Phakomatoses are a **massive** topic. (Don’t believe me? Take a glance at the number of slides in this set.) Try to get through the whole set once a month or so. There’s a TLDR at the end, so when it’s crunch time (ie, the last few weeks before the OKAPs, WQE or Boards), just flip through the TLDR a few times every day to keep it fresh. You got this!
Phakomatoses are known also as what sort of syndrome?
*Phakomatoses are known also as what sort of syndrome?*

Neuro-oculocutaneous syndromes
Phakomatoses are known also as what sort of syndrome?
Neuro-oculocutaneous syndromes

In general terms, how do phakomatoses present?
Phakomatoses are known also as what sort of syndrome? Neuro-oculocutaneous syndromes

In general terms, how do phakomatoses present?
With multiple lesions in two or more organ systems, usually including the CNS, eyes, and skin.
Phakomatoses are known also as what sort of syndrome?
Neuro-oculocutaneous syndromes

In general terms, how do phakomatoses present?
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Phakomatoses are known also as what sort of syndrome? **Neuro-oculo**cutaneous syndromes

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Are the lesions in phakomatoses predominantly choristomas or hamartomas?
**Phakomatoses** are known also as what sort of syndrome?
Neuro-oculocutaneous syndromes

*In general terms, how do phakomatoses present?*
With multiple lesions in two or more organ systems, usually including the CNS, eyes and skin

*Are the lesions in phakomatoses predominantly choristomas or hamartomas?*
Most (but not all) are hamartomas (some are choristomas)
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What’s the difference between a hamartoma and a choristoma? A hamartoma is a nest of abnormal cells in a normal location, whereas a choristoma is a nest of relatively-normal cells in an abnormal location.
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That a lesion is a hamartoma or choristoma indicates what about its onset?
That it is congenital
Phakomatoses are known also as what sort of syndrome? Neuro-oculocutaneous syndromes

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That a lesion is a hamartoma or choristoma indicates what about its status vis a vis malignancy?
Phakomatoses are known also as what sort of syndrome?
Neuro-oculocutaneous syndromes

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A hamartoma is a nest of abnormal cells in a normal location, whereas a choristoma is a nest of relatively-normal cells in an abnormal location.

That a lesion is a hamartoma or choristoma indicates what about its onset?
That it is congenital

That a lesion is a hamartoma or choristoma indicates what about its status vis a vis malignancy?
That it is benign
Phakomatoses are known also as what sort of syndrome?
Neuro-oculocutaneous syndromes

In general terms, how do phakomatoses present?
With multiple lesions in two or more organ systems, usually including the CNS, eyes and skin

Are the lesions in phakomatoses predominantly choristomas or hamartomas?
Hamartomas

Is there a single, universally accepted definition of the term phakomatosis?
Phakomatoses are known also as what sort of syndrome?
Neuro-oculocutaneous syndromes

In general terms, how do phakomatoses present?
With multiple lesions in two or more organ systems, usually including the CNS, eyes, and skin

Are the lesions in phakomatoses predominantly choristomas or hamartomas?
Hamartomas

Is there a single, universally accepted definition of the term phakomatosis?
Unfortunately not, and for this reason, the conditions so labelled will vary from source to source
Abbreviations used henceforth

NF1  •  Neurofibromatosis type 1:

A phakomatosis by any other name...by what other name is each syndrome known?

Start here with the other name for NF1
Abbreviations used henceforth

NF1

- Neurofibromatosis type 1: von Rechlinghausen syndrome

A phakomatosis by any other name... by what other name is each syndrome known?

Start here with the other name for NF1

Abbreviations used henceforth
A phakomatosis by any other name...by what other name is each syndrome known?

Abbreviations used henceforth:

NF1
- Neurofibromatosis type 1: von Rechlinghausen syndrome

TS
- Tuberous sclerosis:
  -
  -
  -
  -

Next for TS

Abbreviations used henceforth:
A phakomatosis by any other name... by what other name is each syndrome known?

Abbreviations used henceforth

NF1  ●  Neurofibromatosis type 1: von Rechlinghausen syndrome

TS  ●  Tuberous sclerosis: Bournville disease

Next for TS

Abbreviations used henceforth
A phakomatosis by any other name... by what other name is each syndrome known?

Abbreviations used henceforth

- NF1: Neurofibromatosis type 1: von Rechlinghausen syndrome
- TS: Tuberous sclerosis: Bournville disease
- SWS: Sturge-Weber syndrome:
  - Etc

Abbreviations used henceforth
A phakomatosis by any other name...by what other name is each syndrome known?

Abbreviations used henceforth

- NF1: Neurofibromatosis type 1: von Rechlinghausen syndrome
- TS: Tuberous sclerosis: Bournville disease
- SWS: Sturge-Weber syndrome: Encephalotrigeminal angiomatosis

Other names you might encounter for SWS:
- Encephalofacial angiomatosis
- Cerebrofacial angiomatosis
A phakomatosis by any other name...by what other name is each syndrome known?

Abbreviations used henceforth

NF1  • Neurofibromatosis type 1: von Rechlinghausen syndrome

TS   • Tuberous sclerosis: Bournville disease

SWS  • Sturge-Weber syndrome: Encephalotrigeminal angiomatosis

vH-L • von Hippel-Lindau:

...
Abbreviations used henceforth

NF1  ● Neurofibromatosis type 1: von Rechlinghausen syndrome

TS  ● Tuberous sclerosis: Bournville disease

SWS  ● Sturge-Weber syndrome: Encephalotrigeminal angiomatosis

vH-L  ● von Hippel-Lindau: Retinal angiomatosis

A phakomatosis by any other name...by what other name is each syndrome known?
A phakomatosis by any other name... by what other name is each syndrome known?

NF1 ● Neurofibromatosis type 1: von Rechlinghausen syndrome
TS ● Tuberous sclerosis: Bournville disease
SWS ● Sturge-Weber syndrome: Encephalotrigeminal angiomatosis
vH-L ● von Hippel-Lindau: Retinal angiomatosis
IP ● Incontinentia pigmenti:

Abbreviations used henceforth
A phakomatosis by any other name...by what other name is each syndrome known?

Abbreviations used henceforth

- **NF1**  
  - Neurofibromatosis type 1: **von Rechlinghausen syndrome**

- **TS**  
  - Tuberous sclerosis: **Bournville disease**

- **SWS**  
  - Sturge-Weber syndrome: **Encephalotrigeminal angiomatosis**

- **vH-L**  
  - von Hippel-Lindau: **Retinal angiomatosis**

- **IP**  
  - Incontinentia pigmenti: **Bloch-Sulzberger syndrome**


**Abbreviations used henceforth**
A phakomatosis by any other name... by what other name is each syndrome known?

Abbreviations used henceforth

NF1 - Neurofibromatosis type 1: von Rechlinghausen syndrome
TS - Tuberous sclerosis: Bournville disease
SWS - Sturge-Weber syndrome: Encephalotrigeminal angiomatosis
vH-L - von Hippel-Lindau: Retinal angiomatosis
IP - Incontinentia pigmenti: Bloch-Sulzberger syndrome
NF2 - Neurofibromatosis type 2:
A phakomatosis by any other name... by what other name is each syndrome known?

Abbreviations used henceforth

NF1  •  Neurofibromatosis type 1: von Rechlinghausen syndrome

TS   •  Tuberous sclerosis: Bournville disease

SWS •  Sturge-Weber syndrome: Encephalotrigeminal angiomatosis

vH-L •  von Hippel-Lindau: Retinal angiomatosis

IP   •  Incontinentia pigmenti: Bloch-Sulzberger syndrome

NF2  •  Neurofibromatosis type 2: MISME syndrome
A phakomatosis by any other name... by what other name is each syndrome known?

Abbreviations used henceforth

NF1  ● Neurofibromatosis type 1: von Rechlinghausen syndrome
TS   ● Tuberous sclerosis: Bournville disease
SWS  ● Sturge-Weber syndrome: Encephalotrigeminal angiomatosis
vH-L ● von Hippel-Lindau: Retinal angiomatosis
IP   ● Incontinentia pigmenti: Bloch-Sulzberger syndrome
NF2  ● Neurofibromatosis type 2: **MISME syndrome**

**MISME is an acronym. What does it stand for?**

- M
- I
- S
- M
- E
A phakomatosis by any other name...by what other name is each syndrome known?

**Abbreviations used henceforth**

- **NF1**: Neurofibromatosis type 1: von Rechlinghausen syndrome
- **TS**: Tuberous sclerosis: Bournville disease
- **SWS**: Sturge-Weber syndrome: Encephalotrigeminal angiomatosis
- **vH-L**: von Hippel-Lindau: Retinal angiomatosis
- **IP**: Incontinentia pigmenti: Bloch-Sulzberger syndrome
- **NF2**: Neurofibromatosis type 2: **MISME syndrome**

*MISME is an acronym. What does it stand for?*

- **M**ultiple
- **I**nherited
- **S**chwannomas, **M**eningiomas (and) **E**pendymomas
Q

A phakomatosis by any other name... by what other name is each syndrome known?

Abbreviations used henceforth

NF1 • Neurofibromatosis type 1: von Rechlinghausen syndrome

TS • Tuberous sclerosis: Bournville disease

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vH-L • von Hippel-Lindau: Retinal angiomatosis

IP • Incontinentia pigmenti: Bloch-Sulzberger syndrome

NF2 • Neurofibromatosis type 2: MISME syndrome

RA • Racemose angioma:
A phakomatosis by any other name…by what other name is each syndrome known?

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NF1 • Neurofibromatosis type 1: von Recklinghausen syndrome
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vH-L • von Hippel-Lindau: Retinal angiomatosis
IP • Incontinentia pigmenti: Bloch-Sulzberger syndrome
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Abbreviations used henceforth

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NF2  • Neurofibromatosis type 2: MISME syndrome
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AT   • Ataxia-telangiectasia:
A phakomatosis by any other name... by what other name is each syndrome known?

Abbreviations used henceforth

NF1 • Neurofibromatosis type 1: von Rechlinghausen syndrome

TS • Tuberous sclerosis: Bournville disease

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vH-L • von Hippel-Lindau: Retinal angiomatosis

IP • Incontinentia pigmenti: Bloch-Sulzberger syndrome

NF2 • Neurofibromatosis type 2: MISME syndrome

RA • Racemose angioma: Wyburn-Mason syndrome

AT • Ataxia-telangiectasia: Louis-Bar syndrome
Phakomatoses: Inheritance patterns

- These four are AD...
- NF2
- NF1
- von Hippel-Lindau
- Tuberous sclerosis

- This one is AR...
- Ataxia-telangiectasia

- Incontinentia pigmenti
- And these two are sporadic/nonhereditary
- Sturge-Weber
- Racemose angioma
Phakomatoses: Inheritance patterns

These four are **AD**…

- NF2
- NF1
- von Hippel-Lindau
- Tuberous sclerosis
Phakomatoses: Inheritance patterns

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- This one is **X-linked dominant**...
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Phakomatoses: Inheritance patterns

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*What does X-linked dominant transmission mean?*

- This one is **X-linked dominant**...
  - Incontinentia pigmenti

- And these two are **sporadic/nonhereditary**
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Phakomatoses: Inheritance patterns

- These four are **AD**…
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  - NF1
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What does X-linked dominant transmission mean?
It means the condition manifests in every conception possessing at least one X chromosome (ie, everyone)

- This one is **X-linked dominant**…
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- And these two are **sporadic/nonhereditary**
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What does X-linked dominant transmission mean?
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But almost all IP pts are female. If IP is X-linked dominant, why don’t male infants present with it?

