Update on Sturge-Weber syndrome research

THE STURGE-WEBER FOUNDATION

Jonathan Pevsner
Chief Scientific Officer
Sturge-Weber Foundation

SWF International Conference
Cincinnati
July 28, 2017

Outline

SWS research and SWF: background and goals

Who's publishing on research & what are they doing?

Science behind SWS

Science behind uveal melanoma

1. Animal models
2. Genomics
3. Biobank
4. Registry
5. Clinical trials

What you can do!

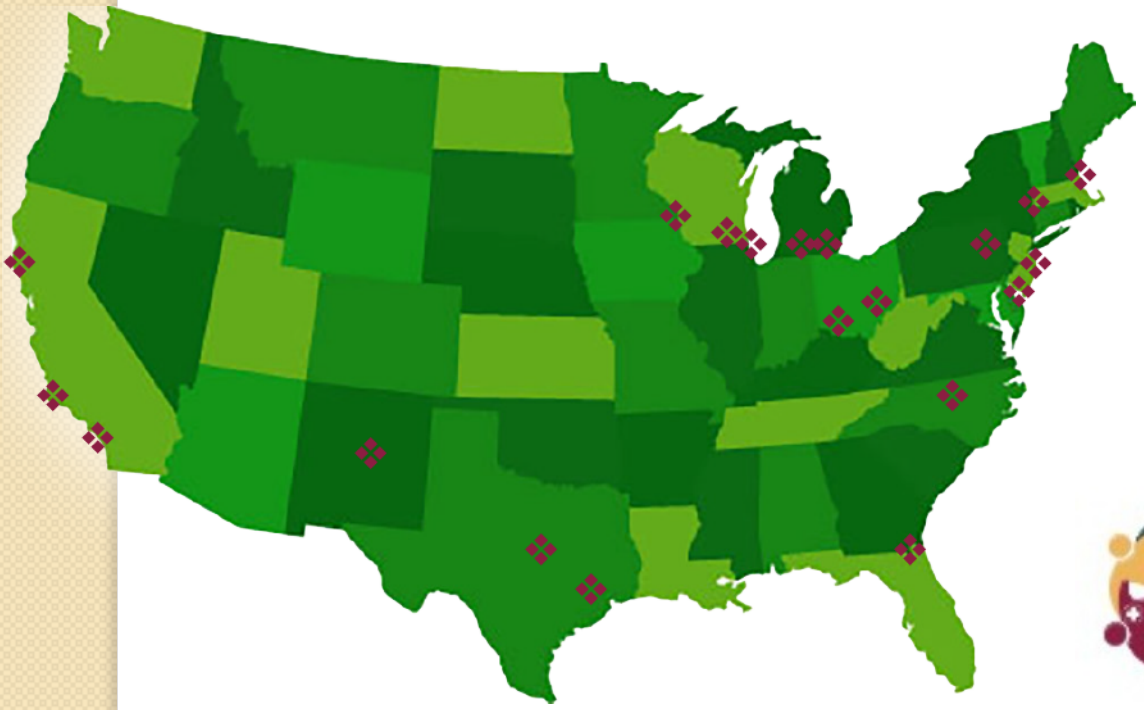
Sturge-Weber Foundation: introduction

- 501(c)(3) non-profit organization
- Founded by Karen Ball (1987)
- Supports individuals with capillary vascular birthmarks, Klippel Trenaunay syndrome, and port-wine birthmarks
- 3900 cases reported to the SWF
- Promoting a SWF Clinical Care Network (>25 centers)

THE STURGE-WEBER FOUNDATION

Sturge-Weber Foundation: Clinical Care Network

- Formerly called Centers of Excellence
- >25 centers (including Cincinnati Children's Hospital Medical Center led by Dr. Adrienne Hammill)



THE STURGE-WEBER FOUNDATION
CLINICAL CARE
NETWORK

Sturge-Weber Foundation: Mission Statement

To improve the quality of life and care for people with Sturge-Weber syndrome and associated Port Wine Birthmark conditions through collaborative education, advocacy, research and friendly support.

Sturge-Weber Foundation: board of directors

Pam McIntyre, Reading, MA
Chairman

Kris Sadens, Glenview, IL
Vice Chairman

Dan Dorney, Monroe, NY
Treasurer

Lisa Dralle Peterson, Decorah, IA
Secretary

Woody Crouch - Scarsdale, NY

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Jeffrey Needham - Los Gatos, CA

Karen Ball, President & CEO, The Sturge-Weber Foundation, Aurora, CO

Sturge-Weber Foundation: emeritus members

Linda Larach Cohen, NY, NY

Roy Geronemus, MD, New York City, NY

Gerard E. Puorro, Wayland, MA

Melanie Wood, Bellaire, TX

Stan M Fisher, Bigfork, MT

Joseph G. Morelli, MD, Denver, CO

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Sturge-Weber Foundation: CSO priorities

My priorities as CSO include the following (all working closely with Dr. Jeffrey Loeb):

- Fostering collaborations
- Support research (e.g. Lisa's Research Fellowship)
- Support funding efforts (e.g. grant applications)
- Establish biobank
- Coordinate sample acquisition ("IRB")
- Facilitate sequencing for diagnosis and discovery
- Facilitate animal model development

Thanks to my predecessor Dr. Charles Swindell!

