Sturge-Weber syndrome through the Brain Vascular Malformation Consortium: What we have learned, future promise and how you can help

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No commercial conflicts of interest to declare.
Off-label Uses of drugs will be discussed.

RARE DISEASES CLINICAL RESEARCH NETWORK

Today's Talk

- Define the Brain Vascular Malformation Consortium and its Mission
- Describe its SWS research to date and the results
- Relate the importance of these findings and some of the future work likely to build on these results
- Provide ways in which patients and families can speed the progress of research and the development of new and better treatment strategies

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BRAIN VASCULAR MALFORMATION CONSORTIUM

Goals of the BVMC

- To carry out multi-centered research better understand, diagnose and treat
  - Cavernous Capillary Malformation
  - Sturge-Weber syndrome
  - Hereditary Hemorrhagic Telangiectasia

Aims of Sturge-Weber syndrome Project

- Aim 1: Develop a SWS National De-identified Database
- Aim 2: To develop new vascular urine biomarkers
- Aim 3: To discover the somatic mutation causing SWS
- Pilot project: SWS Biomarker development
- Training Project: Aspirin and Stimulant Experience at KKI center

Aim 1: National Database

- De-identified Database housed at University of South Florida
- SWF assisting in screening-subjects must have SWS brain involvement shown on MRI
- Consent and questionnaire can be done over phone OR at center visit
- Goal to gather data for study and for future research

Participating Centers

- Hunter Nelson Sturge-Weber Center at the Kennedy Krieger Institute/ Johns Hopkins (Comi)
- Wayne State University (Chugani)
- Nationwide Children's Hospital (Lo)
- Thomas Jefferson University – Wills Eye Institute (Levin)
- Baylor College of Medicine, Texas Children's Hospital (Wilfong)

National Database: Future Directions

- Working with the participating centers and PIs to summarize and publish data so far
- Current data will serve as pilot data for the renewal of the Consortium Grant application
- This database can be used in the future to recruit for studies.

Aim 2: Urine SWS biomarkers study

- Variability in severity and responses in SWS a challenge in treatment
  - A good biomarker should be safe to do, not very expensive, and should be predictive of disease severity, progression or response
  - A good biomarker is helpful for clinical trials and in clinical care of patients
  - We collected urines and SWS neurologic scores from the same visits and compared to controls (KKI center only).

Urine Blood Vessel biomarkers in SWS: Recently published data

- MMP2 and MMP9 more likely to be urine of children and adults with SWS
- MMP9 levels were higher in females with SWS than in males
- Higher MMPs were associated with worse neurologic scores at the time of the clinical visit
- Higher bFGF levels were associated with improved clinical outcome a year after sample collection.

(Adit et al. Vascular Med. 2013)

Urine SWS Biomarkers: Future directions

- We are continuing to study these biomarkers over time and relate them to the medication the subjects take an their neurologic scores
- We will propose in renewal to continue studying these biomarkers as we take next steps towards clinical trials.

Pilot Study: Other SWS biomarkers

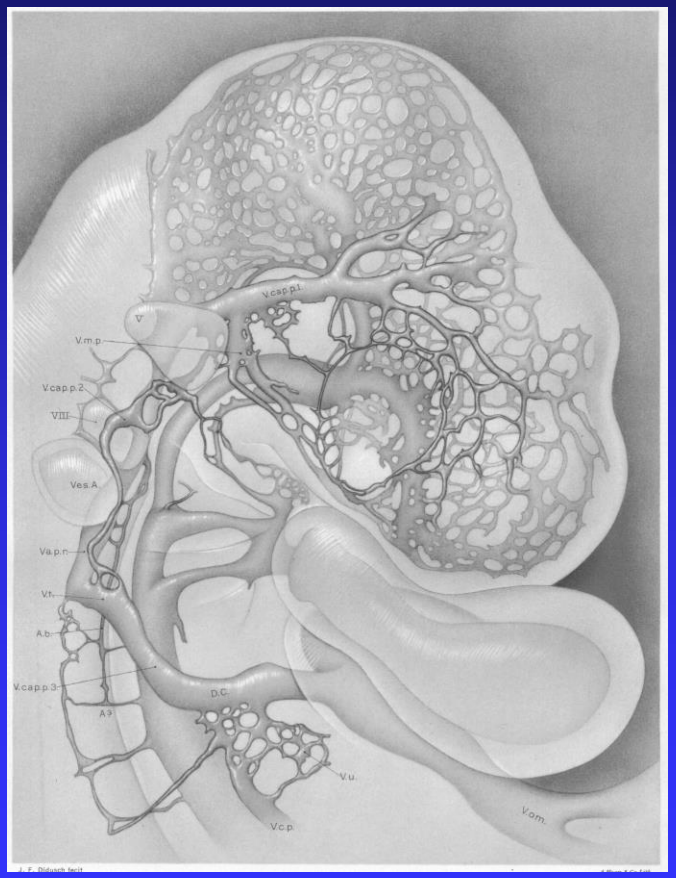
- Quantitative EEG
- Transcranial doppler
- Medical rehabilitation scales
- Optical coherence tomography

Future of SWS Biomarkers

- Biomarkers will have an important role in future clinical trials.
- Enable us to have primary and secondary endpoints to measure and determine effectiveness of treatment.
- May become ways of safely monitoring patient clinical status and treatment reponses.