- This one is X-linked dominant…
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- And these two are sporadic/nonhereditary
  - Sturge-Weber
  - Racemose angioma
**Phakomatoses: Inheritance patterns**

- These four are \textit{AD}...
  - NF2
  - NF1
  - von Hippel-Lindau
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  - Incontinentia pigmenti
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The mutation causing IP is lethal to males in utero. That’s about as ‘manifest’ as it gets.
Phakomatoses: Inheritance patterns

- These four are AD...

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- And these two are sporadic/nonhereditary
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  - Racemose angioma

Hold the phone! To say that ‘almost’ all pts are female means that some IP pts are male. If IP is X-linked dominant and lethal in hemizygous individuals, how could there be any male pts?

It means the condition manifests in every conception possessing at least one X chromosome (ie, everyone)

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Phakomatoses: Inheritance patterns

- These four are AD...

Hold the phone! To say that ‘almost’ all pts are female means that some IP pts are male. If IP is X-linked dominant and lethal in hemizygous individuals, how could there be any male pts? There are two ways by which a male child could be liveborn with IP:

--If the (phenotypically) male child possesses two X chromosomes (eg, Klinefelter syndrome, XXY) and is therefore heterozygous for IP; or

--it can occur in males via a sporadic post-zygotic mutation that renders the male child an IP ‘mosaic’

It means the condition manifests in every conception possessing at least one X chromosome (ie, everyone)

But almost all IP pts are female. If IP is X-linked dominant, why don’t male infants present with it? The mutation causing IP is lethal to males in utero. That’s about as ‘manifest’ as it gets.

- This one is X-linked dominant...
  - Incontinentia pigmenti
  - And these two are sporadic/nonhereditary
    - Sturge-Weber
    - Racemose angioma
**Phakomatoses**

- These four are **AD**...
  - **NF2**
  - **NF1**
  - von Hippel-Lindau
  - Tuberous sclerosis

- This one is **AR**...
  - Ataxia-telangiectasia

- This one is **X-linked dominant**...
  - Incontinentia pigmenti

- And these two are **sporadic/nonhereditary**
  - Sturge-Weber
  - Racemose angioma

Of course, even the inherited conditions can occur sporadically. For each, what percent of cases are sporadic?

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Sporadic</th>
</tr>
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<tbody>
<tr>
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<td>?</td>
</tr>
<tr>
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<td>?</td>
</tr>
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<td>?</td>
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<td>?</td>
</tr>
<tr>
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<td>?</td>
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<tr>
<td>Incontinentia pigmenti</td>
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</table>

51% Sporadic
Phakomatoses: Inheritance patterns

These four are **AD**…
- NF2: 50%
- NF1: 50%
- von Hippel-Lindau: 20%
- Tuberous sclerosis: 80%

This one is **AR**…
- Ataxia-telangiectasia: ~0%

This one is **X-linked dominant**…
- Incontinentia pigmenti: 60%

And these two are **sporadic/nonhereditary**
- Sturge-Weber
- Racemose angioma

Of course, even the inherited conditions can occur sporadically. For each, what percent of cases are sporadic?
Phakomatoses

These four are AD...

- NF2 50
- NF1 50
- von Hippel-Lindau 20
- Tuberous sclerosis 80

This one is AR...

- Ataxia-telangiectasia ~0

This one is X-linked dominant.

- Incontinentia pigmenti 60

And these two are sporadic/nonhereditary

- Sturge-Weber
- Racemose angioma

Of course, even the inherited conditions can occur sporadically. For each, what percent of cases are sporadic?

**% Sporadic**

<p>| | |</p>
<table>
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</tr>
<tr>
<td>NF1</td>
<td>50</td>
</tr>
<tr>
<td>von Hippel-Lindau</td>
<td>20</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>80</td>
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Why is the sporadic-occurrence rate of A-T essentially zero?
Phakomatoses:
- These four are AD...
- NF2 50
- NF1 50
- von Hippel-Lindau 20
- Tuberous sclerosis 80

This one is AR...
- Ataxia-telangiectasia ~0

This one is X-linked dominant...
- Incontinentia pigmenti 60

And these two are sporadic/nonhereditary
- Sturge-Weber
- Racemose angioma

Of course, even the inherited conditions can occur sporadically. For each, what percent of cases are sporadic?

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Why is the sporadic-occurrence rate of A-T essentially zero? Because it is an autosomal-recessive condition, and thus can occur sporadically only if someone heterozygous for it happens to suffer a mutation of the other copy of the responsible gene--a very unlikely event.
Phakomatoses

**NF1**

---

**NF**

- **Peripheral**
- Most lesions due to abnormal melanocytes or neuroglial cells
- Glaucoma associated with ipsilateral upper-lid plexiform fibroma and/or iris ectropion
- Iris lesions include Lisch nodules, JXG nodules, and congenital ectropion
- Optic nerve glioma: Always symptomatic by age 10 years. Classic CT appearance: Kinked ON

**Rule of thumb for Lisch nodule prevalence:** Age in years x 10
Phakomatoses

**NF1**

---**Peripheral NF**

-- Most lesions due to abnormal melanocytes or neuroglial cells
-- Glaucoma associated with ipsilateral upper-lid plexiform fibroma and/or iris ectropion
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---Rule of thumb for Lisch nodule prevalence: Age in years x 10
Phakomatoses

**NF1**
--*Peripheral* NF
--Most lesions due to abnormal one cell type or diff cell type cells

- Glaucoma associated with ipsilateral upper-lid plexiform fibroma and/or iris ectropion
- Iris lesions include Lisch nodules, JXG nodules, and congenital ectropion
- Optic nerve glioma: Always symptomatic by age 10 years. Classic CT appearance: Kinked ON
Phakomatoses

**NF1**

--*Peripheral* NF
--Most lesions due to abnormal *melanocytes* or *neuroglial* cells

Glaucoma associated with ipsilateral upper-lid plexiform fibroma and/or iris ectropion

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Phakomatoses

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How are these cell lines related embryologically?

melanocytes neuroglial cells
Phakomatoses

**NF1**
--Peripheral NF
--Most lesions due to abnormal melanocytes or neuroglial cells
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**How are these cell lines related embryologically?**
Both derive from neural-crest cells
Phakomatoses

**NF1**
--Peripheral NF
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- Optic nerve glioma: Always symptomatic by age 10 years. Classic CT appearance: Kinked ON

**How are these cell lines related embryologically?**
Both derive from **neural-crest cells**

*Given this, it should come as no surprise that NF is associated with other manifestations of disordered neural-crest embryology, including and especially:*

- Oculodermal melanocytosis (aka nevus of Ota)
- Choroidal melanoma
- Conjunctival melanoma stemming from PAM

---

two long words

something of something
NF1
--Peripheral NF
--Most lesions due to abnormal melanocytes or neuroglial cells
--Glaucoma associated with ipsilateral upper-lid plexiform fibroma and/or iris ectropion
--Iris lesions include Lisch nodules, JXG nodules, and congenital ectropion
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How are these cell lines related embryologically?
Both derive from neural-crest cells

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Phakomatoses

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Rule of thumb for Lisch nodule prevalence: Age in years x 10

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yikes
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**Phakomatoses**

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What does PAM stand for in this context?
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What does PAM stand for in this context?
**Primary acquired melanosis**
Phakomatoses

**NF1**

--**Peripheral NF**

--Most lesions due to abnormal **melanocytes** or **neuroglial cells**

**Melanocytic lesions**

---

*Name four common NF1 lesions that derive from melanocytes*
Phakomatoses

**NF1**
--*Peripheral NF*
--Most lesions due to abnormal **melanocytes** or **neuroglial** cells

**Melanocytic lesions**
--Café au lait spots
--Axillary/inguinal freckles
--Lisch nodules
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Name four common NF1 lesions that derive from melanocytes

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**Rule of thumb for Lisch nodule prevalence:** Age in years x 10
Phakomatoses

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- NF1: Melanocytic lesions
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Neuroglial lesions
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Name four common NF1 lesions that derive from neuroglial cells
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Phakomatoses

Optic nerve glioma

Plexiform neurofibroma

Nodular neurofibroma

NF1: Neuroglial lesions
Phakomatoses

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*In what fundamental way do these lesions differ (other than the cell type of origin, duh)?*
Phakomatoses

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Do the neuroglial lesions in NF1 carry a risk of malignant transformation?

Yes, especially the plexiform neurofibromas, which can give rise to lesions known as 'malignant peripheral nerve-sheath tumors.'

What is the lifetime risk of such a transformation?

About 10%
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five words
Phakomatoses

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What does ‘most’ mean in this context?

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Four non-neural-crest-derived malignancies are associated with NF1 (albeit uncommonly). What are they?

- Leukemia
- Rhabdomyosarcoma
- Pheochromocytoma
- Wilms tumor
Phakomatoses

NF1
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What does ‘most’ mean in this context?
It means ‘not all.’ That is, there are lesions associated with NF1 that cannot be attributed to abnormalities of neural-crest derivatives.
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Plexiform neurofibroma

Ectropion uveae

NF1
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How does a plexiform fibroma and/or iris ectropion cause glaucoma?
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So far as we know, they don’t. That is, while they are strongly associated with glaucoma in NF1, there is no known direct causal connection.
Phakomatoses

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*How strong is the association with glaucoma; ie, what percent of NF1 cases with an upper-lid plexiform fibroma and/or ectropion will have ipsilateral glaucoma?*

About 50
Phakomatoses

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*What rule of thumb adheres regarding the appearance of Lisch nodules?*
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What rule of thumb adheres regarding the appearance of Lisch nodules?
Lisch nodules are lighter than the rest of the iris when the iris in question is dark, but darker than the rest when the iris is light.
Phakomatoses

NF1: Lisch nodules

Darker on light iris

Lighter on dark iris
Phakomatoses

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**What does JXG stand for in this context?**

Juvenile xanthogranuloma
Phakomatoses

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In three words, what sort of condition is it?
It is a nonneoplastic histiocytic proliferation

What are the two hallmarks of JXG histology?
The presence of Touton giant cells
The presence of 'foamy macrophages'

At what age does JXG present?
The majority before age 1 year, and almost all by age 2
How does JXG usually present? (Hint: It's not ophthalmic)
As orange skin papules
Phakomatoses

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NF1: JXG nodules
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*(ON = optic nerve)*
Phakomatoses

NF1: Optic nerve gliomas bilaterally. Note the ‘kinked’ appearance
Phakomatoses

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*What percent of NF1 pts develop a glioma of the optic pathway (ie, nerve or chiasm)?*
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What percent of NF1 pts develop a glioma of the optic pathway (ie, nerve or chiasm)?
About 15

About how many of those will be symptomatic?
About 1/3

With what symptoms will they present?
Vision loss and/or proptosis

Are optic-nerve gliomas typically life-threatening?
No

What about NF1 pts with chiasmal gliomas—do they fare better than their non-NF1 counterparts?
Much better
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**Are optic-nerve gliomas typically life-threatening?**
Phakomatoses

**NF1**
--Peripheral NF
--Most lesions due to abnormal melanocytes or neuroglial cells
--Glaucoma associated with ipsilateral upper-lid plexiform fibroma and/or iris ectropion
--Iris lesions include Lisch nodules, JXG nodules, and congenital ectropion
--Optic nerve glioma: Always symptomatic by age **10 years**. Classic CT appearance: **Kinked ON**

What percent of NF1 pts develop a glioma of the optic pathway (ie, nerve or chiasm)?
About 15

Of those, about how many will be symptomatic?
About 1/3

With what symptoms will they present?
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What about NF1 pts with chiasmal gliomas--do they fare better than their non-NF1 counterparts?
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*Are optic-nerve gliomas typically life-threatening?*
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*What about NF1 pts with chiasmal gliomas--do they fare better than their non-NF1 counterparts?*
Much better
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--Rule of thumb for Lisch nodule prevalence: something x something
Phakomatoses