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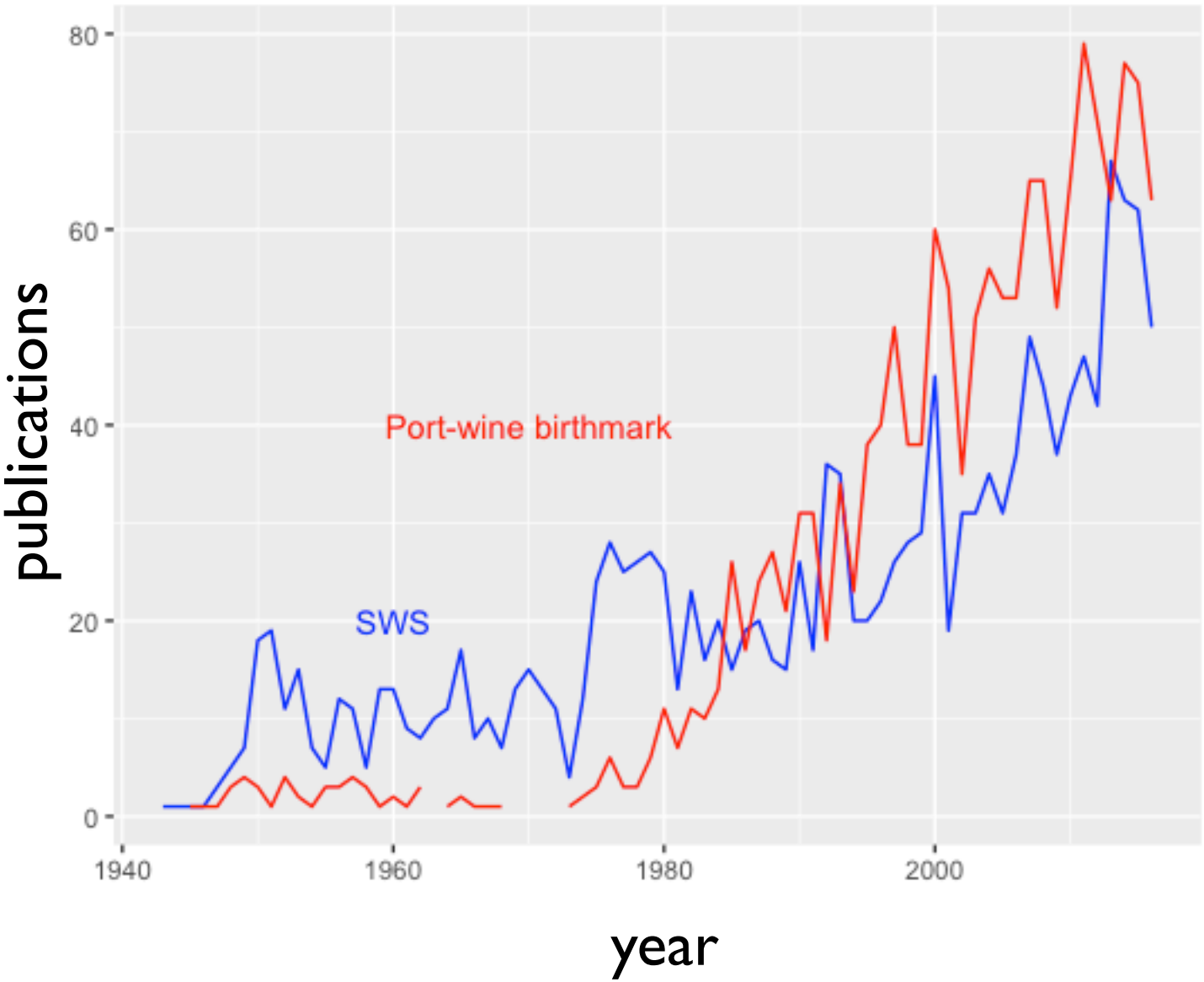
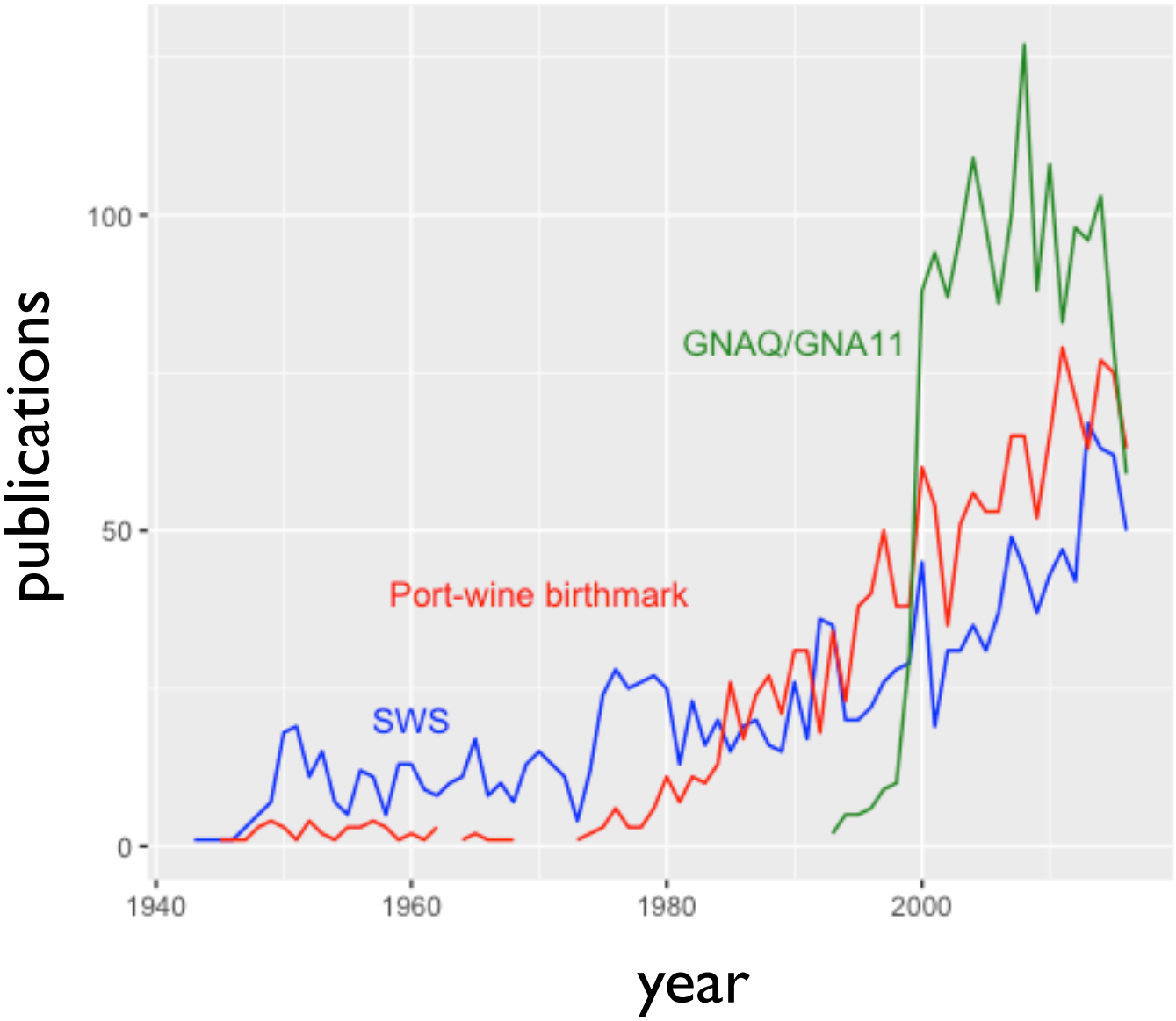
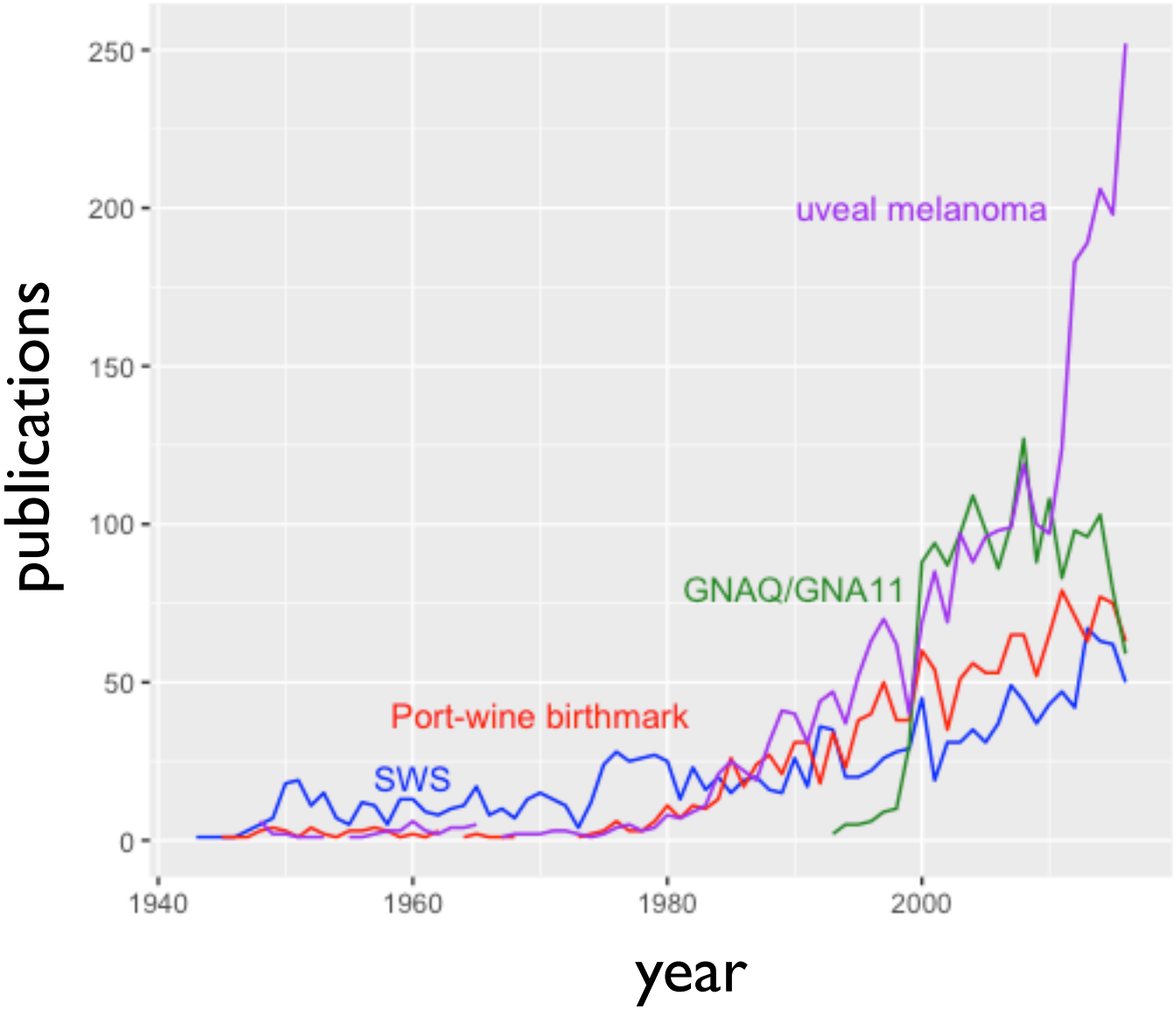
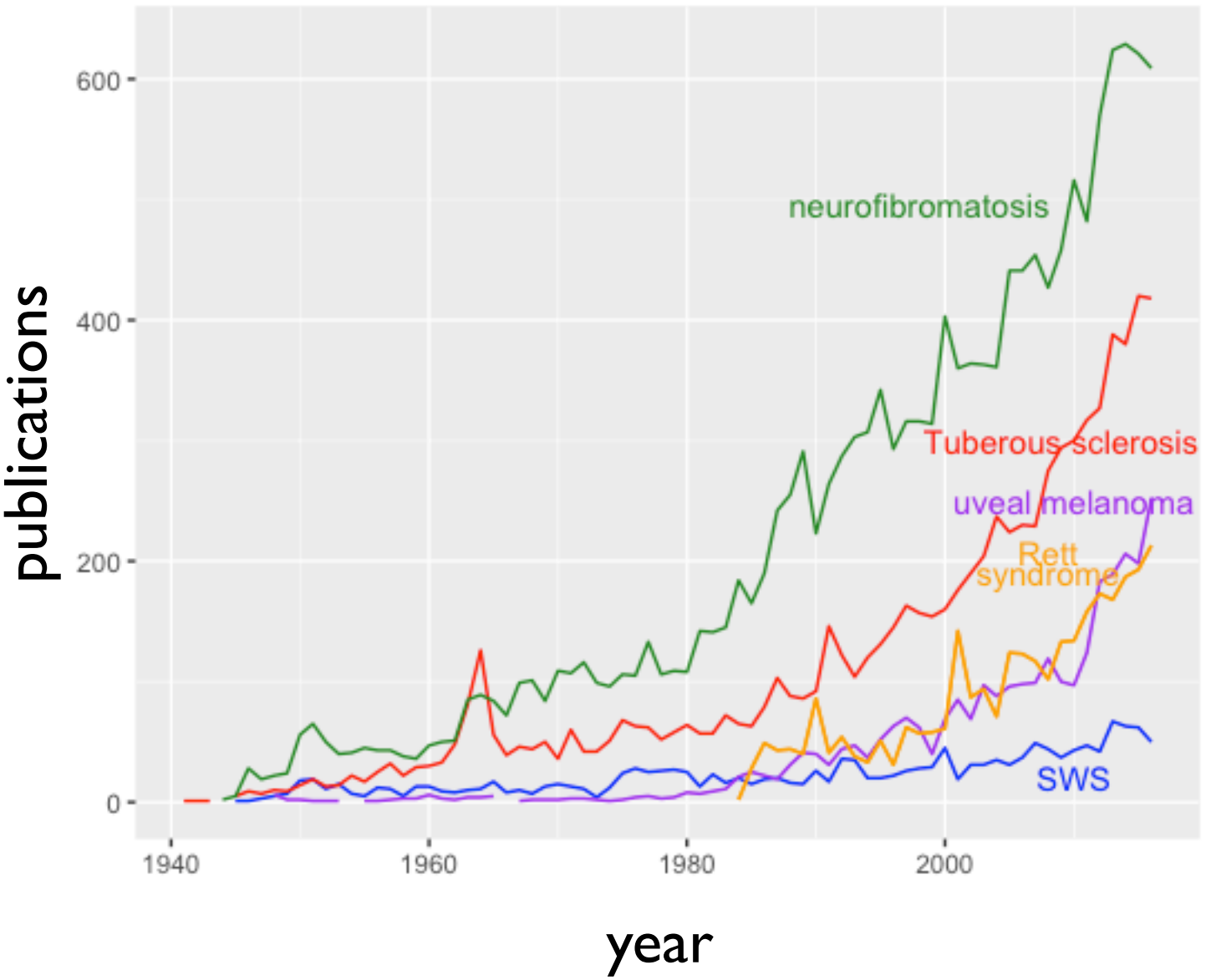
What you can do!