Aim 3: Evidence for a somatic mutation in SWS

- Localized asymmetric abnormalities in vascular development of brain, eye and skin *(Happle, J Am Acad Derm, 1987)*
- Report of one of two monozygotic twins with SWS *(Pedailles, Eur Neurol, 1993)*
- Increased fibronectin expression in SWS PWS fibroblasts *(Comi et al, Ped Res 2003)*
- Chromosomal abnormalities reported in 2 fibroblast cultures from SWS affected regions *(Huq et al, Neurology 2002)*



(Sabin FR. Carnegie Contrib Embryol, 1917)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sturge–Weber Syndrome and Port-Wine Stains Caused by Somatic Mutation in *GNAQ*

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ABSTRACT

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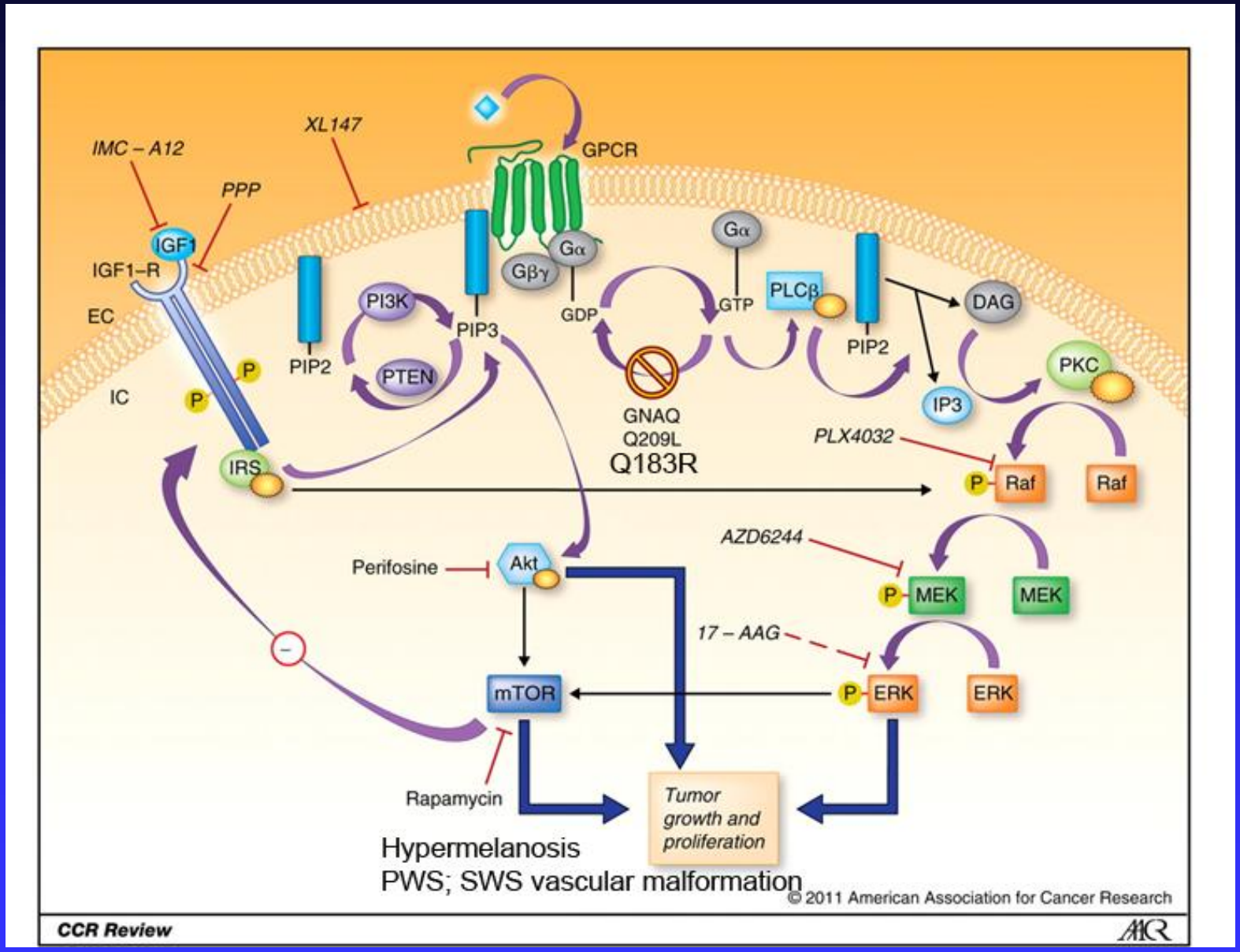
Drs. Marchuk, Comi, and Pevsner contributed equally to this article.

Signaling Pathways in Melanoma and SWS and PWS



Adapted from CCR Review 2011

Thoughts

- The somatic mosaic mutation in GNAQ results in hyper-activation of pathways important in many cell functions.
- A great deal is known about these pathways.
- The same mutation, ocurring in a different cell type, at a different time in development, results in a vascular malformation instead of a tumor.

How can you help?

- National De-identified database: We urgently need participants to contribute to the national de-identified database. Please see SWF staff or myself if you are interested.
- Participate in research where possible.
- Tissue donation is critical. We know the gene, but still need tissue to answer really important next questions.
- Donate. Have a fundraiser. Every donation counts and the need is great!

RARE CLINICAL DISEASES RESEARCH NETWORK

- The Brain Vascular Malformation Consortium has made significant advances in our understanding of SWS and laying the foundation for clinical trials and new future treatments.
- Our multi-centered consortium will lay the foundation for future clinical trials.
- New promising neurologic biomarkers are currently being developed.
- With the discovery of the somatic mutation causing SWS we are standing at the dawn of a new day for SWS-the promise is great…

….. and our work continues.

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Thank You!