t export metabolic byproducts of the visual cycle, leading to their accumulation within the segments
--As part of the normal retinal renewal process, byproduct-laden outer segments are shed, then phagocytized by RPE cells
--Within RPE cells, the byproduct is converted to A2E, which eventually kills the cell
--When the RPE cell dies, photoreceptors that depend on it die as well

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- Fundus appearance: fovea surrounded by flecks
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The RPE
Stargardt Disease/Fundus Flavimaculatus

Stargardt: RPE-level flecks
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Gene responsible for most cases? ABCA4

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At what level of the retina do the flecks occur?
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Yellow-white findings in the RPE--that sounds like drusen. How do Stargardt/FF flecks differ ophthalmoscopically from drusen?

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--Drusen are round(-ish), whereas some flecks are elongated
--The flecks often touch one another, rendering their aggregate appearance ‘net-like’
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What does pisciform mean?
It means ‘fish shaped’

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How does that come about?

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What does pisciform mean?
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How does that come about?
If two of these elongated flecks touch one another at just the right angle, their appearance will be reminiscent of a fish’s tail. Drusen. How do drusen differ ophthalmoscopically from Stargardt/FF flecks? Drusen are round(-ish), whereas some flecks are elongated. The flecks often touch one another, rendering their aggregate appearance ‘net-like’
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Pisciform lesions
Q

- Inheritance? AR (in most cases; a small % are AD)
- Gene responsible for most cases? ABCA4
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Which appears first--foveal atrophy, or the flecks?
Stargardt Disease/Fundus Flavimaculatus

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Which appears first--foveal atrophy, or the flecks?
In most cases, the atrophy
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‘Beaten bronze’
Stargardt disease. Macular atrophy, pisciform yellow-white flecks, and a beaten-bronze appearance. Note the peripapillary sparing of retina.
Inheritance? **AR (in most cases; a small % are AD)**

Gene responsible for most cases? **ABCA4**

Fundus appearance: **Atrophic** fovea surrounded by **white-yellow pisciform** flecks

- If pisciform lesions are in macula only, is **Stargardt Disease**
- If they are widely scattered, is **Fundus Flavimaculatus**
Inheritance? AR (in most cases; a small % are AD)
Gene responsible for most cases? ABCA4
Fundus appearance: Atrophic fovea surrounded by white-yellow pisciform flecks
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  - If they are widely scattered, is fundus flavimaculatus
Stargardt Disease/Fundus Flavimaculatus

Stargardt

Fundus flavimaculatus
Inheritance? AR (in most cases; a small % are AD)

Gene responsible for most cases? ABCA4

Fundus appearance: Atrophic fovea surrounded by white-yellow pisciform flecks

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- If they are widely scattered, is fundus flavimaculatus

Pts present with c/o decreased vision, usually in life period
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  - If they are widely scattered, is fundus flavimaculatus
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Which appears first--changes in the fundus, or decreased vision?
Inheritance? AR (in most cases; a small % are AD)

Gene responsible for most cases? ABCA4

Fundus appearance:
- Atrophic fovea surrounded by white-yellow pisciform flecks

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- If they are widely scattered, is fundus flavimaculatus

Pts present with c/o decreased vision, usually in childhood

Which appears first--changes in the fundus, or decreased vision?
Usually the decreased vision (especially in childhood onset cases)
Q  

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- Pts present with c/o **decreased vision**, usually in childhood

Which appears first--changes in the fundus, or decreased vision?  
**Usually the decreased vision (especially in childhood onset cases)**

What is the classic scenario you should be on the lookout for?
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Stargardt—*dark choroid* appearance on FA
Inheritance? AR (in most cases; a small % are AD)

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Blocking

At what level of the retina is blocking occurring?
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**Blocking**

At what level of the retina is blocking occurring?  
The RPE
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In Stargardt, what causes the RPE to block choroidal FA fluorescence?
Again, in FA parlance--is the choroidal hypofluorescence secondary to blocking, or to a filling defect?
Blocking

In what level of the retina is blocking occurring?

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In Stargardt, what causes the RPE to block choroidal FA fluorescence?
The accumulation of abnormal lipofuscin/A2E within RPE cells

Again, in FA parlance--is the choroidal hypofluorescence secondary to blocking, or to a filling defect?
Blocking

In what level of the retina is blocking occurring?
The RPE
Q

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What test has supplanted FA for working up suspected Stargardt?

What should you do if/when encountering such a child (either on the OKAP/Boards or IRL)? The answer used to be ‘order an FA,’ so we’ll address that first…
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**Why is FAF preferred?**
It is more reliable (not all Stargardt eyes manifest the dark choroid phenomenon)

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What is the classic FAF appearance of Stargardt?

