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

**Stargardt Disease/Fundus Flavimaculatus**

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As hereditary maculopaties go, where does Stargardt rank in terms of prevalence? Stargardt is the most common hereditary maculopathy.
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As hereditary maculopathies go, is AR inheritance the norm?
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*As hereditary maculopathies go, where does Stargardt rank in terms of prevalence?*
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No--most are inherited in an AD fashion
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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…”
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Stargardt Disease/Fundus Flavimaculatus

What does ABCA4 stand for?
A

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

They are (out of) cells. They are...
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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.

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For example…?
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*So what does the ABCA4 transporter have to do with the eye?*
Inheritance? AR (in most cases; a small % are AD)
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So what does the \textit{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 rod outer segment.
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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

And death of the RPE leads to…?
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Q Stargardt Disease/Fundus Flavimaculatus

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

- Inheritance? **AR (in most cases; a small % are AD)**
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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'. How do Stargardt/FF flecks differ ophthalmoscopically from drusen?

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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 differ ophthalmoscopically from Stargardt/FF flecks?

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Which appears first--foveal atrophy, or the flecks?
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In most cases, the atrophy
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*The classic appearance of the fovea in Stargardt is described with a two-word alliteration. What is it?*
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  - If pisciform lesions are in macula only, is
  - If they are widely scattered, is
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- Pts present with c/o **decreased vision**, usually in **life period**
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- 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

Which appears first--changes in the fundus, or decreased vision? Usually the decreased vision (especially in childhood onset cases)
Inheritance? AR (in most cases; a small % are AD)
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Stargardt Disease/Fundus Flavimaculatus

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

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The answer used to be ‘order an FA,’ so we’ll address that first…
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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Pts present with c/o **decreased vision**, usually in **childhood**

Classic FA appearance: **two words**
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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Pts present with c/o decreased vision, usually in childhood
Classic FA appearance: dark choroid
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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Classic FA appearance: dark choroid

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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?
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Blocking
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Blocking

At what level of the retina is blocking occurring?
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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
What level of the retina is blocking occurring?
The RPE
Inheritance? AR (in most cases; a small % are AD)

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‘Dark choroid’--what does that mean?
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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

The RPE
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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)?
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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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A bull’s eye maculopathy—a ring of perifoveal hyperfluorescence 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

What should you do if/when encountering such a child (either on the OKAP/Boards or IRL)?
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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 hypofluorescence

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

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Classic FA appearance: dark choroid
Ultimate vision is usually in the 20/50 – 20/200 range
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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.
Stargardt Disease/Fundus Flavimaculatus

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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.*
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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).
**Q**

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So, all of these conditions are caused by mutations on ABCA4?
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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.

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 can be caused by ABCA4 mutations? No and yes. All of these can be caused by ABCA4 mutations. But all of these can be caused by mutations in other genes as well.

For each condition, what percent of cases are caused by ABCA4 mutation?
- Stargardt:
- Cone dystrophy:
- Cone-rod dystrophy:
- RP:
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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?
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Treatment? No effective treatments are available