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-- Optic nerve glioma: Always symptomatic by age 10 years. Classic CT appearance: Kinked ON
-- Rule of thumb for Lisch nodule prevalence: Age in years x 10
Phakomatoses

NF1
--Peripheral NF
--Most lesions due to abnormal melanocytes or neuroglial cells
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--Optic nerve glioma: Always symptomatic by age 10 years. Classic CT appearance: Kinked ON
--Rule of thumb for Lisch nodule prevalence: **Age in years x 10**

In other words, about 10% of 1 year olds will have Lisch nodules, 40% of 4 yo, 60% of 6 yo, etc. *By the age of 10 years, essentially 100% of NF1 pts will manifest Lisch nodules.*
Phakomatoses

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**Tuberous sclerosis**
--Classic triad is epiloia
Phakomatoses

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**Tuberous sclerosis**
--Classic triad is *epiloia*

*What does epiloia stand for?*
--Epi
--Los
--A
Phakomatoses

**NF1**
--Peripheral NF
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--Rule of thumb for Lisch nodule prevalence: Age in years x 10

**Tuberous sclerosis**
--Classic triad is **epiloia**

*What does epiloia stand for?*
--Epilepsy
--Low intelligence
--Angiomas
NF1
--Peripheral NF
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Tuberous sclerosis
--Classic triad is epiloia

What does epiloia stand for?
--Epilepsy
--Low Intelligence
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What is the eponymous name of this triad?
Phakomatoses

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**Tuberous sclerosis**
--Classic triad is *epiloia*

**What does epiloia stand for?**
--Epi*lepsy*
--Low* intelligence*
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**What is the eponymous name of this triad?**
*Vogt’s triad*
Phakomatoses

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**Tuberous sclerosis**
--Classic triad is *epiloia*

What does *epiloia* stand for?
--Epilepsy: ?
--Low intelligence
--Angiomas

What % of TS pts have seizures?

What is the eponymous name of this triad? *Vogt’s triad*
**Phakomatoses**

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**Tuberous sclerosis**
--Classic triad is *epiloia*

What does *epiloia* stand for?
--Epilepsy: 80
--Low intelligence
--Angiomas

What % of TS pts have seizures?

What is the eponymous name of this triad?
Vogt’s triad
Phakomatoses

**NF1**
---Peripheral NF
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---Rule of thumb for Lisch nodule prevalence: Age in years x 10

**Tuberous sclerosis**
---Classic triad is *epiloia*

*What does *epiloia* stand for?*
---Epilepsy: 80
---Low intelligence: ?
---Angiomas

*What % of TS pts have cognitive impairment?*

*What is the eponymous name of this triad? Vogt’s triad*
Phakomatoses

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--Peripheral NF
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--Rule of thumb for Lisch nodule prevalence: Age in years x 10

**Tuberous sclerosis**
--Classic triad is *epiloia*
--Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso
--CNS: Cortical tubers, other benign tumors
--Benign tumors of heart and kidney as well
--Retinal tumor is astrocytic hamartoma; can appear smooth or lumpy (mulberry)

**What does epiloia stand for?**
---Epilepsy: 80
---Low Intelligence: 50
---Angiomas

**What % of TS pts have cognitive impairment?**

**What is the eponymous name of this triad?**
*Vogt’s triad*
Phakomatoses

**NF1**
--*Peripheral NF*
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**Tuberous sclerosis**
--Classic triad is *epiloia*

*What does epiloia stand for?*
--*Epi*lepsy: 80
--*Lo*w *Intelligence*: 50
--*An*giomas: ?

*What % of TS pts have facial angifibromas; ie, adenoma sebaceum?*

*What is the eponymous name of this triad? Vogt’s triad*
Phakomatoses

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--Rule of thumb for Lisch nodule prevalence: Age in years x 10

**Tuberous sclerosis**
--Classic triad is *epiloia*

*What does epiloia stand for?*
--Epilepsy: 80
--Low intelligence: 50
--Angiomas: 75

*What % of TS pts have facial angifibromas; ie, adenoma sebaceum?*

*What is the eponymous name of this triad? Vogt’s triad*
Phakomatoses

**NF1**
--Peripheral NF
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**Tuberous sclerosis**
--Classic triad is *epiloia*

- *Epi*lepsy PLUS
- *Lo*w *Intelligence* PLUS
- *Angiomas*

What % of TS pts have all three?

What is the eponymous name of this triad?
*Vogt’s triad*
Phakomatoses

**NF1**
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**Tuberous sclerosis**
-- Classic triad is *epiloia*

--- What does *epiloia* stand for?
  -- Epilepsy PLUS
  -- Low intelligence PLUS
  -- Angiomas

--- What % of TS pts have all three? Only 30

--- What is the eponymous name of this triad? Vogt’s triad
Phakomatoses

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**Tuberous sclerosis**
-- Classic triad is *epiloia*
-- Skin: adenoma sebaceum of face; ditto and ditto on torso
Phakomatoses

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**Tuberous sclerosis**
--Classic triad is *epiloia*
--Skin: *Adenoma sebaceum* of face; *ash-leaf spots* and *shagreen patches* on torso
Phakomatoses

Tuberous sclerosis: Adenoma sebaceum
Phakomatoses

Tuberous sclerosis: Ash leaf spots
Phakomatoses

Tuberous sclerosis: Shagreen patch
Phakomatoses

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**Tuberous sclerosis**
-- Classic triad is epilooia
-- Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso

Skin Lesions: Matching!

- **Adenoma sebaceum**
  - ?
  - Appear in infancy

- **Shagreen patches**
  - ?
  - Usually in lumbosacral region

- **Ash-leaf spots**
  - ?
  - Appear in childhood
Phakomatoses

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**Tuberous sclerosis**
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**Skin Lesions: Matching!**

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Skin Lesions: Not Matching!

**Adenoma sebaceum**

**Shagreen patches**

**Ash-leaf spots**
Phakomatoses

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**Tuberous sclerosis**
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--Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso

Skin Lesions: Not Matching!

- **Adenoma sebaceum**
  - Raised

- **Shagreen patches**
  - Flat

- **Ash-leaf spots**
  - Flat

*Which lesion(s) is/are raised, and which is/are flat?*
**Phakomatoses**

**NF1**
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**Skin Lesions: Not Matching!**

*Adenoma sebaceum*  
*Shagreen patches*  
*Ash-leaf spots*  

Which lesion(s) is/are hyperpigmented, and which is/are hypopigmented?
Phakomatoses

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**Skin Lesions: Not Matching!**

- *Adenoma sebaceum*  
  - Hyperpigmented

- *Shagreen patches*
  
- *Ash-leaf spots*
  - Hypopigmented

*Which lesion(s) is/are hyperpigmented, and which is/are hypopigmented?*
Phakomatoses

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**Skin Lesions: Not Matching!**

---

*Adenoma sebaceum* ☐

*Shagreen patches* ☐

*Ash-leaf spots* ☐

*Which lesion(s) fluoresce under a Woods lamp, and which do/does not?*
Phakomatoses

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--Peripheral NF
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**Tuberous sclerosis**
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--Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso

Skin Lesions: Not Matching!

<table>
<thead>
<tr>
<th>Adenoma sebaceum</th>
<th>Don’t fluoresce</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shagreen patches</td>
<td></td>
</tr>
<tr>
<td>Ash-leaf spots</td>
<td>Fluoresce</td>
</tr>
</tbody>
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*Which lesion(s) fluoresce under a Woods lamp, and which do/does not?*
NF1
--Peripheral NF
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Tuberous sclerosis
--Classic triad is epiloia
--Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso

Skin Lesions: Not Matching!

Adenoma sebaceum
Shagreen patches
Ash-leaf spots

Which lesion(s) is/are considered pathognomonic for TS, and which is/are not?
**Phakomatoses**

**NF1**
- *Peripheral* NF
- Most lesions due to abnormal melanocytes or neuroglial cells
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**Tuberous sclerosis**
- Classic triad is *epiloia*
- Skin: *Adenoma sebaceum* of face; *ash-leaf spots* and *shagreen patches* on torso

---

**Skin Lesions: Not Matching!**

- *Adenoma sebaceum*  
  Not

- *Shagreen patches*  
  Pathognomonic

- *Ash-leaf spots*  
  Not

---

*Which lesion(s) is/are considered pathognomonic for TS, and which is/are not?*
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**Tuberous sclerosis**
--Classic triad is *epiloeia*
--Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso
--CNS: other benign tumors
Phakomatoses

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**Tuberous sclerosis**
-- Classic triad is *epiloia*
-- Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso
-- CNS: Cortical tubers, other benign tumors
Phakomatoses

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--*Peripheral* NF
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**Tuberous sclerosis**
--Classic triad is epiloia
--Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso
--CNS: **Cortical tubers**, other benign tumors

*What is a cortical tuber?*
Phakomatoses

**NF1**
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**Tuberous sclerosis**
--Classic triad is *epiloia*
--Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso
--CNS: **Cortical tubers**, other benign tumors

*What is a cortical tuber?*
A benign tumor of the brain
Phakomatoses

Tuberous sclerosis: Cortical tuber
Phakomatoses

**NF1**
--*Peripheral* NF
--Most lesions due to abnormal *melanocytes* or *neuroglial* cells
--Glaucoma associated with ipsilateral *upper-lid plexiform fibroma* and/or *iris ectropion*
--Iris lesions include *Lisch nodules, JXG nodules, and congenital ectropion*
--Optic nerve glioma: Always symptomatic by age 10 years. Classic CT appearance: *Kinked ON*
--Rule of thumb for Lisch nodule prevalence: *Age in years x 10*

**Tuberous sclerosis**
--Classic triad is *epiloia*
--Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso
--CNS: **Cortical tubers**, other benign tumors

**What is a cortical tuber?**
A benign tumor of the brain

**Why is it called a ‘tuber’?**
**Phakomatoses**

**NF1**
--- *Peripheral* NF
--- Most lesions due to abnormal melanocytes or neuroglial cells
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**Tuberous sclerosis**
--- Classic triad is *epiloia*
--- Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso
--- CNS: **Cortical tubers**, other benign tumors

*What is a cortical tuber?*
A benign tumor of the brain

*Why is it called a ‘tuber’?*
Because it’s shaped like a potato (sort of)
Phakomatoses

**NF1**
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**Tuberous sclerosis**
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-- CNS: *Cortical tubers*, other benign tumors

*What is a cortical tuber?*
A benign tumor of the brain

*Why is it called a ‘tuber’?*
Because it’s shaped like a potato (sort of)

*What basic geometric shape do tubers often take?*
Phakomatoses

**NF1**
--Peripheral NF
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--Rule of thumb for Lisch nodule prevalence: Age in years x 10

**Tuberous sclerosis**
--Classic triad is epiloia
--Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso
--CNS: **Cortical tubers**, other benign tumors

*What is a cortical tuber?*
A benign tumor of the brain

*Why is it called a ‘tuber’?*
Because it’s shaped like a potato (sort of)

*What basic geometric shape do tubers often take?*
A triangle
Phakomatoses

**NF1**
-- *Peripheral NF*
-- Most lesions due to abnormal melanocytes or neuroglial cells
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Which way does the apex of the triangle point?
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What basic geometric shape do tubers often take?
A triangle

Which way does the apex of the triangle point?
Toward a ventricle
**Phakomatoses**

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**Tuberous sclerosis**
-- Classic triad is epiloia
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-- CNS: Cortical tubers, other benign tumors
-- Benign tumors of not eye and not eye as well
Phakomatoses

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*Other than their location, in what key way do the heart and kidney tumors differ?*
Phakomatoses

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**Tuberous sclerosis**
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--- Other than their location, *in what key way do the heart and kidney tumors differ?*
--- The ▼/not▼ tumors are not associated with an increased risk of morbidity/mortality, whereas the ▼/not▼ tumors are
Phakomatoses

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The **kidney** tumors are not associated with an increased risk of morbidity/mortality, whereas the **heart** tumors are
Phakomatoses

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--Benign tumors of heart and kidney as well
--Retinal tumor is *something something*
# Phakomatoses

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Phakomatoses

Tuberous sclerosis: Astrocytic hamartoma
Phakomatoses

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--CNS: Cortical tubers, other benign tumors--Benign tumors of heart and kidney as well
--Retinal tumor is astrocytic hamartoma

By what other name is the astrocytic hamartoma of the retina known?