Scientific papers on Sturge-Weber syndrome




publications
100
50
0
1940
1960
1980
2000
year
GNAQ/GNA11
Port-wine birthmark
SWS


publications
250
200
150
100
50
0
1940
1960
1980
2000
year
uveal melanoma
GNAQ/GNA11
Port-wine birthmark
SWS


publications
600
400
200
0
1940
1960
1980
2000
year
neurofibromatosis
Tuberous sclerosis
uveal melanoma
Rett syndrome
SWS

Sturge-Weber syndrome: topics of publications

- analysis
- anatomy and histology
- blood
- blood supply
- cerebrospinal fluid
- classification
- complications
- congenital
- cytology
- diagnosis
- diagnostic imaging
- diet therapy
- drug therapy
- embryology
- epidemiology
- etiology
- genetics
- history
- metabolism
- nursing
- pathology
- physiology
- physiopathology
- psychology
- radiotherapy
- rehabilitation
- statistics and numerical data
- surgery
- therapy
- ultrastructure
- urine
- veterinary

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What you can do!

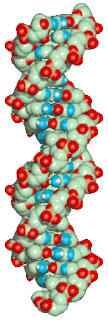
Sturge-Weber syndrome presentation

Features of SWS can be highly variable, and may include:

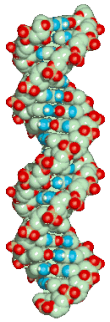
- Port-wine birthmark
- Seizures
- Intellectual disability
- Abnormal capillary venous vessels in the leptomeninges of the brain and choroid
- Glaucoma
- Stroke

Finding a mutation that causes Sturge-Weber syndrome

DNA from port-wine birthmark (presumed **affected**)

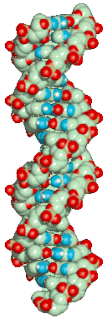


DNA from blood (presumed **unaffected**)



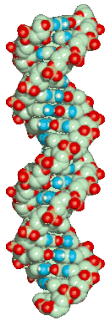
Finding a mutation that causes Sturge-Weber syndrome

DNA from port-wine birthmark (presumed **affected**)



sequence the genome

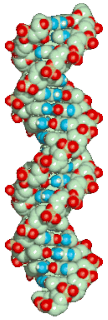
DNA from blood (presumed **unaffected**)



sequence the genome

Finding a mutation that causes Sturge-Weber syndrome

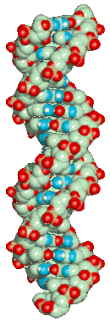
DNA from port-wine birthmark (presumed **affected**)



sequence the genome

compare

DNA from blood (presumed **unaffected**)



sequence the genome

We identified a mosaic mutation in *GNAQ* as causing Sturge-Weber syndrome and port-wine birthmarks.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Matthew D. Shirley, Ph.D., Hao Tang, Ph.D., Carol J. Gallione, B.A., Joseph D. Baugher, Ph.D., Laurence P. Frelin, M.S., Bernard Cohen, M.D., Paula E. North, M.D., Ph.D., Douglas A. Marchuk, Ph.D., Anne M. Comi, M.D., and Jonathan Pevsner, Ph.D.

ABSTRACT

BACKGROUND

The Sturge–Weber syndrome is a sporadic congenital neurocutaneous disorder characterized by a port-wine stain affecting the skin in the distribution of the ophthalmic branch of the trigeminal nerve, abnormal capillary venous vessels in the leptomeninges of the brain and choroid, glaucoma, seizures, stroke, and intellectual disability. It has been hypothesized that somatic mosaic mutations disrupting vascular development cause both the Sturge–Weber syndrome and port-wine stains, and the severity and extent of presentation are determined by the developmental time point at which the mutations occurred. To date, no such mutation has been identified.

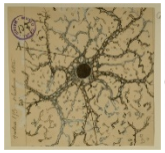
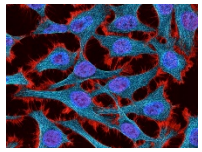
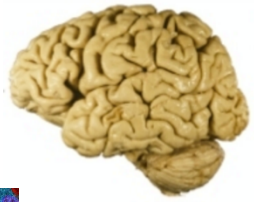
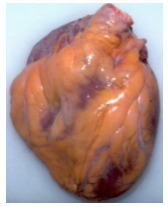
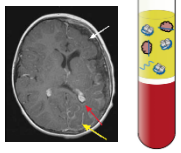
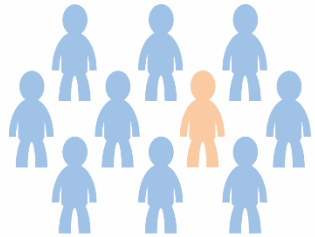
PMID: 23656586

From genotype (your DNA) to phenotype (your body)

- Genotype  Phenotype

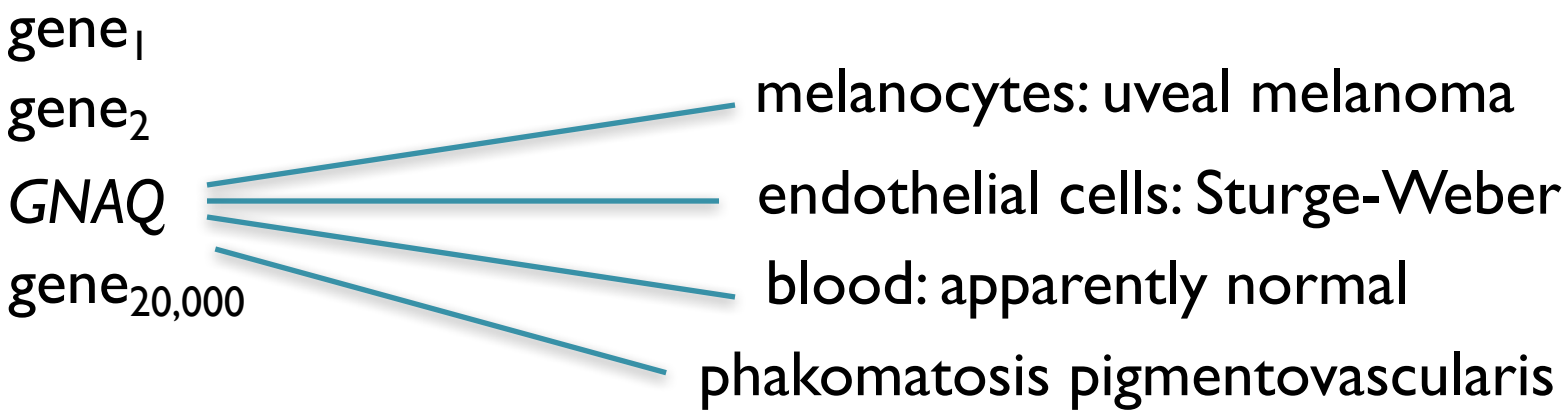
DNA	protein	cell	organ	individual	population

From genotype (your DNA) to phenotype (your body)

DNA	protein	cell	organ	individual	population
$gene_1$ $gene_2$ ... $gene_{20,000}$		 	 	 	

From genotype (your DNA) to phenotype (your body)

DNA	protein	cell	organ	individual	population



One gene mutation can have different consequences: *when* and *where* mutations occur is crucial.

From genotype (your DNA) to phenotype (your body)

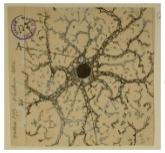
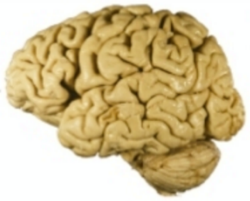
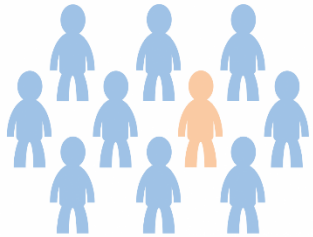
DNA | protein | cell | organ | individual | population

$gene_1$
$gene_2$
...
$gene_{20,000}$

one disease phenotype,
multiple genetic contributors

It's likely that other gene mutations can cause SWS.

