Inheritance?

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?
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How common is ‘very common’? What percentage of the population is carrying one of the many disease-causing ABCA4 alleles?

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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…
Q

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

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What does ABCA4 stand for?
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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?
Q/A

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**OK, but what do they do?**
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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

ModBC-A
Hollenstein et al.,

Nutrient uptake
(sugars, ions, amino acids)

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

Nutrient uptake
(vitamin B$_{12}$, heme, siderophores)

Sav1866
Dawson et al.,
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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?

**‘Drugs going out’**—what does that mean? ABC transporters are how cells rid themselves of therapeutic compounds. For example, bacterial drug resistance is often secondary 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.
A

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October 2: Monday

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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.
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So what does the ABCA4 transporter have to do with the eye?
Q/A

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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?**

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
Stargardt Disease/Fundus Flavimaculatus

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At what level of the retina do the flecks occur?
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Stargardt: RPE-level flecks
Q

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At what level of the retina do the flecks occur?
The RPE

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
--The flecks often touch one another, rendering their aggregate appearance ‘net-like’
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The RPE

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--The flecks often touch one another, rendering their aggregate appearance ‘net-like’
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What does pisciform mean?

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It means ‘fish shaped’

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**What does pisciform mean?**
It means ‘fish shaped’

**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?

--Drusen are round(-ish), whereas some flecks are elongated
--**The flecks often touch one another**, rendering their aggregate appearance ‘net-like’
Stargardt Disease/Fundus Flavimaculatus

Pisciform lesions
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

Which appears first--foveal atrophy, or the flecks?
- 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

Which appears first--foveal atrophy, or the flecks?
In most cases, the atrophy
Inheritance? AR (in most cases; a small % are AD)

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Fundus appearance:

- **Atrophic fovea**
- **pisciform flecks**

Which appears first--foveal atrophy, or the flecks? In most cases, the atrophy

_The classic appearance of the fovea in Stargardt is described with a two-word alliteration. What is it?_
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‘Beaten bronze’
Stargardt Disease/Fundus Flavimaculatus

Stargardt—beaten bronze appearance
Stargardt Disease/Fundus Flavimaculatus

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

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- 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
Stargardt Disease/Fundus Flavimaculatus

Stargardt

Fundus flavimaculatus
Stargardt Disease/Fundus Flavimaculatus

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- Pts present with c/o decreased vision, usually in life period
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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)
Q

- 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
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Which appears first--changes in the fundus, or decreased vision?
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What is the classic scenario you should be on the lookout for?
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Which appears first--changes in the fundus, or decreased vision?

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What is the classic scenario you should be on the lookout for?
That of a child with a ‘normal’ eye exam who ‘refuses’ to read the Snellen chart (not uncommonly, such cases are labelled ‘functional vision loss’ until the appearance of their fundus changes)
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What should you do if/when encountering such a child (either on the OKAP/Boards or IRL)?
Stargardt Disease/Fundus Flavimaculatus

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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…
Q

- 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: **two words**
Stargardt Disease/Fundus Flavimaculatus

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Stargardt Disease/Fundus Flavimaculatus

Stargardt—*dark choroid* appearance on FA
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'Dark choroid'--what does that mean?
Q/A

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‘Dark choroid’--what does that mean?
It means the normal FA ‘glow’ of the choroid is absent
(in FA parlance, the choroid is hypofluorescent)
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Again, in FA parlance--is the choroidal hypofluorescence secondary to blocking, or to a filling defect?
A

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Blocking

At what level of the retina is blocking occurring?
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Again, in FA parlance--is the choroidal hypofluorescence secondary to blocking, or to a filling defect? Blocking

At what level of the retina is blocking occurring? The RPE
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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‘Dark choroid’--what does that mean?
It means the normal FA ‘glow’ of the choroid is absent
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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?
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In what level of the retina is blocking occurring?

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It means the normal FA ‘glow’ of the choroid is absent
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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
Stargardt Disease/Fundus Flavimaculatus

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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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What test has supplanted FA for working up suspected Stargardt?
Fundus autofluorescence (FAF)

Why is FAF preferred?
It is more reliable (not all Stargardt eyes manifest the dark choroid phenomenon)

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Classic FA appearance: dark choroid Bull’s 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 hypo-fluorescence

Why is FAF preferred?
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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/Fundus Flavimaculatus

Stargardt—hyper/hypopigmentation on FAF
Q

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What test has supplanted FA for working up suspected Stargardt?
Fundus autofluorescence (FAF)

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

What should you do if/when encountering such a child (either on the OKAP/Boards or IRL)?
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Why is FAF preferred?
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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…

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

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What is the classic scenario you should be on the lookout for? That of a child with a ‘normal’ eye exam who ‘refuses’ to read the Snellen chart (not uncommonly, such cases are labelled ‘functional vision loss’ until the appearance of their fundus changes)

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

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Other diseases associated with ABCA4 dysfunction include cone dystrophy, cone-rod dystrophy and RP
Stargardt Disease/Fundus Flavimaculatus

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How can one dysfunction of a single protein cause such a variety of pathology?
Inheritance? AR (in most cases; a small % are AD)

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Fundus appearance: Atrophic fovea surrounded by white-yellow pisciform flecks
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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.
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? 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?
Inheritance? AR (in most cases; a small % are AD)
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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**

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:
--Cone dystrophy:
--Cone-rod dystrophy:
--RP:

So, all of these conditions (except RP) can be caused by ABCA4 mutations (Stargardt to cone-rod dystrophy) but RP can be caused by ABCA4 mutations or mutations to other genes.
Stargardt Disease/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
  - 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

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

So, all of these diseases are the same? No.
Yes and no.
But all of these conditions are caused by mutations on ABCA4.
Stargardt disease is essentially a manifesting phenotype of ABCA4 dysfunction ranging from completely normal (= cone-rod 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
  - If pisciform lesions are in macula only, is Stargardt
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Other diseases associated with ABCA4 dysfunction include cone dystrophy, cone-rod dystrophy and RP

Treatment?
Stargardt Disease/Fundus Flavimaculatus

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- Gene responsible for most cases? ABCA4
- Fundus appearance: Atrophic fovea surrounded by white-yellow pisciform flecks
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- 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? No effective treatments are available