1/3 to 1/2

Yes

Yes

No
Phakomatoses

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Phakomatoses

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--Retinal tumors: astrocytic hamartoma

**By what other name is the astrocytic hamartoma of the retina known?**
Retinal phakoma

**What proportion of TS pts develop a phakoma?**
1/3 to 1/2
Yes
Yes
No
Phakomatoses

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---By what other name is the astrocytic hamartoma of the retina known?
Retinal phakoma

---What proportion of TS pts develop a phakoma?
1/3 to 1/2

---Can they present bilaterally?
Yes
Phakomatoses

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By what other name is the astrocytic hamartoma of the retina known?
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**Phakomatoses**

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--- By what other name is the astrocytic hamartoma of the retina known? Retinal phakoma
--- What proportion of TS pts develop a phakoma? 1/3 to 1/2
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--- Can multiple phakomas be found in one eye?
Phakomatoses

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By what other name is the astrocytic hamartoma of the retina known?  
Retinal phakoma  

What proportion of TS pts develop a phakoma?  
1/3 to 1/2  

Can they present bilaterally?  
Yes  

Can multiple phakomas be found in one eye?  
Yes
Phakomatoses

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**Tuberous sclerosis**
--Classic triad is epilepsy
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--CNS: Cortical tubers, other benign tumors
--Benign tumors of heart and kidney as well
--Retinal tumors are astrocytic hamartoma

---

*By what other name is the astrocytic hamartoma of the retina known?*
Retinal phakoma

*What proportion of TS pts develop a phakoma?*
1/3 to 1/2

*Can they present bilaterally?*
Yes

*Can multiple phakomas be found in one eye?*
Yes

*Are they pathognomonic for TS?*
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Can they present bilaterally? 
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No

Phakomas typically present with one of two appearances--what are they? 

---
Phakomatoses

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1/3 to 1/2

---Can they present bilaterally?
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---Can multiple phakomas be found in one eye?
Yes

---Are they pathognomonic for TS?
No

---Phakomas typically present with one of two appearances--what are they?
--Smooth, nearly flat, with poorly-defined margins
--Irregular, elevated, and sharply demarcated
**Phakomatoses**

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**By what other name is the astrocytic hamartoma of the retina known?**
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**What proportion of TS pts develop a phakoma?**
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**Can they present bilaterally?**
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**Tuberous sclerosis**
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**Phakomatoses**

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**What proportion of TS pts develop a phakoma?**
- 1/3 to 1/2

**Can they present bilaterally?**
- Yes

**Can multiple phakomas be found in one eye?**
- Yes

---

**The appearance of this lesion-type has been likened to that of a fruit, and a foodstuff. What are they?**
- Fruit:
- Foodstuff:
Phakomatoses

NF1

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By what other name is the astrocytic hamartoma of the retina known?
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What proportion of TS pts develop a phakoma?
- 1/3 to 1/2

Can they present bilaterally?
- Yes

Can multiple phakomas be found in one eye?
- Yes

Are the pathognomonic for TS?
- No

Phakomas typically present with one of two appearances--what are they?
- Smooth, nearly flat, with poorly-defined margins
- Irregular, elevated, and sharply demarcated

What is the appearance of this lesion-type has been likened to that of a fruit, and a foodstuff. What are they?
- Fruit: ‘Mulberry’
- Foodstuff: Mulberry
Phakomatoses

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- Glaucoma associated with ipsilateral upper-lid plexiform fibroma and/or iris ectropion.
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**Tuberous Sclerosis**
- Classic triad is epiloia.
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- CNS: Cortical tubers, other benign tumors.
- Benign tumors of heart and kidney as well.
- Retinal tumor is astrocytic hamartoma.

**By what other name is the astrocytic hamartoma of the retina known?** Retinal phakoma.

**What proportion of TS pts develop a phakoma?** 1/3 to 1/2.
**Can they present bilaterally?** Yes.
**Can multiple phakomas be found in one eye?** Yes.
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**Phakomas typically present with one of two appearances—what are they?**
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**The appearance of this lesion-type has been likened to that of a fruit, and a foodstuff. What are they?**
- Fruit: ‘Mulberry’
- Foodstuff: ‘Tapioca’
Phakomatoses

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**Tuberous sclerosis**
-- Classic triad is *epiloia*
-- Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso
-- CNS: Cortical tubers, other benign tumors
-- Benign tumors of heart and kidney as well
-- Retinal tumor is astrocytic hamartoma; can appear smooth or lumpy (*mulberry*)

**Von Hippel-Lindau**
-- Skin: trick question
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**von Hippel-Lindau**
--Skin: None! Despite this, is still considered a phakomatosis (and a classic one to boot)
**Phakomatoses**

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-- Classic triad is *epiloia*
-- Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso
-- CNS: Cortical tubers, other benign tumors
-- Benign tumors of heart and kidney as well
-- Retinal tumor is astrocytic hamartoma; can appear smooth or lumpy (*mulberry*)

**von Hippel-Lindau**
-- Skin: None! Despite this, is still considered a phakomatosis (and a classic one to boot)
-- CNS: tumor type, classically of tumor location (if absent, is called not von Hippel-Lindau syndrome)
Phakomatoses

**NF1**
-- *Peripheral NF*
-- Most lesions due to abnormal melanocytes or neuroglial cells
-- Glaucoma associated with ipsilateral upper-lid plexiform fibroma and/or iris ectropion
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-- CNS: Hemangioblastomas, classically of cerebellum (if absent, is called *von Hippel disease*)
Phakomatoses

von Hippel-Lindau: Cerebellar hemangioblastoma
# Phakomatoses

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(short for *Pheochromocytoma*)
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Phakomatoses

von Hippel-Lindau: Capillary hemangioblastoma
Phakomatoses

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By what other name is this lesion known (it’s a subtle change)?

Capillary hemangioblastoma (ie, no ‘-blasto-’)

Can the retinal lesions be present bilaterally?
Yes, in about 1/2 of cases

Can there be multiple lesions in the same eye?
Yes, these occur in about 1/3 of cases

Are all retinal hemangio(blasto)mas associated with vHL?
No, they can be sporadic
Phakomatoses

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--Tumor leaks → \[\text{abb.}\] → \[\text{abb.}\] → decreased VA; treat with \[\text{abb.}\] or \[\text{abb.}\]
Phakomatoses

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--Tumor leaks → SRF → ERD → decreased VA; treat with laser or cryo

*subretinal fluid* (exudative retinal detachment)
Phakomatoses

von Hippel-Lindau: Edema
Phakomatoses

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--Management

  --*Ocular*: DFE frequency
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  - **Systemic:** Complete PE q1 year with test 1; test 2; MRI brain until age yrs; after that, MRI brain frequency
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  --**Systemic:** Complete PE q1year with renal u/s, 24° urine for VMA; MRI brain q3 years until age 40; after that, MRI brain q5 years

(Vanillylmandelic acid)
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--Rule of thumb for Lisch nodule prevalence: Age in years x 10

**Tuberous sclerosis**
--Classic triad is epilolalia
--Skin: Adenoma sebaceum of face; ash-leaf spots and shagreen patches on torso
--CNS: Cortical tubers, other benign tumors
--Benign tumors of heart and kidney as well
--Retinal tumor is astrocytic hamartoma; can appear smooth or lumpy (*mulberry*)

**von Hippel-Lindau**
--Skin: None! Despite this, is still considered a phakomatosis (and a classic one to boot)
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*Is vH-L a potentially fatal condition?* Yes
Two components are most likely to result in death. What are they? The cerebellar hemangioma and the renal carcinoma
Phakomatoses

**NF1**
--Peripheral NF
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**Is vH-L a potentially fatal condition?**

*Yes*

Two components are most likely to result in death. What are they?

The **cerebellar hemangioma** and the renal carcinoma.

The cerebellar hemangioma??!! I thought that was a benign lesion. How could it be fatal?

It is a benign lesion. However, it is notoriously ‘leaky,’ and the accumulating exudate can lead to compression of vital intracranial structures.
Phakomatoses

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The cerebellar hemangioma??!! I thought that was a benign lesion. How could it be fatal?
- It is a benign lesion. However, it is notoriously ‘leaky,’ and the accumulating exudate can lead to compression of vital intracranial structures
Phakomatoses

**NF2**

*Which is more common, NF1 or NF2?*
Phakomatoses

**NF2**

*Which is more common, NF1 or NF2?*

NF1 is about 10x more common

Central NF -- Classic finding: bilateral acoustic neuromas -- Eye findings:

- **Common:** PSC/cortical cataracts
- **Rare:** combined hamartoma of retina and RPE
- **Rarer:** Lisch nodules
Phakomatoses

**NF2**
- Peripheral vs central NF
Phakomatoses

**NF2**
--Central NF

**Central NF**

**NF2**
--Central NF

Common: PSC/cortical cataracts;
Rare: combined hamartoma of retina and RPE;
Rarer: Lisch nodules
Phakomatoses

**NF2**
-- *Central* NF
-- Classic finding: bilateral

not eye
Phakomatoses

**NF2**
--*Central* NF
--Classic finding: bilateral *acoustic neuromas*
Phakomatoses

Tuberous sclerosis: Astrocytic hamartoma. Note large feeder/drainage vessels

14 y.o. with NF2

His 50 y.o. uncle with NF2
Phakomatoses

**NF2**
--Central NF
--Classic finding: bilateral **acoustic neuromas**

What sort of tumor is the acoustic neuroma of NF2; ie, what specific cell type is involved?
Phakomatoses

NF2
--Central NF
--Classic finding: bilateral acoustic neuromas

What sort of tumor is the acoustic neuroma of NF2; ie, what specific cell type is involved?
A schwannoma
Phakomatoses

**NF2**
-- Central NF
-- Classic finding: bilateral **acoustic neuromas**

*What are the three most common symptoms of acoustic neuroma?*

- **#1:** Reduced hearing  
- **#2:** Tinnitus  
- **#3:** Balance issues
Phakomatoses

**NF2**
--Central NF
--Classic finding: bilateral **acoustic neuromas**

**What are the three most common symptoms of acoustic neuroma?**

#1: Reduced hearing
#2: Tinnitus
#3: Balance issues
Phakomatoses

**NF2**
-- *Central* NF
-- Classic finding: bilateral *acoustic neuromas*
-- Eye findings: *Common*: anterior segment

Eye findings: *Rare*: combined hamartoma of retina and RPE; *Rarer*: Lisch nodules
Phakomatoses

**NF2**
--*Central* NF
--Classic finding: bilateral *acoustic neuromas*
--Eye findings: *Common*: PSC/cortical cataracts
Phakomatoses

**NF2**
--Central NF
--Classic finding: bilateral acoustic neuromas
--Eye findings: Common: **PSC/cortical cataracts**

Are the cataracts visually significant?
NF2
--Central NF
--Classic finding: bilateral acoustic neuromas
--Eye findings: Common: PSC/cortical cataracts