From genotype (your DNA) to phenotype (your body)

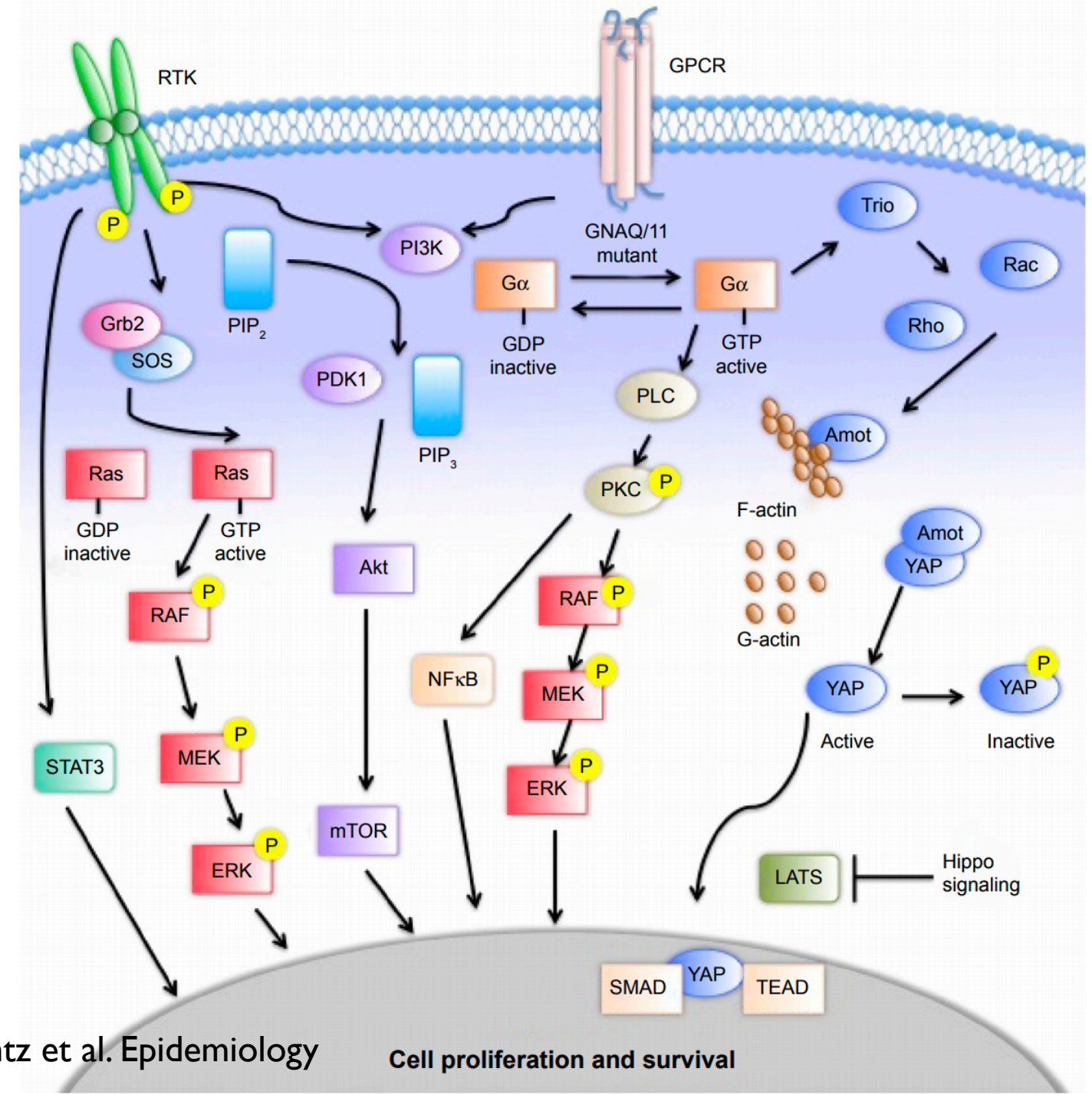
DNA	protein	cell	organ	individual	population
$gene_1$ $gene_2$ ... $gene_{20,000}$					

Now let's look inside a cell to see what a *GNAQ* mutation can do.

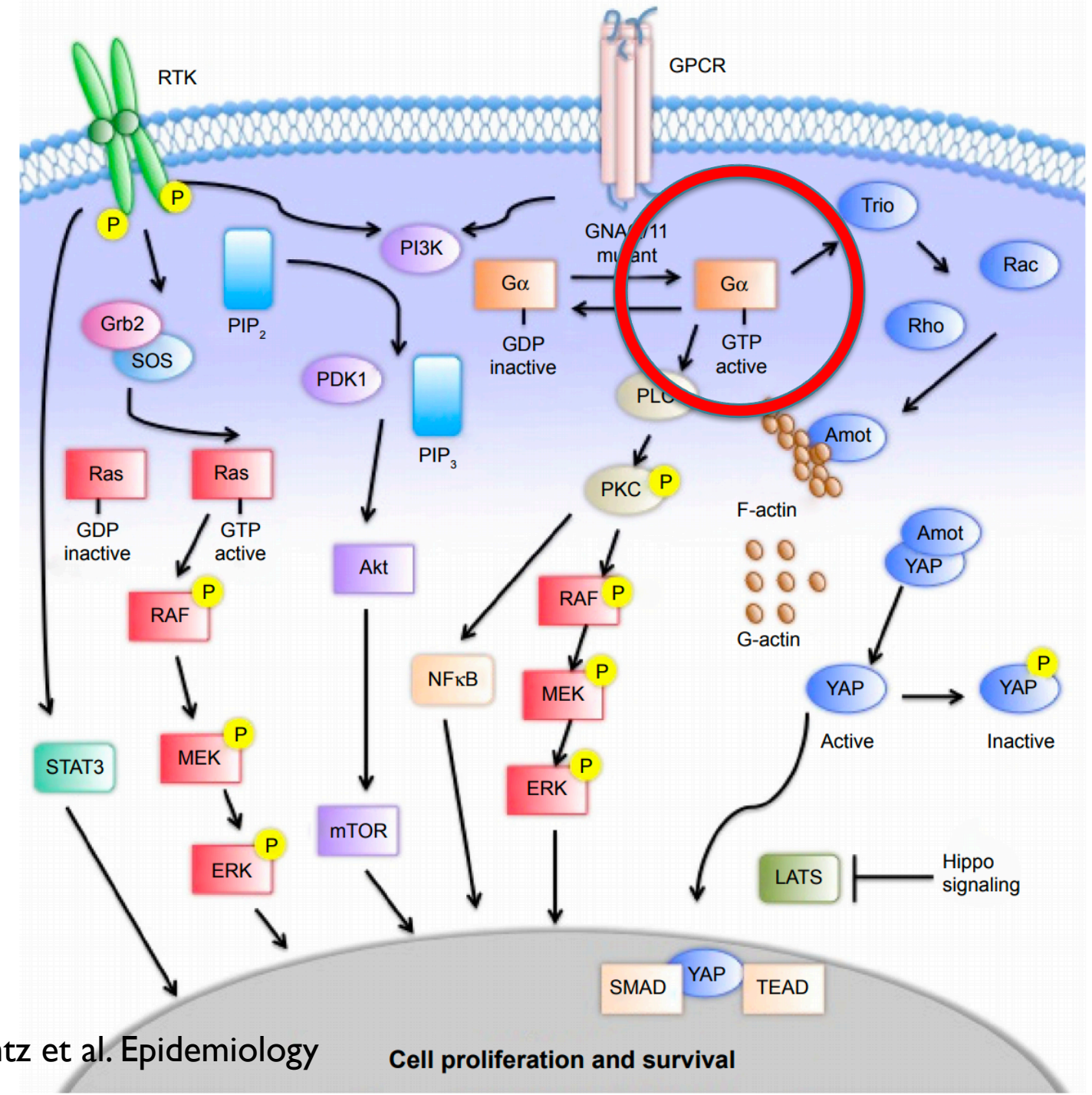
Sturge-Weber syndrome: affected cells

In 2016 and 2017 Dr. Lan Huang, working in Dr. Joyce Bischoff's lab, reported that the *GNAQ* mutation is enriched in endothelial cells.

Lan was a recipient of Lisa's Research Fellowship from the SWF. Great work Dr. Huang!



