What Syndrome’s That?

Syndromes Associated with Vascular Anomalies

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Learning objectives

• Recognize the syndromic features associated with vascular anomalies and infantile hemangiomas

• Learn about genotype-phenotype correlations for these disorders
De novo germline and postzygotic mutations in AKT3, PIK3R2, PIK3CA cause a spectrum of related megalencephaly syndromes

Large head, prominent forehead

Diffuse capillary malformation

Digital anomalies and syndactyly

PI3K pathway

- Signaling enzymes, regulate wide range of processes

- Cell growth, proliferation, survival, migration, angiogenesis, apoptosis, tumorigenesis, brain development

Somatic Mosaic Activating Mutations in \textit{PIK3CA} Cause CLOVES Syndrome

Kurek et al, Am J Hum Gen, 2012
Somatic gain-of-function mutations in *PIK3CA* in patients with macrodactaly

Rios et al, Human Molecular Genetics 2013
De Novo somatic mutations in components of PI3K-AKT3-mTOR pathway cause hemimegalecencephaly

Lee et al, Nature Genetics, 2012
PIK3CA Activating Mutations in Facial Infiltrating Lipomatosis
Vascular Overgrowth Syndromes

• Mutations in the \textit{PIK3CA} gene can cause many different phenotypes
  – Likely based on the tissue distribution of the mosaic mutations
Sturge-Weber is caused by mutations in GNAQ
GNAQ

- Capillary malformation
  - GNAQ p.Arg183Gln

- Uveal melanoma
Sturge-Weber Syndrome

1 in 20,000 to 50,000 live births

Venous-capillary abnormalities of the leptomeninges and choroid plexus

Neurological
– Seizures
– Developmental delay
– Calcification of the occipital and/or temporal cortex

Ocular findings:
– Congenital glaucoma
– Increased choroidal vascularity
Spectrum of phenotypes associated with G-proteins

• Capillary malformations
• Phakomatosis pigmentovascularis
• Sturge-Weber
• Patient with multiple capillary malformations

• **Family History**: Stroke in Maternal Uncle in 30’s
Capillary Malformation AVM - Cutaneous findings

- CMs are small, oval multifocal and randomly distributed
- Pink-to-red or brown
CM-AVM Extracutaneous features

- AVM’s and AVF’s in 18.5%
  - Brain 7.1%
  - Limb 3.6%
  - Face 7.8%

Revencu et al, Human Mutation 29(7),959-965, 2008
CM-AVM Extracutaneous features: spinal AVM

- 5 index cases of AVM and AVF
  - 3 AVM’s on the lower spine
  - 2 AVF’s on the cervico-thoracic spine

- Age of presentation: 16 months and 23 years
  - Upper spine: headache
  - Lower spine: Neurogenic bladder and hemiplegia

- Treatment: embolization, surgery
CM-AVM- Molecular Genetics

- Autosomal dominant
- Loss of function mutations in RASA1 gene
Segmental patterning

• S1: upper eyelid, temple

• S2: lower eyelid, cheek

• S3: jaw, beard

• S4: nose and glabella
PHACES syndrome and ectopia cordis.

- Ectopia cordis
- Parotid Hemangioma
- Supraumbilical raphe
- Aberrant communication between the left common carotid and subclavian arteries
Ventral midline blanching

- 9 infants with segmental IH and areas of midline ventral blanching
  - 5 ventral wall defects
  - 6 cardiac anomalies
  - 6 intracranial anomalies

- 5 definite PHACE
- 3 possible PHACE

Supraumbilical raphe
Variations of PHACE syndrome
Consensus statement on PHACE syndrome diagnostic criteria

• Multidisciplinary group met in Houston, Texas at the PHACE research conference in 2008

• Definite PHACE:
  – Segmental hemangioma or hemangioma > 5 cm on the face or scalp PLUS 1 major criterion OR 2 minor criteria

“PHACE without face”

- **Cardiac**
  - Right-sided aortic arch
  - Narrowing of distal transverse aortic arch
  - Tetralogy of Fallot

- **Arteriopathy**
  - Aberrant left subclavian artery/vascular ring
  - Tortuosity of right internal carotid and basilar arteries

- **Sternal scar**

*Pediatric Dermatology*
*Vol. 28 No. 3 235–241, 2011*
PHACE syndrome: Consensus-Derived Diagnosis and Care Recommendations

Garzon et al
The Journal of Pediatrics
Volume 178, November 2016, Pages 24–33.e2
LUMBAR syndrome

- **L**ower body hemangioma/ cutaneous defects
- **U**rogenital anomalies/ Ulceration
- **M**yelopathy
- **B**ony deformities
- **A**norectal /Arterial anomalies
- **R**enal anomalies
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