Are the cataracts visually significant?
Yes
Phakomatoses

**NF2**
--Central NF
--Classic finding: bilateral acoustic neuromas
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**Are the cataracts visually significant?**
Yes

**Do they manifest prior to or after the acoustic neuromas?**
Phakomatoses

**NF2**
--Central NF
--Classic finding: bilateral acoustic neuromas
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Are the cataracts visually significant?
Yes

Do they manifest prior to or after the acoustic neuromas?
Usually prior
Phakomatoses

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*Are the cataracts visually significant?*
Yes

*Do they manifest prior to or after the acoustic neuromas?*
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*At what age do they become clinically significant?*
Phakomatoses

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Usually in the 30s
Phakomatoses

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Are the cataracts visually significant?
Yes

Do they manifest prior to or after the acoustic neuromas?
Usually prior

At what age do they become clinically significant?
**Usually in the 30s**

Pro tip: If you see a pt <30 years old with significant PSCs and/or cortical cataracts, consider whether s/he might have NF2!
Phakomatoses

**NF2**
--Central NF
--Classic finding: bilateral acoustic neuromas
--Eye findings: Common: **PSC/cortical cataracts**

**Are the cataracts visually significant?**
Yes

**Do they manifest prior to or after the acoustic neuromas?**
Usually prior

**At what age do they become clinically significant?**
Usually in the 30s

**Are they unilateral, or bilateral?**
**Phakomatoses**

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--Central NF
--Classic finding: bilateral acoustic neuromas
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*Are the cataracts visually significant?*
Yes

*Do they manifest prior to or after the acoustic neuromas?*
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*At what age do they become clinically significant?*
Usually in the 30s

*Are they unilateral, or bilateral?*
Both presentations are common
Phakomatoses

**NF2**

--*Central* NF

--Classic finding: bilateral *acoustic neuromas*

--Eye findings: *Common*: PSC/cortical cataracts;

*Rare*: posterior segment
Phakomatoses

**NF2**

--- *Central* NF

--- Classic finding: bilateral acoustic neuromas

--- Eye findings: *Common*: PSC/cortical cataracts; *Rare*: Combined hamartoma of retina and RPE
Phakomatoses

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Phakomatoses

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# Phakomatoses

**NF2**
- *Central* NF
- Classic finding: bilateral *acoustic neuromas*
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<tr>
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<th>Neuroglial lesions</th>
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*One key difference between NF1 and NF2 is this:*
In NF1, both melanocytic and neuroglial lesions are common, whereas…
Phakomatoses

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Phakomatoses

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*Do melanocytic lesions occur in NF2 at all?*
Phakomatoses

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--- Neuroglial lesions
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One key difference between NF1 and NF2 is this:  
In NF1, both melanocytic and neuroglial lesions are common, whereas…

**In NF2, neuroglial lesions predominate.**

*Do melanocytic lesions occur in NF2 at all?*
Yes. The occasional café au lait spot and/or Lisch nodule shows up now and then
Phakomatoses

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Do NF2 pts get peripheral-nerve tumors like NF1 pts?

**Neuroglial lesions**
-- *Nodular* neurofibromas?
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Phakomatoses

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Do NF2 pts get peripheral-nerve tumors like NF1 pts?
Yes, but at much lower rates

Neuroglial lesions
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OK then, other than acoustic neuromas, what sorts of neuroglial lesions occur in NF2?

**Neuroglial lesions**
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Neuroglial lesions

--Nodular neurofibromas
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--Schwannomas of the SC
--Meningiomas (intracranial)
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Phakomatoses

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This propensity for manifesting mainly as CNS tumors is why NF2 is referred to as ‘central’ NF

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NF2 is also known as MISME syndrome. MISME is an acronym. What does it stand for?
- M
- I
- S
- M
- E

Phakomatoses

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*What is an ependymoma?*
*Ependymomas is an acronym.*
Neuroglial lesions
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What is an ependymoma?
A glioma consisting of ependymal cells
Phakomatoses

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  Rare: Combined hamartoma of retina and RPE; Rarer: Lisch nodules

Do NF2 pts get peripheral-nerve tumors like NF1 pts?
Yes, but at much lower rates.

OK then, other than acoustic neuromas, what sorts of neuroglial lesions occur in NF2?
CNS neuroglial lesions; eg, spinal-cord schwannomas, intracranial meningiomas, and ependymomas

**Neuroglial lesions**
--Nodular neurofibromas
--Plexiform neurofibromas
--Optic glioma
--Prominent corneal nerves

--Schwannomas of the SC
--Meningiomas (intracranial)
--Ependymomas

What is an ependymoma?
A glioma consisting of ependymal cells

OK smart guy, what are ependymal cells?

What does MISME syndrome stand for?
M - Multiple
I - Inherited
S - Schwannomas
M - Meningiomas,
E - Ependymomas
Phakomatoses

NF2
--Central NF
--Classic finding: bilateral acoustic neuromas
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What is an ependymoma?
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OK smart guy, what are ependymal cells?
The epithelial-like glial cells that form the inner lining of the cerebral ventricles and the central canal of the spinal cord
Phakomatoses

**NF2**

---Central NF

--Classic finding: bilateral **acoustic neuromas**

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Do NF2 pts get *peripheral-nerve tumors* like NF1 pts?

Yes, but at much lower rates.

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Do the neuroglial lesions in NF2 carry a risk of malignant transformation?

The epithelial-like glial cells that form the inner lining of the cerebral ventricles and the central canal of the spinal cord

--Ependymomas
Phakomatoses

**NF2**

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Do the neuroglial lesions in NF2 carry a risk of malignant transformation?

**No.** Unlike in NF1, malignant transformation of benign lesions in NF2 is almost unheard of.

The epithelial-like glial cells that form the inner lining of the cerebral ventricles and the central canal of the spinal cord

--Ependymomas
Phakomatoses

NF2
--Central NF
--Classic finding: bilateral acoustic neuromas
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By way of a refresher: What is a hamartoma?
Phakomatoses

NF2
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By way of a refresher: What is a hamartoma?
A tumor composed of histologically normal cells found in their clinical state
Phakomatoses

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By way of a refresher: What is a hamartoma?
A tumor composed of histologically abnormal cells found in their normal location
Phakomatoses

NF2
--Central NF
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Again, a refresher: What is the name of the reverse clinical entity, ie, one with normal cells found in an abnormal location?

Lisch nodules

By way of a refresher: What is a hamartoma? A tumor composed of histologically abnormal cells found in their normal location.
Phakomatoses

NF2
--Central NF
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Again, a refresher: What is the name of the reverse clinical entity, ie, one with normal cells found in an abnormal location?
A choristoma

By way of a refresher: What is a hamartoma?
A tumor composed of histologically normal cells found in their normal location

Lisch nodules
NF2
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By way of a refresher: What is a hamartoma?
A tumor composed of histologically abnormal cells found in their normal location

So, what combination of hamartomatous cells of the retina and RPE are involved in a combined hamartoma of the retina and RPE?
Phakomatoses

NF2
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So, what combination of hamartomatous cells of the retina and RPE are involved in a combined hamartoma of the retina and RPE?
RPE cells (duh) and retinal glial cells
Phakomatoses

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How does it present clinically?
Phakomatoses

NF2
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So, what combination of hamartomatous cells of the retina and RPE are involved in a combined hamartoma of the retina and RPE?
RPE cells (duh) and retinal glial cells

How does it present clinically?
As a variably pigmented, slightly elevated retinal mass of the retina
Phakomatoses

NF2
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By way of a refresher: What is a hamartoma?
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RPE cells (duh) and retinal glial cells

How does it present clinically?
As a variably pigmented, slightly elevated retinal mass of the peripapillary retina
Phakomatoses

Combined hamartoma of retina and RPE
Phakomatoses

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RPE cells (duh) and retinal glial cells

How does it present clinically?
As a variably pigmented, slightly elevated retinal mass of the peripapillary retina

With what more sinister dz entity is it often confused?
Phakomatoses

NF2
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RPE cells (duh) and retinal glial cells

How does it present clinically?
As a variably pigmented, slightly elevated retinal mass of the peripapillary retina

With what more sinister dz entity is it often confused?
Choroidal melanoma--eyes have been enucleated because of this misdiagnosis
Phakomatoses

**NF2**
--Central NF
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By way of a refresher: What is a hamartoma?
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How does it present clinically?
As a variably pigmented, slightly elevated retinal mass of the peripapillary retina

With what more sinister dz entity is it often confused?
Choroidal melanoma

How can one avoid making such a disastrous mistake?
By taking pains to carefully determine the anatomic location of the tumor in question—choroidal melanomas originate behind Bruch’s membrane, whereas combined hamartomas of the retina and RPE are located wholly in front of it.
Phakomatoses

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*By way of a refresher: What is a hamartoma?*
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RPE cells (duh) and retinal glial cells.

*How does it present clinically?*
As a variably pigmented, slightly elevated retinal mass of the peripapillary retina.

With what more sinister dz entity is it often confused? Choroidal melanoma

*How can one avoid making such a disastrous mistake?*
By taking pains to carefully determine the anatomic location of the tumor in question--choroidal melanomas originate behind Bruch’s membrane, whereas combined hamartomas of the retina and RPE are located wholly in front of it.
Phakomatoses

Combined hamartoma of retina and RPE. Note the entire lesion is above Bruchs
Acoustic neuroma

Another eye finding associated with acoustic neuroma is corneal decompensation. By what two mechanisms might this occur?
Phakomatoses

**NF2**
--Central NF
--Classic finding: bilateral **acoustic neuromas**
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**Acoustic neuroma**

Bag CN V1

*Another eye finding associated with acoustic neuroma is corneal decompensation. By what two mechanisms might this occur?*

Corneal decompensation

Bag CN VII

?
Phakomatoses

NF2
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**Acoustic neuroma**

Bag CN V1

- Decreased corneal sensation

Bag CN VII

- Lagophthalmos

**Corneal decompensation**

*Another eye finding associated with acoustic neuroma is corneal decompensation. By what two mechanisms might this occur?*
Phakomatoses

B. acoustic neuroma

NF2: Acoustic neuroma
**Phakomatoses**

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**Sturge-Weber**
-- Classic stigmata is the **port-wine stain**
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Sturge-Weber: Port-wine stain
Phakomatoses

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**Sturge-Weber**
--Classic stigmata is the port-wine stain

**In one word, what sort of lesion is the port-wine stain?**

An angioma

By what 'official' name is it known?

Nevus flammeus

When does it present?

At birth

What is the typical pattern of distribution?

It comports to the distribution of one or more divisions of CN5

Does it always present in this manner?

No. Some cases will cross the midline of the face

All infants with SWS have a port-wine stain. Do all infants with a port-wine stain have SWS?

No

If the port-wine stain involves the eyelid, what adjacent structure is commonly affected as well?