Krantz et al. Epidemiology



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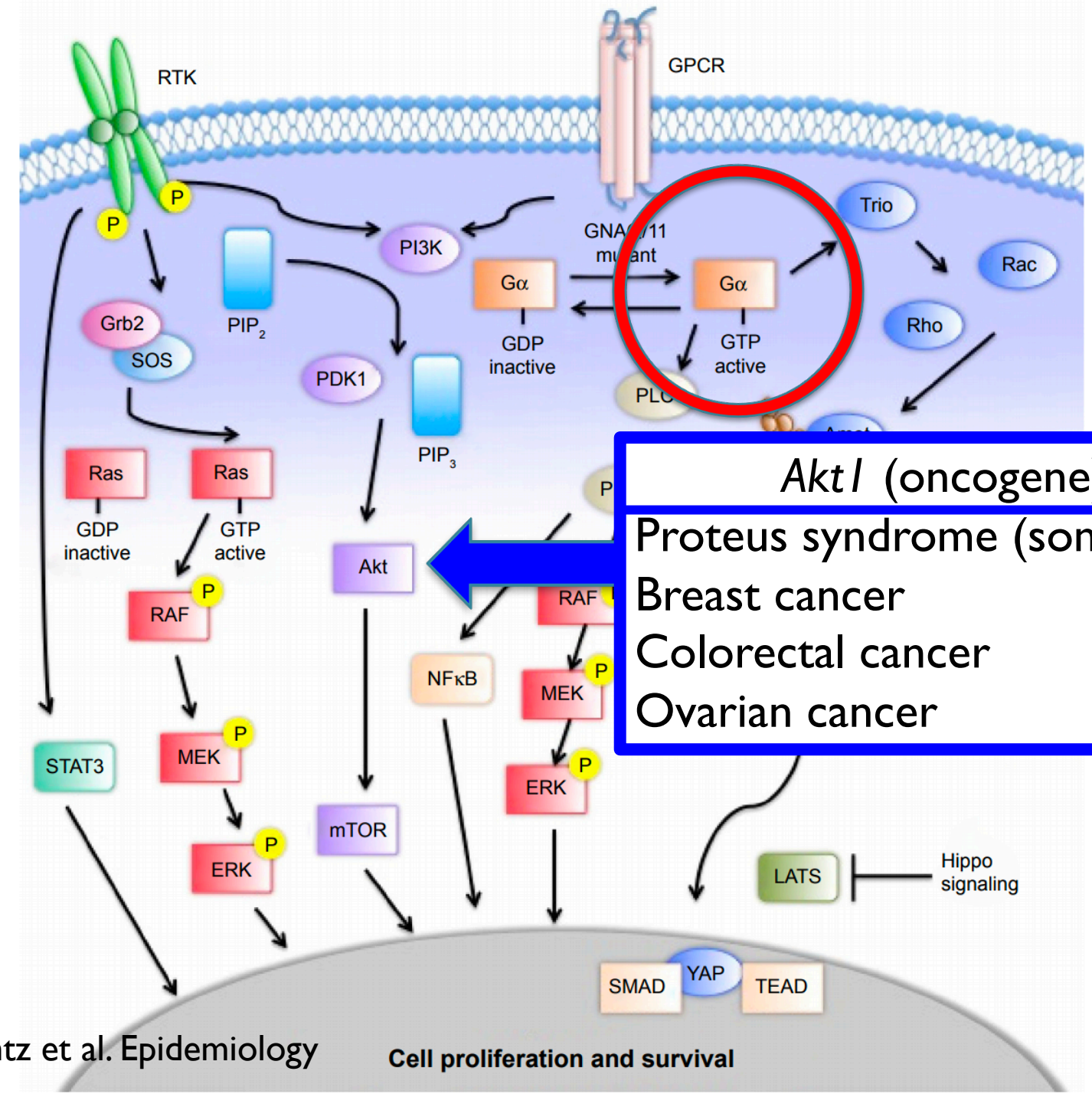


Akt1 (oncogene)

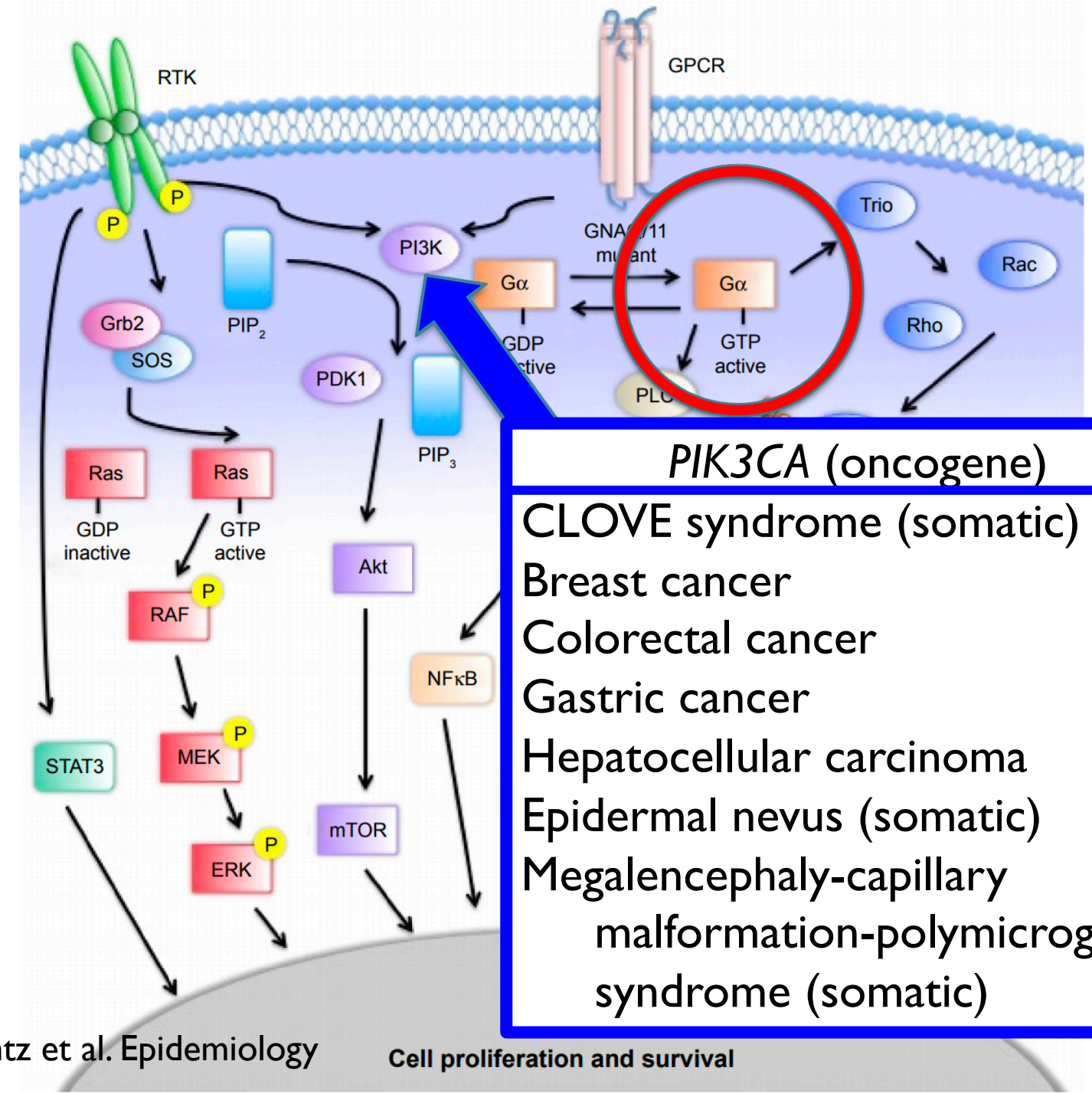
Proteus syndrome (somatic)

Breast cancer

Colorectal cancer

Ovarian cancer

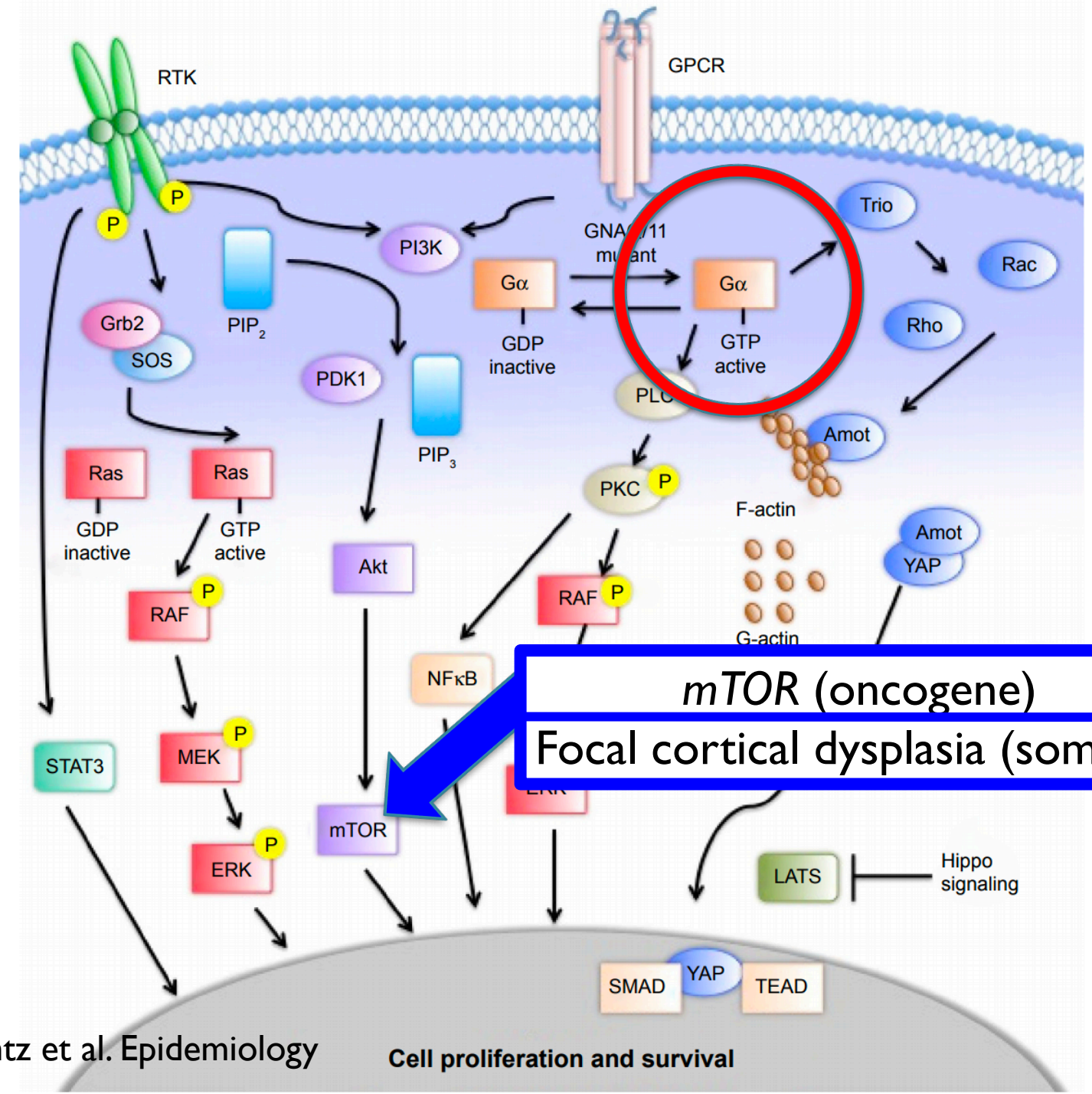
Krantz et al. Epidemiology



PIK3CA (oncogene)