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What is the classic FAF appearance of Stargardt?
A bull’s eye maculopathy--a ring of perifoveal hypo- vs hyperfluorescence surrounding a central foveal area of hypo- vs hyperfluorescence

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What should you do if/when encountering such a child (either on the OKAP/Boards or IRL)?
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Stargardt disease. The right eye (A) and left eye (B) demonstrate classic pisciform yellow-white flecks throughout the macula, with mottling of the central retinal pigment epithelium (RPE).
Stargardt Disease/Fundus Flavimaculatus

Stargardt disease. The right eye (A) and left eye (B) demonstrate classic pisciform yellow-white flecks throughout the macula, with mottling of the central retinal pigment epithelium (RPE). Corresponding right (C) and left (D) FAF images reveal mottled hypo- and hyperautofluorescence with hyperautofluorescent flecks (corresponding to the pisciform flecks) and a bull’s-eye maculopathy, greater in the left eye than in the right eye.
What is the classic FAF appearance of Stargardt?

- A bull’s eye maculopathy—a ring of perifoveal hyperfluorescence surrounding a central foveal area of hypofluorescence.

Why does the perifoveal macula hyperfluoresce?

- It is more reliable (not all Stargardt eyes manifest the dark choroid phenomenon).

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What is the classic FAF appearance of Stargardt?
A bull’s eye maculopathy--a ring surrounding a central foveal area of hypofluorescence

Why does the perifoveal macula hyperfluoresce?
Because its RPE cells are stuffed with lipofuscin-containing A2E, a substance that autofluoresces particularly well

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OK, but then why does the central foveal area hypofluoresce?
Because its RPE cells are dead and gone, leaving little lipofuscin in that area

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Ultimate vision is usually in the 20/50 – 20/200 range
Other diseases associated with ABCA4 dysfunction include cone dystrophy, cone-rod dystrophy and RP
Inheritance? AR (in most cases; a small % are AD)

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How can one dysfunction of a single protein cause such a variety of pathology?
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How can one dysfunction of a single protein cause such a variety of pathology? Because it is not the case that the ABCA4 transporter is either fully functional or completely dysfunctional. Rather, ABCA4 function exists on a continuum, from completely intact (= normal/non-diseased) to mildly impaired (= mild Stargardt) to moderately impaired (= worse Stargardt) to severely impaired (= cone-rod dystrophy) to completely nonfunctional (= RP).
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So, all of these conditions are caused by mutations on ABCA4?
Stargardt Disease/Fundus Flavimaculatus

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So, all of these conditions are caused by mutations on ABCA4? Yes and no. All of these conditions can be caused by ABCA4 mutations. But all of them can be caused by mutations to other genes as well.
Stargardt Disease/Fundus Flavimaculatus

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For each condition, what percent of cases are caused by ABCA4 mutation?
- Stargardt: Yes and no
- Cone dystrophy:
- Cone-rod dystrophy:
- RP:

So, all of these conditions are caused by mutations in ABCA4? No. Yes and no.
But all of these conditions are caused by mutations in genes other than ABCA4? Yes.
In Stargardt disease, how can a single protein cause a variety of symptoms? (Yes and no. It is from completely normal (= normal vision) to mildly impaired (= worse Stargardt) to moderately impaired (= cone dystrophy) to completely nonfunctional (= RP).
Inheritance? AR (in most cases; a small % are AD)

Gene responsible for most cases? ABCA4

Fundus appearance: Atrophic fovea surrounded by white-yellow pisciform flecks

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Other diseases associated with ABCA4 dysfunction include cone dystrophy, cone-rod dystrophy and RP

For each condition, what percent of cases are caused by ABCA4 mutation?

--Stargardt: >95
--Cone dystrophy: don’t have a number for this
--Cone-rod dystrophy: 30-50
--RP: 5-10
Inheritance? AR (in most cases; a small % are AD)

Gene responsible for most cases? ABCA4

Fundus appearance: Atrophic fovea surrounded by white-yellow pisciform flecks
  - If pisciform lesions are in macula only, is Stargardt
  - If they are widely scattered, is fundus flavimaculatus

Pts present with c/o decreased vision, usually in childhood

Classic FA appearance: dark choroid

Ultimate vision is usually in the 20/50 – 20/200 range

Other diseases associated with ABCA4 dysfunction include cone dystrophy, cone-rod dystrophy and RP

Treatment?
Stargardt Disease/Fundus Flavimaculatus

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- Other diseases associated with ABCA4 dysfunction include cone dystrophy, cone-rod dystrophy and RP
- Treatment? No effective treatments are available