The conjunctiva. It will have increased vascularity and hyperemia, producing a false impression of 'pink eye'
Phakomatoses

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**Phakomatoses**

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- In one word, what sort of lesion is the port-wine stain? An angioma
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Sturge-Weber: Port-wine stain
Phakomatoses

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**Q&A**

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**Phakomatoses**

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Phakomatoses

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Phakomatoses

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Phakomatoses

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In one word, what sort of lesion is the port-wine stain?
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Phakomatoses

Sturge-Weber: Conjunctival hyperemia
Phakomatoses

**NF2**
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*Rare*: Combined hamartoma of retina and RPE; *Rarer*: Lisch nodules

**Sturge-Weber**
--Classic stigmata is the *port-wine stain*
--Ipsilateral meningeal AVM → symptom/sign
Phakomatoses

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**Sturge-Weber**
- Classic stigmata is the port-wine stain
- Ipsilateral meningeal AVM → seizures
**Phakomatoses**

**NF2**
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**Sturge-Weber**
-- Classic stigmata is the *port-wine stain*  
-- Ipsilateral meningeal AVM $\rightarrow$ seizures

*Is the meningeal AVM prone to bleeding?*
**Phakomatoses**

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**Sturge-Weber**
-- Classic stigmata is the *port-wine stain*
-- *Ipsilateral meningeal AVM* → *seizures*

*Is the meningeal AVM prone to bleeding?*
No
**Phakomatoses**

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**Sturge-Weber**
--- Classic stigmata is the *port-wine stain*
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*How prevalent is seizure activity in SWS?*
**Phakomatoses**

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**Sturge-Weber**
-- Classic stigmata is the **port-wine stain**
-- Ipsilateral meningeal AVM → **seizures**

*How prevalent is seizure activity in SWS?*
Very--estimates run as high as 90% of cases
**NF2**
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**Sturge-Weber**
--Classic stigmata is the **port-wine stain**
--Ipsilateral meningeal AVM → **seizures**
--Classic [ ] **mmm...** fundus appearance is due to a [ ] lesion (something something something)
Phakomatoses

**NF2**
-- *Central* NF
-- Classic finding: bilateral **acoustic neuromas**
-- Eye findings: *Common*: PSC/cortical cataracts;
  *Rare*: Combined hamartoma of retina and RPE; *Rarer*: Lisch nodules

**Sturge-Weber**
-- Classic stigmata is the **port-wine stain**
-- Ipsilateral meningeal AVM → **seizures**
-- Classic *tomato catsup* fundus appearance is due to a **diffuse choroidal hemangioma**
Phakomatoses

Sturge-Weber: Tomato catsup fundus OD
Phakomatoses

**NF2**
--Central NF
--Classic finding: bilateral acoustic neuromas
--Eye findings: Common: PSC/cortical cataracts; Rare: Combined hamartoma of retina and RPE; Rarer: Lisch nodules

**Sturge-Weber**
--Classic stigmata is the *port-wine stain*
--Ipsilateral meningeal AVM → seizures
--Classic *tomato catsup* fundus appearance is due to a **diffuse choroidal hemangioma**

*Diffuse choroidal hemangioma is present in what percent of SWS?*
NF2
--Central NF
--Classic finding: bilateral acoustic neuromas
--Eye findings: Common: PSC/cortical cataracts;
 Rare: Combined hamartoma of retina and RPE; Rarer: Lisch nodules

Sturge-Weber
--Classic stigmata is the port-wine stain
--Ipsilateral meningeal AVM \(\rightarrow\) seizures
--Classic tomato catsup fundus appearance is due to a diffuse choroidal hemangioma

Diffuse choroidal hemangioma is present in what percent of SWS?
About 50%
**Phakomatoses**

**Sturge-Weber**
--Classic stigmata is the **port-wine stain**
--Ipsilateral meningeal AVM $\rightarrow$ seizures
--Classic *tomato catsup* fundus appearance is due to a **diffuse choroidal hemangioma**

**Diffuse choroidal hemangioma is present in what percent of SWS?**
**About 50%**

**Can the choroidal hemangioma be present bilaterally?**

---

**NF2**
--Central NF
--Classic finding: bilateral acoustic neuromas
--Eye findings: Common: PSC/cortical cataracts;
Rare: Combined hamartoma of retina and RPE; Rarer: Lisch nodules
**Phakomatoses**

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--Central NF
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**Sturge-Weber**
--Classic stigmata is the **port-wine stain**
--Ipsilateral meningeal AVM → seizures
--Classic **tomato catsup** fundus appearance is due to a **diffuse choroidal hemangioma**

*Diffuse choroidal hemangioma is present in what percent of SWS?*
*About 50%*

*Can the choroidal hemangioma be present bilaterally?*
*Yes, but it's uncommon*
Phakomatoses

**NF2**
--Central NF
--Classic finding: bilateral acoustic neuromas
--Eye findings: Common: PSC/cortical cataracts; Rare: Combined hamartoma of retina and RPE; Rarer: Lisch nodules

**Sturge-Weber**
--Classic stigmata is the port-wine stain
--Ipsilateral meningeal AVM → seizures
--Classic tomato catsup fundus appearance is due to a diffuse choroidal hemangioma

---

**Diffuse choroidal hemangioma** is present in what percent of SWS?
**About 50%**

**Can the choroidal hemangioma be present bilaterally?**
**Yes, but it’s uncommon**

**Does the choroidal hemangioma have malignant potential?**
Phakomatoses

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--Central NF
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Diffuse choroidal hemangioma is present in what percent of SWS?
About 50%

Can the choroidal hemangioma be present bilaterally?
Yes, but it’s uncommon

Does the choroidal hemangioma have malignant potential?
No
Phakomatoses

**NF2**
--*Central* NF
--Classic finding: bilateral acoustic neuromas
--Eye findings: *Common*: PSC/cortical cataracts;
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**Sturge-Weber**
--Classic stigmata is the *port-wine stain*
--Ipsilateral meningeal AVM → seizures
--Classic *tomato catsup* fundus appearance is due to a diffuse choroidal hemangioma
--Another classic finding on DFE: non-retinal pathology
Phakomatoses

**NF2**
-- *Central* NF
-- Classic finding: bilateral *acoustic neuromas*
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**Sturge-Weber**
-- Classic stigmata is the *port-wine stain*
-- Ipsilateral meningeal AVM → *seizures*
-- Classic *tomato catsup* fundus appearance is due to a *diffuse choroidal hemangioma*
-- Another classic finding on DFE: *Glaucomatous cupping in the ipsilateral ONH only*

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Phakomatoses

Sturge-Weber: Note the glaucomatous cupping on the affected side
Phakomatoses

Sturge-Weber: Note the subtle PWS; also the buphthalmos, and enlarged cornea typical of congenital glaucoma
Phakomatoses

**NF2**
--*Central* NF
--Classic finding: bilateral *acoustic neuromas*
--Eye findings: *Common*: PSC/cortical cataracts;
   *Rare*: Combined hamartoma of retina and RPE; *Rarer*: Lisch nodules

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--Classic stigmata is the *port-wine stain*
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*What percent of SWS pts develop glaucoma?*
Phakomatoses

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*What percent of SWS pts develop glaucoma?*
Estimates run as high as 70
**Phakomatoses**

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**What percent of SWS pts develop glaucoma?**
Estimates run as high as 70

**Is there a relationship between the port-wine stain and risk of glaucoma?**
Phakomatoses

**NF2**

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*What percent of SWS pts develop glaucoma?*
Estimates run as high as 70

*Is there a relationship between the port-wine stain and risk of glaucoma?*
Yes. If the port-wine stain involves the *structure* the risk is **increased v decreased**
Phakomatoses

**NF2**

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**What percent of SWS pts develop glaucoma?**
Estimates run as high as 70

**Is there a relationship between the port-wine stain and risk of glaucoma?**
Yes. If the port-wine stain involves the **eyelid**, the risk is **increased**
Phakomatoses

**NF2**
--Central NF
--Classic finding: bilateral acoustic neuromas
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**What percent of SWS pts develop glaucoma?**
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**Is there a relationship between the port-wine stain and risk of glaucoma?**
Yes. If the port-wine stain involves the eyelid, the risk is increased

**Elevated IOP in SWS stems from three different mechanisms. What are they?**
--
--
--

*Hint forthcoming…*
Phakomatoses

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**Elevated IOP in SWS stems from three different mechanisms. What are they?**
---
---
--- 2° to ocular circulatory anomalies
--- A noncirculatory anomaly
Phakomatoses

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Elevated IOP in SWS stems from three different mechanisms. What are they?
--Increased episcleral venous pressure (EVP)
--Increased ciliary-body perfusion → aqueous hypersecretion
--Developmental abnormality of the drainage angle

2° to ocular circulatory anomalies
A noncirculatory anomaly
**Phakomatoses**

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---

**What percent of SWS pts develop glaucoma?**

*Estimates run as high as 70%.*

---

**Rule of thumb regarding the mechanism of glaucoma and SWS:**

**Elevated IOP in SWS stems from three different mechanisms.** What are they?
--Increased episcleral venous pressure (EVP)
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Phakomatoses

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What percent of SWS pts develop glaucoma?

**Rule of thumb regarding the mechanism of glaucoma and SWS:**
--If glaucoma is **evident at birth**, the angle is to blame; but

**Elevated IOP in SWS stems from three different mechanisms.** What are they?
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Phakomatoses

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---

What percent of SWS pts develop glaucoma?

**Rule of thumb regarding the mechanism of glaucoma and SWS:**
--If glaucoma is **evident at birth**, the angle is to blame; but
--If glaucoma doesn’t manifest until **after age 10**, increased EVP is the cause

**Elevated IOP in SWS stems from three different mechanisms.** What are they?
--Increased episcleral venous pressure (EVP)
--Increased ciliary-body perfusion → aqueous hypersecretion
--Developmental abnormality of the drainage angle
Phakomatoses

\[ IOP = \frac{\text{Aqueous Formation Rate (} \mu\text{L/min)} \rightleftharpoons \text{Outflow Facility (} \mu\text{L/min/mmHg)} + \text{Episceral Venous Pressure (mmHg)} \]

*Recalling the Goldmann equation for IOP…*

---

What percent of SWS pts develop glaucoma?
Estimates run as high as 70%

Is there a relationship between the port-wine stain and risk of glaucoma?
Yes. If the port-wine stain involves the eyelid, the risk is increased.

Elevated IOP in SWS stems from three different mechanisms. What are they?
--Increased episcleral venous pressure (EVP)
--Increased ciliary-body perfusion → aqueous hypersecretion
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Phakomatoses

\[ IOP = \frac{\text{Aqueous Formation Rate (}\mu\text{L/min})}{\text{Outflow Facility (}\mu\text{L/min/mmHg})} + \text{Episceral Venous Pressure (mmHg)} \]

Recalling the Goldmann equation for IOP...

\[ \uparrow IOP \text{ in SWS is secondary to} \]

Aqueous hypersecretion
Abnormal drainage angle

\[ \uparrow \text{Episceral Venous Pressure} \]

...we can see how all three components are involved in SWS glaucoma!