- CLOVE syndrome (somatic)
- Breast cancer
- Colorectal cancer
- Gastric cancer
- Hepatocellular carcinoma
- Epidermal nevus (somatic)
- Megalencephaly-capillary malformation-polymicrogyria syndrome (somatic)

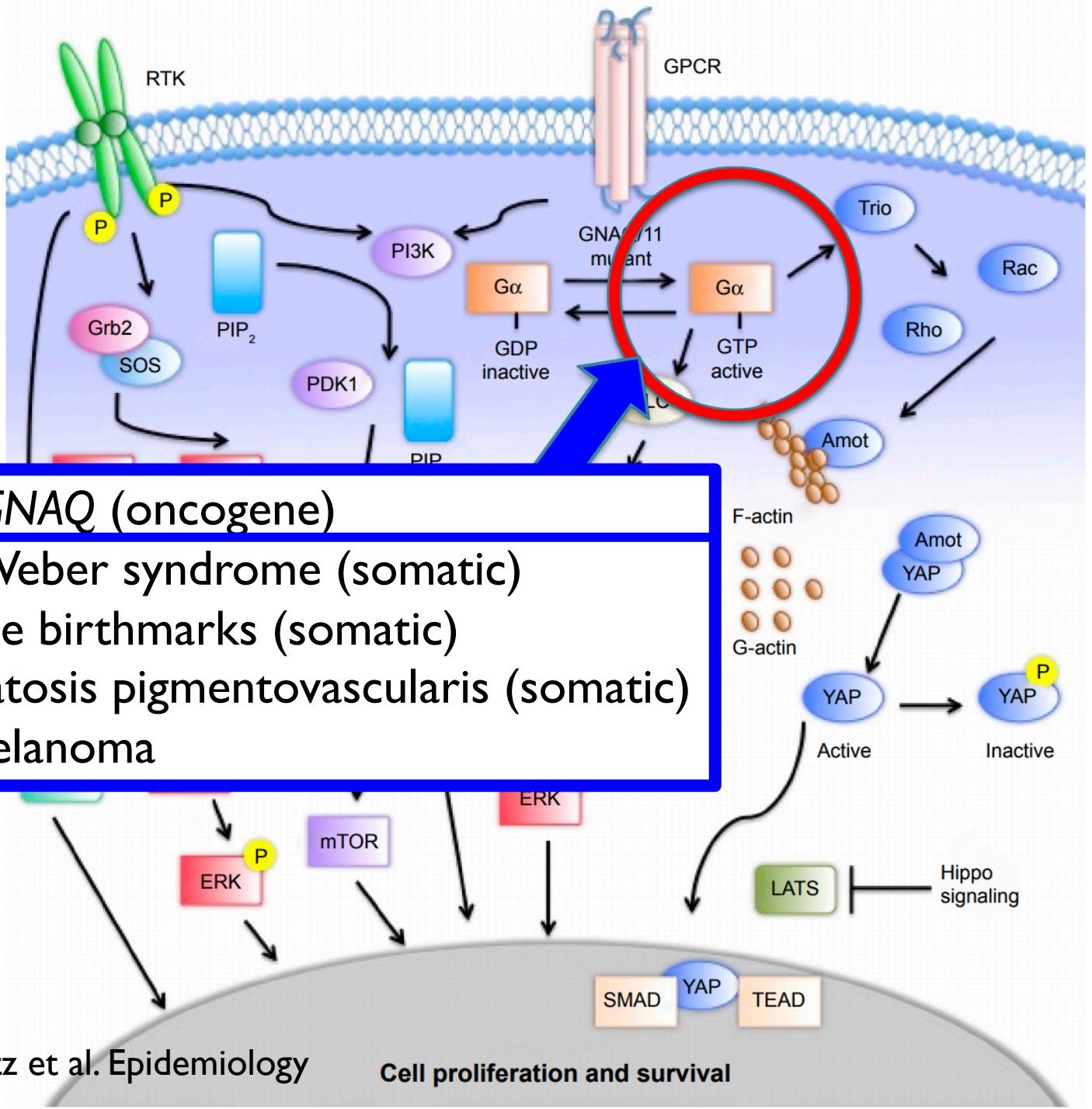
Krantz et al. Epidemiology



mTOR (oncogene)

Focal cortical dysplasia (somatic)

Krantz et al. Epidemiology



GNAQ (oncogene)

Sturge-Weber syndrome (somatic)

Port-wine birthmarks (somatic)

Phakomatosis pigmentovascularis (somatic)

Uveal melanoma

Krantz et al. Epidemiology

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Science behind uveal melanoma

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What you can do!

Sturge-Weber syndrome and uveal melanoma

The same mutation in the *GNAQ* gene can result in SWS or uveal melanoma.

It appears to matter **when** and **where** the mutation occurs.

When: before development versus later in life.

Where: endothelial cells versus melanocytes.

So the SWS community can look to the uveal melanoma community to see what progress they have made.

Gene mutations in uveal melanoma

	Cutaneous melanoma TCGA (N = 333) [12]	Uveal melanoma (primary) TCGA (N = 80) [13]	Uveal melanoma (metastatic) Piperno-Neumann et al. (N = 52) [14]
BRAF	52%	0	1%
NRAS	28%	0	1%
NF1	14%	0	1%
KIT	7%	0	Not reported
GNAQ	2%	50%	63%
GNA11	3%	46%	33%

Komatsubara KM, Carvajal RD. Immunotherapy for the Treatment of Uveal Melanoma: Current Status and Emerging Therapies. Curr Oncol Rep. 2017 Jul;19(7):45. PMID: 28508938

Clinical trials are underway for uveal melanoma

Table 2 Current adjuvant clinical trials in uveal melanoma

Agent	Phase	Mechanism of action	Trial identifier	Status
Dacarbazine + IFN	II	Alkylating agent + immunostimulant	NCT01100528	Active, not recruiting
Fotemustine IV vs observation	III	Alkylating agent	EudraCT 2008-005691-27	Ongoing
Crizotinib	II	c-Met, ALK, *ROS1* kinase inhibitor	NCT02223819	Recruiting
Sunitinib vs valproic acid	II	RTK inhibitor vs HDAC inhibitor	NCT02068586	Recruiting
Cisplatin, tamoxifen + Sunitinib	II	Alkylating agent, estrogen receptor modulator, RTK inhibitor	NCT00489944	Unknown
ICON-1	I	Tissue factor	NCT02771340	Recruiting
Ipilimumab	II	Anti-CTLA4	NCT01585194	Closed
Dendritic cell vaccination	I/II	Immunotherapy	NCT00929019	Active, not recruiting
Dendritic cell vaccination	III	Immunotherapy	NCT01983748	Recruiting

Abbreviation: IV, intravenous.

Krantz et al. Epidemiology

Uveal melanoma: immune-based clinical trials

Agent	Mechanism of action	Phase	Trial ID	Status
Ipilimumab + nivolumab	Anti-CTLA-4 + anti-PD-1	II	NCT01585194	Recruiting
Ipilimumab + nivolumab	Anti-CTLA-4 + anti-PD-1	II	NCT02626962	Recruiting
Pembrolizumab	Anti-PD-1	II	NCT02359851	Recruiting
Ipilimumab + nivolumab + radioembolization	Anti-CTLA-4 + PD-1 + radioembolization	Feasibility	NCT02913417	Not yet recruiting
Pembrolizumab + entinostat	Anti-PD-1 + HDAC inhibitor	II	NCT02697630	Not yet recruiting
IMCgp100	Bi-specific biologic to gp100 and CD3	I/II	NCT02570308	Recruiting
Glembatumumab vedotin	Anti-gpNBM antibody	II	NCT02363283	Recruiting
Epacadostat + MELITAC 12.1	IDO-1 + melanoma vaccine	II	NCT01961115	Recruiting
Tumor infiltrating lymphocytes	Immunotherapy	II	NCT01814046	Recruiting

Komatsubara KM, Carvajal RD. Immunotherapy for the Treatment of Uveal Melanoma: Current Status and Emerging Therapies. Curr Oncol Rep. 2017 Jul;19(7):45. PMID: 28508938

Uveal melanoma

New concepts in the molecular understanding of uveal melanoma

David Reichstein

MONOSOMY 3

Initial reports of nonrandom abnormalities of chromosomes 3, 6 and 8 occurring in uveal melanoma are now nearly 30 years old. Karyotyping demonstrated that loss of a copy of chromosome 3 (aka monosomy 3) occurred along with gain of the q arm of chromosome 8 in uveal melanoma [1]. The

Reichstein D. New concepts in the molecular understanding of uveal melanoma. Curr Opin Ophthalmol. 2017 May;28(3):219-227. PMID: 28257297.