What percent of SWS pts develop glaucoma?
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Is there a relationship between the port-wine stain and risk of glaucoma?
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Elevated IOP in SWS stems from three different mechanisms. What are they?
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--Glaucoma surgery: ↑ risk of massive bad surgical complication due to abnormal two words
**Phakomatoses**

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Phakomatoses

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**Sturge-Weber syndrome**
--Classic stigmata is the *port-wine stain*
--Ipsilateral meningeal AVM → *seizures*
--Classic *tomato catsup* fundus appearance is due to a *diffuse choroidal hemangioma*
--Another classic finding on DFE: *Glaucomatous cupping in the ipsilateral ONH only*
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*There is another phakomatosis--less well-known than SWS--that also presents with a port-wine stain. What is it?*
Phakomatoses

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*There is another phakomatosis--less well-known than SWS--that also presents with a port-wine stain. What is it? Klippel-Trénaunay syndrome (sometimes you’ll see Klippel-Trénaunay-**Weber** syndrome). KTS is the essential rule-out on the DDx for SWS.*
Phakomatoses

Klippel-Trénaunay syndrome
Phakomatoses

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--Central NF
--Classic finding: bilateral acoustic neuromas
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*How is Klippel-Trénaunay pronounced?*
Phakomatoses

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**Klippel-Trénaunay(-Weber) syndrome**

*How is Klippel-Trénaunay pronounced?*
CLIP-el tri-NO-nay
Phakomatoses

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There is another phakomatosis--less well-known than SWS--that also presents with a **port-wine stain**. **What is it?**
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Like SWS, is KTS…
--associated with glaucoma?
Phakomatoses

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Like SWS, is KTS…
--associated with glaucoma? **Yes**
Phakomatoses

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*Like SWS, is KTS…
--associated with glaucoma? Yes
--nonhereditary?*
Phakomatoses

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**Klippel-Trénaunay(-Weber) syndrome**

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*Like SWS, is KTS…*
--associated with glaucoma? **Yes**
--nonhereditary? **Yes**
Phakomatoses

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Like SWS, is KTS...
--associated with glaucoma? Yes
--nonhereditary? Yes
--associated with meningeal AVMs/seizures?
Phakomatoses

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Like SWS, is KTS…
- associated with glaucoma? **Yes**
- nonhereditary? **Yes**
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Phakomatoses

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Sturge-Weber
--Classic stigmata is the *port-wine stain*
--Ipsilateral meningeal AVM → seizures
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There is another phakomatosis--less well-known than SWS--that also presents with a *port-wine stain.*
*What is it?*
Klippel-Trénaunay syndrome (sometimes you’ll see Klippel-Trénaunay-Weber syndrome). *KTS is the essential rule-out on the DDx for SWS.*

*Like SWS, is KTS…*
--associated with glaucoma? **Yes**
--nonhereditary? **Yes**
--associated with meningeal AVMs/seizures? **No**
--associated with diffuse choroidal hemangioma? **No**
Phakomatoses

NF2
--Central NF
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Are there other associations of note?
Phakomatoses

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Which limb is involved?

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*Which limb is involved? In the vast majority (~90%) of cases, a leg*

*Is the limb hypertrophy present at birth?*

*Are there other associations of note? Yes--vascular lesions of the trunk and a single limb, along with marked hypertrophy of that limb*
Phakomatoses

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**Ataxia-telangiectasia**
-- Most common cause of **main symptom** in childhood
**Phakomatoses**

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**Ataxia-telangiectasia**
-- Most common cause of *progressive ataxia* in childhood
Phakomatoses

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**Ataxia-telangiectasia**
--Most common cause of *progressive ataxia* in childhood
--Only phakomatosis with no abnormalities of the *eye part*
**Phakomatoses**

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Phakomatoses

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**Ataxia-telangiectasia**
--- Most common cause of *progressive ataxia* in childhood
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--- Classic finding of conjunctival telangiectasia typically appear between ages of # to # years
Phakomatoses

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Phakomatoses

Ataxia-telangiectasia: Conj telangiectasias
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Phakomatoses

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--Other eye findings include:

  - EOM problem 1
  - EOM test
  - EOM prob 2
  - EOM prob 3

  with intact
Phakomatoses

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Phakomatoses

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*Abnormal saccades*

*A-T toddlers have difficulty initiating saccades, and sometimes use a head turn/thrust to do so. What more-common, less-devastating oculomotor disorder presents similarly?*
Phakomatoses

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*A-T toddlers have difficulty initiating saccades, and sometimes use a head turn/thrust to do so.*
*What more-common, less-devastating oculomotor disorder presents similarly?*
**Congenital ocular motor apraxia (COMA)**
Phakomatoses

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--Classic finding of conjunctival telangiectasia typically appear between ages of 3-5 years
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--Abnormal immune function→↑ susceptibility to infections→risk of death in teens
Phakomatoses

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--Abnormal immune function \(\rightarrow\) ↑ susceptibility to **respiratory tract** infections \(\rightarrow\) risk of death in teens
**Phakomatoses**

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- Abnormal immune function → ↑ susceptibility to respiratory tract infections → risk of death in teens
- Also have significantly increased risk of leukemia and lymphoma (cause of death in up to ½)
- Heterozygotes (~2% of population) have increased risk of malignancy as well

**What aspects of the immune system are abnormal?**

- T-cells are abnormal in both function and number
- Immunoglobulin levels are abnormal
- These immunodeficiencies are due in large part to hypoplasia of what immune organ?
  - The thymus
Phakomatoses

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**Abnormally high, or low?**

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**Phakomatoses**

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-- T-cells are abnormal in both function and *number*
-- Immunoglobulin levels are *abnormal*

*Abnormally high, or low? Low*
Phakomatoses

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*What buzzword is used to define the specific sort of RT infection A-T pts are vulnerable to?***

*Sinopulmonary* infections

**NF2**
--Central NF
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--↑ risk of death in teens
--Also have significantly increased risk of leukemia and lymphoma (cause of death in up to ½)
--Heterozygotes (~2% of population) have increased risk of malignancy as well

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What buzzword is used to define the specific sort of RT infection A-T pts are vulnerable to?
‘Sinopulmonary’ infections
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Phakomatoses

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**Ataxia-telangiectasia**
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-- Only phakomatosis without ocular abnormalities
-- Classic finding: conjunctival telangiectasia typically appear between ages of 3-5 years
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*Your A-T pt may have a sinus infection. Should you get a CT to confirm?*
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*Your A-T pt may have a sinus infection. Should you get a CT to confirm?*
**NO!** A-T pt's DNA is extremely vulnerable to damage from ionizing radiation--X-rays should be performed only if no other imaging modality will suffice
Phakomatoses

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*The unfortunate truth of the matter is this:*
--In countries with less-robust healthcare systems (ie, without readily-available antibiotics), A-T pts die of sinopulmonary infections in their teens; whereas

--Abnormal immune function $\rightarrow$ ↑ susceptibility to *respiratory tract* infections $\rightarrow$ risk of death in teens
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The unfortunate truth of the matter is this:
--In countries with less-robust healthcare systems (ie, without readily-available antibiotics), A-T pts die of sinopulmonary infections in their teens; whereas
--In countries *with* robust healthcare systems, sinopulmonary infections can be kept at bay long enough for A-T pts to die of cancer (usually leukemia or lymphoma).

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*For what cancer are A-T heterozygotes at particular risk?*
Phakomatoses

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*For what cancer are A-T heterozygotes at particular risk? Breast*
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-- Skin manifestation: not surprisingly...
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**At what age do cutaneous telangiectasias begin to appear?**
3-5 years (ie, at about the same time the conj ones do)

**At what location do they typically appear first?**
The malar region of the face

--They typically spread across the face and neck, and new ‘crops’ will appear on the limbs
Phakomatoses

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Ataxia-telangiectasia: Facial telangiectasias
**Phakomatoses**

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--Ipsilateral meningeal AVM ➞ seizures
--Classic [tomato catsup](http://www.mayoclinic.org/diseases-conditions/port-wine-stain/symptoms-causes/syc-20355291) fundus appearance is due to a diffuse choroidal hemangioma
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No, they typically spread across the face and neck, and new 'crops' will appear on the limbs
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Ataxia-telangiectasia: Telangiectasias
Phakomatoses

**Incontinentia pigmenti**

--Skin normal at birth, but abnormality 1 and abn 2 develop by age; only later develops the classic appearance
Incontinentia pigmenti
--Skin normal at birth, but erythema and bullae develop by 1 week; only later develops the classic ‘splashed paint’ appearance
Phakomatoses

Incontinentia pigmenti: Splashed-paint appearance
Incontinentia pigmenti
--Skin normal at birth, but erythema and bullae develop by 1 week; only later develops the classic ‘splashed paint’ appearance
--Eye finding: $\frac{x}{x}$ will have peripheral retina problem that looks just like a more common dz
**Phakomatoses**

*Incontinentia pigmenti*

--Skin normal at birth, but *erythema* and *bullae* develop by 1 week; only later develops the classic ‘splashed paint’ appearance

--Eye finding: 1/3 will have peripheral *proliferative retinopathy* that looks just like ROP
Phakomatoses

Incontinentia pigmenti: ROP-like retinal appearance
Incontinentia pigmenti
--Skin normal at birth, but erythema and bullae develop by 1 week; only later develops the classic ‘splashed paint’ appearance
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**Phakomatoses**

*Incontinentia pigmenti*
-- Skin normal at birth, but **erythema** and **bullae** develop by **1 week**; only later develops the classic ‘splashed paint’ appearance
-- Eye finding: **1/3** will have **peripheral proliferative retinopathy** that looks just like **ROP**
---- Eye findings are usually **uni- vs bilateral**
Incontinentia pigmenti
--Skin normal at birth, but erythema and bullae develop by 1 week; only later develops the classic ‘splashed paint’ appearance
--Eye finding: 1/3 will have peripheral proliferative retinopathy that looks just like ROP
----Eye findings are usually unilateral
Phakomatoses

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-- Skin normal at birth, but erythema and bullae develop by 1 week; only later develops the classic 'splashed paint' appearance
-- Eye finding: 1/3 will have peripheral **proliferative retinopathy** that looks just like ROP
---- Eye findings are usually unilateral

How is the peripheral proliferative retinopathy managed?
**Phakomatoses**

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--Skin normal at birth, but erythema and bullae develop by 1 week; only later develops the classic 'splashed paint' appearance

--Eye finding: 1/3 will have peripheral **proliferative retinopathy** that looks just like ROP

----Eye findings are usually unilateral

*How is the peripheral proliferative retinopathy managed?*

Basically, in the same manner as ROP
**Phakomatoses**

*Incontinentia pigmenti*
--Skin normal at birth, but *erythema* and *bulla* develop by *1 week*; only later develops the classic ‘splashed paint’ appearance
--Eye finding: *1/3* will have peripheral *proliferative retinopathy* that looks just like *ROP*
----Eye findings are usually *unilateral*
--*2/3* will also have abnormal *mouth issue*
Incontinentia pigmenti
--Skin normal at birth, but erythema and bullae develop by 1 week; only later develops the classic ‘splashed paint’ appearance
--Eye finding: 1/3 will have peripheral proliferative retinopathy that looks just like ROP
----Eye findings are usually unilateral
--2/3 will also have abnormal dentition
Incontinentia pigmenti: Abnormal dentition
Phakomatoses

Incontinentia pigmenti

--Skin normal at birth, but erythema and bullae develop by 1 week; only later develops the classic 'splashed paint' appearance

--Eye finding: 1/3 will have peripheral proliferative retinopathy that looks just like ROP

----Eye findings are usually unilateral

--2/3 will also have abnormal dentition

Name two other congenital eye syndromes associated with abnormal dentition:

--

--
Phakomatoses

**Incontinentia pigmenti**
--Skin normal at birth, but erythema and bullae develop by 1 week; only later develops the classic 'splashed paint' appearance
--Eye finding: 1/3 will have peripheral proliferative retinopathy that looks just like ROP
----Eye findings are usually unilateral
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Name two other congenital eye syndromes associated with abnormal dentition:
--Axenfeld-Rieger syndrome
--Congenital syphilis
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Name two other congenital eye syndromes associated with abnormal dentition:
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--Congenital syphilis

In three words, what sort of condition is Axenfeld-Reiger?
It is an...
**Phakomatoses**

---

**Incontinentia pigmenti**
- Skin normal at birth, but erythema and bullae develop by 1 week; only later develops the classic 'splashed paint' appearance
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Name two other congenital eye syndromes associated with abnormal dentition:
- **Axenfeld-Rieger syndrome**
- Congenital syphilis

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*In three words, what sort of condition is Axenfeld-Reiger?*
It is an... **anterior-segment dysgenesis**
**Incontinentia pigmenti**

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---- Eye findings are usually unilateral

-- 2/3 will also have abnormal **dentition**

Name two other congenital eye syndromes associated with abnormal dentition:

-- **Axenfeld-Rieger syndrome**

-- Congenital syphilis

*In three words, what sort of condition is Axenfeld-Reiger?*

It is an... **anterior-segment dysgenesis**

*If limited to one word, what sort of condition is Axenfeld-Reiger?*

It is a...
**Phakomatoses**

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Name two other congenital eye syndromes associated with abnormal dentition:
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*In three words, what sort of condition is Axenfeld-Reiger?*
It is an... **anterior-segment dysgenesis**

*If limited to one word, what sort of condition is Axenfeld-Reiger?*
It is a... **neurocristopathy**
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**Name two other congenital eye syndromes associated with abnormal dentition:**

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*In three words, what sort of condition is Axenfeld-Reiger?*

It is an... anterior-segment dysgenesis

*If limited to one word, what sort of condition is Axenfeld-Reiger?*

It is a... neurocristopathy

*What is the eponymous name for abnormal dentition in congenital syphilis?*
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If limited to one word, what sort of condition is Axenfeld-Reiger?
It is a... neurocristopathy

What is the eponymous name for abnormal dentition in congenital syphilis?
Hutchinson's teeth
Phakomatoses

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Racemose angioma
--Characterized by AVM of the eye and brain
Phakomatoses

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**Phakomatoses**

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In basic terms, what is an AVM?