Uveal melanoma

GNAQ

GNAQ is the most commonly mutated gene in uveal melanoma. Most melanoma-associated mutations in GNAQ have been detected at codon 209 within exon 5 of the gene, a region within the catalytic (GTPase) domain of GNAQ. Mutation at this site inactivates the GTPase domain, resulting in a constitutively active GNAQ protein. A constitutively active GNAQ protein results in melanocyte transformation. Mutation of GNAQ occurs in tumors at all stages of malignant progression and is independent of chromosome 3 status or GEP profile. This suggests that mutation in GNAQ is an early event in the development of uveal melanoma [57]. GNAQ mutation profile is thus not a good candidate for prognostication of metastasis [58]. When GNAQ itself is not mutated, mutation of its paralogue GNA11 is often observed. It is estimated that 83% of all uveal melanomas contain mutations of GNAQ or GNA11 [59,60]. GNAQ and GNA11 are not good candidate genes for prognostication of metastasis [61], but because the genes are so often mutated in uveal melanoma, targeting the gene itself or inhibition of its downstream effects has been a focus for development of targeted uveal melanoma therapy [62].

One possible mechanism for GNAQ/GNA11 effect is through activating a protein known as YAP, which controls tissue growth and cell fate through the regulation of cell proliferation and apoptosis [63]. Inhibition of YAP with verteporforin can block tumor growth [64▪]. Functionalized gold nanoparticles have also been developed that target GNAQ mRNA. These can result in knockdown of GNAQ activity with reduction of downstream signals and decreased cell viability in uveal melanoma cells [65▪]. GNAQ/GNA11 mutation may also have effects on the BET family of proteins. These proteins are involved in regulation of key cell division processes such as DNA replication, chromatin remodeling and mRNA transcription. BET inhibitors such as JQ1 can lead to significant inhibition of growth in uveal melanoma cells containing GNAQ/GNA11 mutations [66]. Finally, it has been demonstrated that GNAQ may affect multiple cell signaling pathways through a single node known as ARF6. Blocking ARF6 can reduce growth of GNAQ-dependent uveal melanoma cells, suggesting another possible therapeutic strategy [67].

The SWF has reached out to leading researchers in the field of uveal melanoma.

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What you can do!

We held a SWFIRN meeting in Atlanta last September. We welcomed a set of fantastic speakers, and had an excellent exchange of ideas. Here are some of our research priorities.

Outline

SWS research and SWF: background and goals

Who's publishing on research & what are they doing?

Science behind SWS

Science behind uveal melanoma

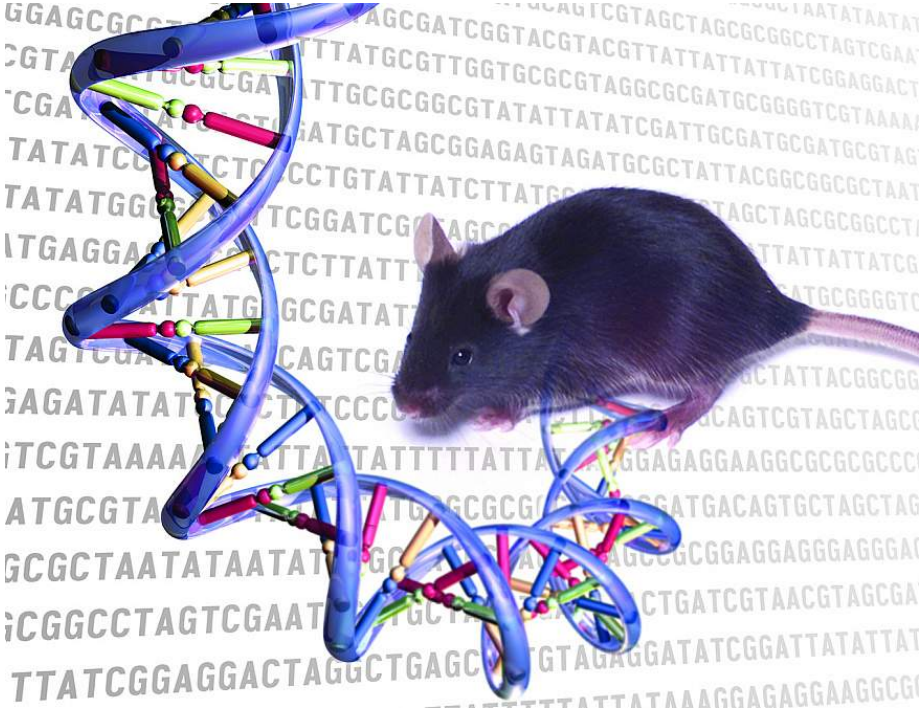
1. Animal models
2. Genomics
3. Biobank
4. Registry
5. Clinical trials

What you can do!

Animal models

We want to create an animal that has the *GNAQ* mutation in order to give it the equivalent of SWS, and then figure out how to fix it.

I'm aware of six groups interested in making a mouse model. We are working on coordinating efforts, and it can be very useful to have multiple mouse models.



Animal models

Two labs have reported mouse models of uveal melanoma involving a *GNAQ* activating mutation (in a different cell type, melanocytes). This leads to better understanding of the consequence of the mutation, and new ideas for therapies.

One lab reported a zebrafish model (of a related gene, *GNA11*).

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What you can do!

Genomics

Genomics is the study of genomes (the collection of DNA that makes up an organism). We can use genomics technologies to sequence all of a person's DNA.

We do not believe every person with SWS (or related conditions) needs to have his/her genome sequenced, at this time, because in most cases it would not lead to improved care.

There are many genomics experiments we would like to do to make more progress toward understanding SWS.

Genomics: a generous gift from Macrogen

Humanizing Genomics
macrogen

Thank you Macrogen for donating sequencing services!

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What you can do!

Establishing a Sturge-Weber syndrome biobank

- Patients and families offer to donate precious cells and tissues to science. What's the plan? Are there informed consent issues?
- The *GNAQ* mutation occurs primarily in endothelial cells, and cell lines have been established from brain biopsies. How can researchers share and access these cell lines?
- Are there standards that we should follow in describing the genotype and phenotype of Sturge-Weber syndrome samples and patients?
- Have these problems been addressed by those studying related diseases?

Establishing a Sturge-Weber syndrome biobank

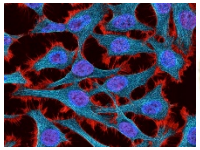
DNA	protein	cell	organ	individual	population

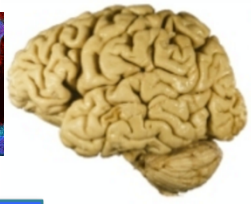
$gene_1$

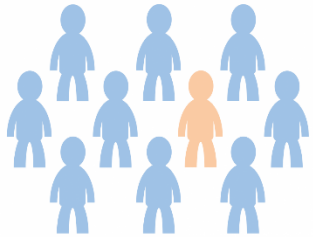
$gene_2$

GNAQ

$gene_{20,000}$







It's important to link clinical data (e.g. from a patient registry) with data generated from biospecimens!

Establishing a Sturge-Weber syndrome biobank

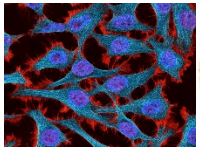
DNA	protein	cell	organ	individual	population

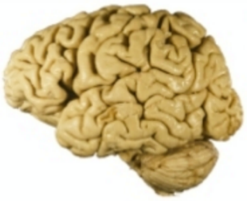
$gene_1$

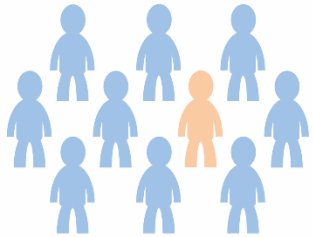
$gene_2$

GNAQ

$gene_{20,000}$







What information do we need to capture about cell lines, brain, and skin samples?

Establishing a Sturge-Weber syndrome biobank

DNA	protein	cell	organ	individual	population

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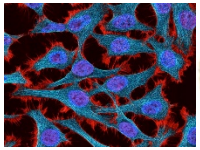
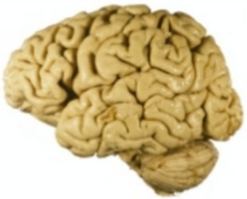
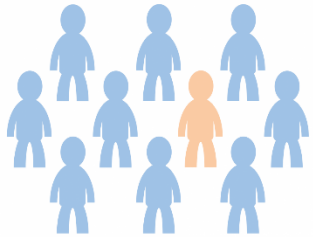
GNAQ

$gene_{20,000}$







What information do we need to capture about cell lines, brain, and skin samples?

How do we relate DNA findings to the samples?

Establishing a Sturge-Weber syndrome biobank

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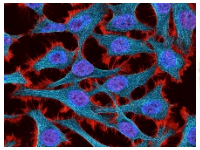

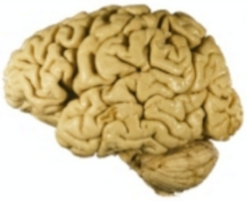

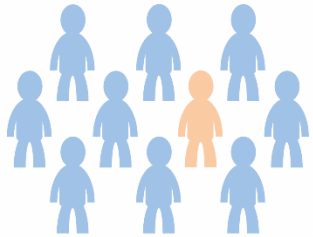

What information do we need to capture about cell lines, brain, and skin samples?

How do we relate DNA findings to the samples?

What information do we need to capture about the phenotypes as we collect samples at diverse sites?

Examples of existing biobanks and projects

- Coriell Biorepository
  The NIGMS collection has >11,000 cell lines and ~6,000 DNA samples.
  https://catalog.coriell.org/

- NIH NeuroBioBank
  6 sites. The University of Maryland Brain & Tissue Bank has distributed 35,000 tissue samples to >900 researchers.
  https://neurobiobank.nih.gov/

- NIH Common Data Elements (CDE) Repository
  "designed to provide access to structured human and machine-readable definitions of data elements."
  https://cde.nlm.nih.gov/home

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What you can do!