A direct communication between the arterial and venous sides of the circulation; ie, without benefit of an intervening capillary bed
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*In basic terms, what is an AVM?*
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*In RA, are the AVM of the eye unilateral or bilateral?*
Phakomatoses

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Phakomatoses

Racemose angioma
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Phakomatoses

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---How about the AVM of the brain?

Racemose angioma

--Characterized by AVM of eye and brain
**Phakomatoses**

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--- **How about the AVM of the brain?**
Also unilateral

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Also unilateral

--- **Are the eye and brain AVM ipsilateral or contralateral with respect to one another?**
**Phakomatoses**

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*Are the eye and brain AVM ipsilateral or contralateral with respect to one another?*
Ipsilateral
Phakomatoses

A, The color fundus photo of the left eye shows the racemose angioma of the retina.
B, The vascular lumen (arrow) was documented with the optical coherence tomography scan.
C, The MRI angiogram of the brain shows the arteriovenous malformation on the left side.

Racemose angioma
**Phakomatoses**

**Racemose angioma**
--Characterized by AVM of eye and brain

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Ipsilateral

---Where specifically are the AVM located in RA?

---The eye AVM are usually found in the temporal retina
---The brain AVM are usually in the midbrain
**Phakomatosises**

**Racemose angioma**
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Is there some sort of fundamental relationship between the AVM of the eye and brain in RA, or is their co-existence simply a matter of happenstance?
Phakomatoses

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**Racemose angioma**
--Characterized by AVM of eye and brain

*Is there some sort of fundamental relationship between the AVM of the eye and brain in RA, or is their co-existence simply a matter of happenstance?*
There is definitely a fundamental relationship between the two. This relationship stems from an abnormality of the cerebral vascular plexus of the embryo. We know this because pathologic exam has in some cases revealed the presence of a direct connection between the AVM in the eye and the AVM in the brain!
Phakomatoses

**Incontinentia pigmenti**
--Skin normal at birth, but *erythema* and *bullae* develop by 1 week; only later develops the classic ‘*splashed paint*’ appearance
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----Eye findings are usually *unilateral*
--2/3 will also have abnormal *dentition*

**Racemose angioma**
--Characterized by AVM of *eye* and *brain*
--Brain AVM frequently bleed, leading to *bad* and *worse*
Phakomatoses

**Incontinentia pigmenti**
-- Skin normal at birth, but **erythema** and **bullae** develop by 1 week; only later develops the classic ‘splashed paint’ appearance
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**Racemose angioma**
-- Characterized by AVM of **eye** and **brain**
-- Brain AVM frequently bleed, leading to **hemiparesis** and **death**
Phakomatoses

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**Racemose angioma**
--Characterized by AVM of eye and brain
--Brain AVM frequently bleed, leading to hemiparesis and death

At what age do RA pts begin to suffer these brain bleeds?
**Phakomatoses**

**Incontinentia pigmenti**
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**Racemose angioma**
--Characterized by AVM of *eye* and *brain*
--Brain AVM frequently bleed, leading to *hemiparesis* and *death*

*At what age do RA pts begin to suffer these brain bleeds?*
*Usually at some point from the teen years into their 20s*
Phakomatoses

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*What about seizures? How prevalent is seizure activity in RA?*
Phakomatoses

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**Racemose angioma**
--Characterized by AVM of *eye* and *brain*
--Brain AVM frequently bleed, leading to *hemiparesis* and *death*

*What about seizures? How prevalent is seizure activity in RA?*
*Not very--estimates run as low as 5% of cases*
Phakomatoses

**Incontinentia pigmenti**
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**Racemose angioma**
-- Characterized by AVM of *eye* and *brain*
-- Brain AVM frequently bleed, leading to *hemiparesis* and *death*
-- Retinal AVM *do/don’t* leak on FA
Phakomatoses

**Incontinentia pigmenti**
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**Racemose angioma**
--Characterized by AVM of **eye** and **brain**
--Brain AVM frequently bleed, leading to hemiparesis and death
--Retinal AVM **don’t** leak on FA

*Does this mean RA pts don’t have eye/vision trouble related to their condition?*
Phakomatoses

Incontinentia pigmenti
--Skin normal at birth, but erythema and bullae develop by 1 week; only later develops the classic ‘splashed paint’ appearance
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Racemose angioma
--Characterized by AVM of eye and brain
--Brain AVM frequently bleed, leading to hemiparesis and death
--Retinal AVM don’t leak on FA

Does this mean RA pts don’t have eye/vision trouble related to their condition? Far from it. Like the AVM found in the brain, the AVM in the eye tend to bleed, thus predisposing these pts to retinal and/or vitreous hemorrhages. Some pts develop retinal ischemia, resulting in neovascularization and ultimately NVG.
Incontinentia pigmenti
--Skin normal at birth, but erythema and bullae develop by 1 week; only later develops the classic ‘splashed paint’ appearance
--Eye finding: 1/3 will have peripheral proliferative retinopathy that looks just like ROP
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Racemose angioma
--Characterized by AVM of eye and brain
--Brain AVM frequently bleed, leading to hemiparesis and death
--Retinal AVM don’t leak on FA
--Skin finding = ?

What about skin findings? If this condition is a phakomatosis (aka a neurocutaneous syndrome), shouldn’t the skin be affected as well?
Phakomatoses

**Incontinentia pigmenti**
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**Racemose angioma**
--Characterized by AVM of eye and brain
--Brain AVM frequently bleed, leading to hemiparesis and death
--Retinal AVM don’t leak on FA

---

**What about skin findings? If this condition is a phakomatosis (aka a neurocutaneous syndrome), shouldn’t the skin be affected as well?**
It should be, and in fact it is—at least 50% of RA pts manifest angiomas, vascular nevi, etc (usually on the face). However, the skin findings are not a prominent feature of the condition.
As promised, next is a TLDR. There are two versions. The first lists the characteristics of the phakomatoses and asks you to provide their names; the second does the opposite. For each version, toggle back and forth between the Q&A slides until you’ve got them all.
### Phakomatoses aka neuro-oculocutaneous syndromes: TLDR

<table>
<thead>
<tr>
<th>Neuro</th>
<th>Oculo</th>
<th>Cutaneous</th>
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<tbody>
<tr>
<td>Optic nerve glioma</td>
<td>Lisch nodules; upper-lid plexiform neurofibroma</td>
<td>Café-au-lait spots</td>
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<tr>
<td>Bilateral acoustic neuromas</td>
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<td>Seizures</td>
<td>Diffuse choroidal hemangioma</td>
<td>Port-wine stain</td>
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<tr>
<td>Cortical tubers</td>
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<tr>
<td>Cerebellar hemangioblastoma</td>
<td>Capillary hemangioblastoma</td>
<td>None</td>
</tr>
<tr>
<td>Seizures</td>
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<td>Erythema/bullae: ‘Splashed paint’</td>
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<td>Ataxia</td>
<td>Conj telangiectasias</td>
<td>Telangiectasias</td>
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<tr>
<td>A-V malformation</td>
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Phakomatoses aka neuro-oculocutaneous syndromes: TLDR

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<thead>
<tr>
<th>Tuberous sclerosis: ‘EPILOA’</th>
</tr>
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<tbody>
<tr>
<td><strong>Neuro</strong></td>
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<tr>
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<table>
<thead>
<tr>
<th>von Hippel-Lindau</th>
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<tr>
<th>Racemose angioma (Wyburn-Mason)</th>
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</table>
(Next, Version 2)
# Phakomatoses aka neuro-oculocutaneous syndromes: TLDR

<table>
<thead>
<tr>
<th>Incontinentia pigmenti</th>
<th>Sturge-Weber</th>
</tr>
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<tbody>
<tr>
<td>Neuro</td>
<td>?</td>
</tr>
<tr>
<td>Oculo</td>
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<table>
<thead>
<tr>
<th>NF2: ‘Central’ NF</th>
<th>NF1: ‘Peripheral’ NF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro</td>
<td>?</td>
</tr>
<tr>
<td>Oculo</td>
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<tr>
<td><strong>Incontinentia pigmenti</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Neuro</strong></td>
<td>Seizures</td>
</tr>
<tr>
<td><strong>Oculo</strong></td>
<td>Unilateral ROP-like appearance</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
<td>Erythema/bullae: ‘Splashed paint’</td>
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<tr>
<td><strong>Racemose angioma (Wyburn-Mason)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Neuro</strong></td>
<td>A-V malformation</td>
</tr>
<tr>
<td><strong>Oculo</strong></td>
<td>A-V malformation</td>
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<tr>
<td><strong>Cutaneous</strong></td>
<td>Not much</td>
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<tr>
<td><strong>Tuberous sclerosis: ‘EPILOA’</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Neuro</strong></td>
<td>Cortical tubers</td>
</tr>
<tr>
<td><strong>Oculo</strong></td>
<td>Astrocytic hamartoma</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
<td>Adenoma sebaceum; ash-leaf spots; shagreen patches</td>
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<tr>
<td><strong>NF2: ‘Central’ NF</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Neuro</strong></td>
<td>Bilateral acoustic neuromas</td>
</tr>
<tr>
<td><strong>Oculo</strong></td>
<td>Early PSCs</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
<td>Occasional café-au-lait spots</td>
</tr>
<tr>
<td><strong>Sturge-Weber</strong></td>
<td></td>
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<tr>
<td><strong>Neuro</strong></td>
<td>Seizures</td>
</tr>
<tr>
<td><strong>Oculo</strong></td>
<td>Diffuse choroidal hemangioma</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
<td>Port-wine stain</td>
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<tr>
<td><strong>von Hippel-Lindau</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Neuro</strong></td>
<td>Cerebellar hemangioblastoma</td>
</tr>
<tr>
<td><strong>Oculo</strong></td>
<td>Capillary hemangioblastoma</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
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<td><strong>Ataxia-telangiectasia (Louis-Bar)</strong></td>
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<tr>
<td><strong>Neuro</strong></td>
<td>Ataxia</td>
</tr>
<tr>
<td><strong>Oculo</strong></td>
<td>Conj telangiectasias</td>
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<tr>
<td><strong>Cutaneous</strong></td>
<td>Telangiectasias</td>
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<tr>
<td><strong>NF1: ‘Peripheral’ NF</strong></td>
<td></td>
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<tr>
<td><strong>Neuro</strong></td>
<td>Optic nerve glioma</td>
</tr>
<tr>
<td><strong>Oculo</strong></td>
<td>Lisch nodules; upper-lid plexiform neurofibroma</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
<td>Café-au-lait spots</td>
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