Registry

Visit the registry via sturge-weber.org

Please join!!

Registry: why get involved

- Help us understand how SWS, PWB, and related conditions affect people.
- Help us move research and clinical studies forward.
- We do not receive any identifying information about you, your child, or any family members—unless you request that we do.

Registry

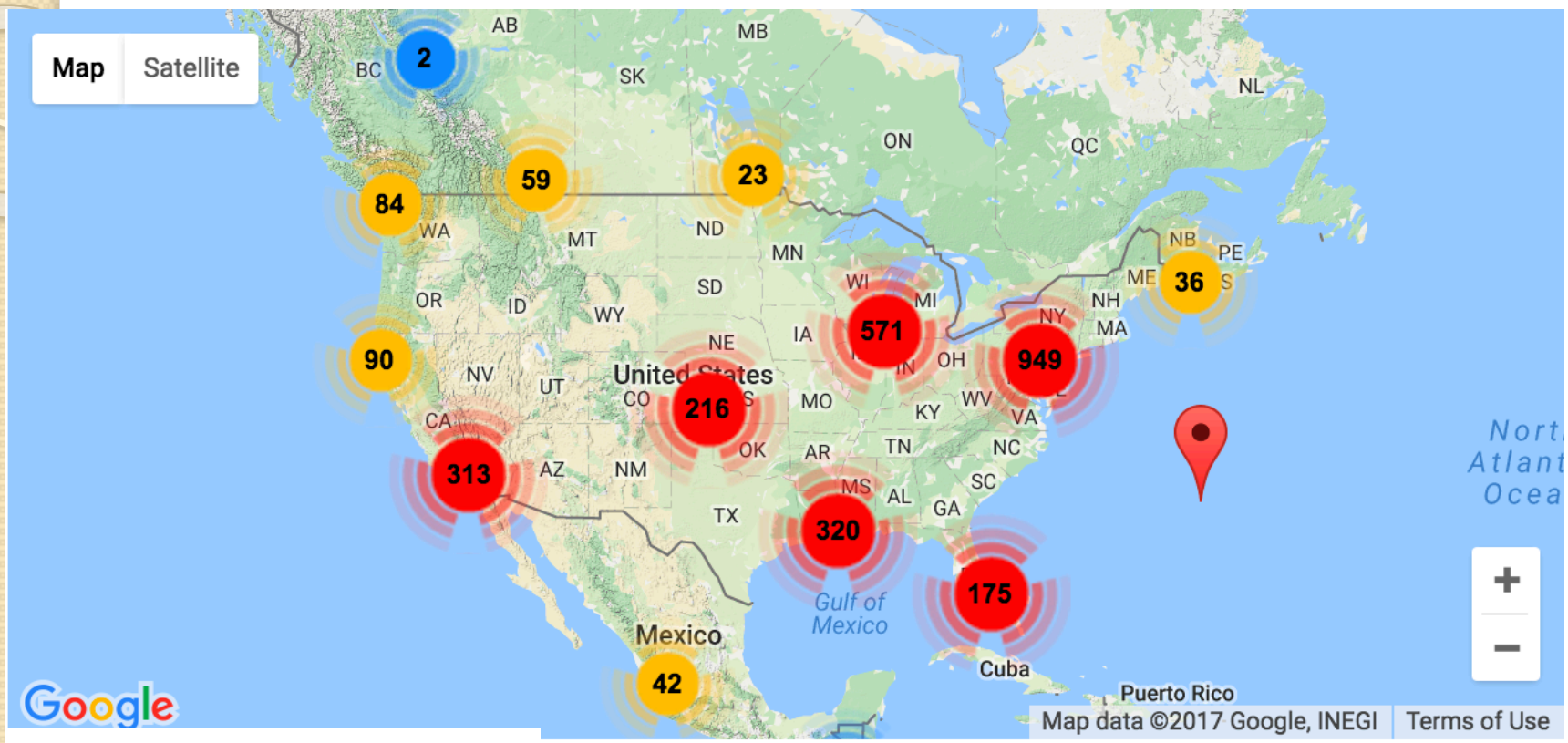
[1] Read "Understanding Your Participation" at https://swsregistry.patientcrossroads.org/

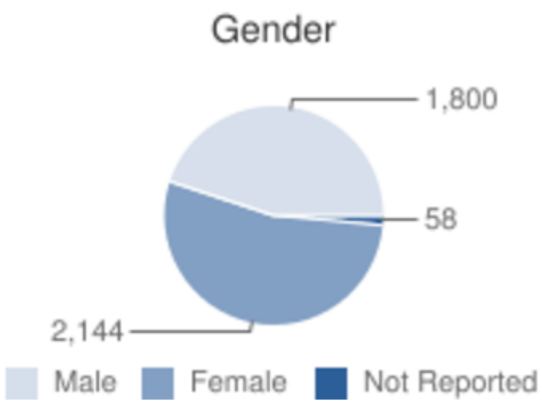
[2] If you agree to participate, then indicate your consent.

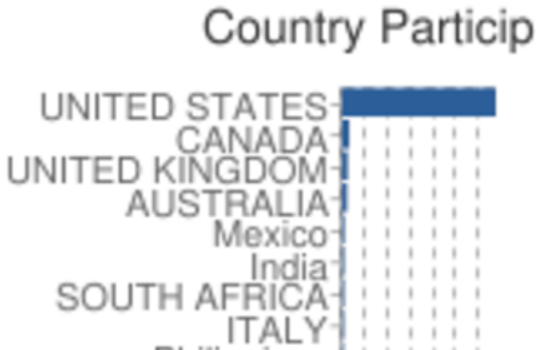
[3] Get a login username and password.

[4] Create a profile and add your information.

Registry: thousands have participated







Registry: areas covered

STURGE-WEBER SURVEY

- **Diagnosis**
- Brain
- Seizures
- Seizure Treatment
- Eye
- Birthmarks
- Growth and Development
- For the Biological Mother
- Oral/Dental
- Medical History
- Quality of Life
- Family History
- Research

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What you can do!

Clinical trials for SWS

According to clinicaltrials.gov there are 5 studies actively recruiting participants.

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Recruiting	Innovative Approaches to Gauge Progression of Sturge-Weber Syndrome	Sturge-Weber Syndrome	
2	☐	Recruiting	Trial of Sirolimus for Cognitive Impairment in Sturge-Weber Syndrome	Sturge-Weber Syndrome	Drug: Sirolimus
3	☐	Recruiting	Treatment of Port-wine Mark in Sturge-Weber Syndrome Using Topical Timolol	Sturge Weber Syndrome; Port-wine Mark	Drug: Timolol; Drug: Preservative free artificial tear gel.
4	☐	Recruiting	Institutional Registry of Haemorrhagic Hereditary Telangiectasia	Haemorrhagic Hereditary Telangiectasia	
5	☐	Recruiting	Lymphatic Anomalies Registry	Lymphatic Malformation; Generalized Lymphatic Anomaly (GLA); Central Conducting Lymphatic Anomaly; CLOVES Syndrome; Gorham-Stout Disease ("Disappearing Bone Disease"); Blue Rubber Bleb Nevus Syndrome; Kaposiform Lymphangiomatosis; Kaposiform Hemangioendothelioma/Tufted Angioma; Klippel-Trenaunay Syndrome; Lymphangiomatosis	

Row	Saved	Status	Study Title	Conditions	Interventions
1	☐	Active, not recruiting	Cannabidiol Expanded Access Study in Medically Refractory Sturge-Weber Syndrome	Sturge-Weber Syndrome	Drug: Cannabidiol
2	☐	Withdrawn	Adjunctive Everolimus (RAD 001) Therapy for Epilepsy in Children With Sturge-Weber Syndrome (SWS)	Sturge Weber Syndrome	Drug: Everolimus
3	☐	Completed	Efficacy and Safety Study of Topical Rapamycin Associated With Pulsed Dye Laser in Patients With Sturge-Weber Syndrome	Sturge- Weber Syndrome	Drug: Drug: Topical Rapamycin
4	☐	Completed	Biomarker Development in Sturge-Weber Syndrome	Sturge-Weber Syndrome	
5	☐	Completed	Use of the Atkins Diet for Children With Sturge Weber Syndrome	Epilepsy; Sturge Weber Syndrome	Dietary Supplement: modified Atkins diet
6	☐	Completed	Incidence of Ocular Antibodies in Patients With Sturge - Weber Syndrome (SWS)	Sturge - Weber Syndrome (SWS)	Other: blood sample tear drop sample
7	☐	Active, not recruiting	French National Cohort of Children With Port Wine Stain	Port Wine Stain; Klippel Trenaunay Syndrome; Parkes Weber Syndrome	Genetic: search for polymorphisms of RASA1 gene
8	☐	Completed	Tranexamic Acid and Epistaxis in Hereditary Hemorrhagic Telangiectasia (HHT)	Hereditary Hemorrhagic Telangiectasia	Drug: Tranexamic acid first, than placebo; Drug: First placebo, than Tranexamic acid.

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What you can do!

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What you can do!

- We are a community. We welcome you to keep actively involved with the Foundation.
- Communicate with the scientists (at events such as this). At a 2016 SWFIRN / PEN meeting in Atlanta the scientists were very eager to hear from families about their questions and priorities.
- Join the registry.
- Feel free to contact me with any questions or concerns (cso@sturge-weber.org).

Thank you!!