PHACE Research and Genetics Updates

Dawn Siegel, MD
Associate Professor Dermatology and Pediatrics
Medical College of Wisconsin/Children's Hospital Wisconsin
June 19th, 2014

Educational Objectives

1. Provide an update on the current status of the PHACE syndrome International Clinical Registry and Genetic Repository

2. Provide an overview of latest publications on PHACE syndrome, focusing on those originating from the PHACE registry

PHACE syndrome International Clinical Registry and Genetic Repository

PHACE Syndrome Clinical Registry and International Repository

2006	Founded the PHACE Syndrome Clinical Registry and Genetic Repository at UCSF with Ilona Frieden.
2010	The registry was relocated to Medical College of Wisconsin in collaboration with Beth Drolet
2011	Joined forces with Denise Metry and the Texas Children's PHACE Syndrome Clinical Registry
2014	Received R01 funding to study the natural history and pathogenesis of PHACE syndrome

Families have joined the registry from around the world:

PHACE registry current numbers:

- 186 individuals enrolled
- 51 additional enrollees from Denise Metry registry, that we hope to enroll into our registry as well
- Total 237 individuals in combined registries

What happens when you enroll in the study?

- We will do consent forms
- We will review your child's medical history
- We will order a small blood draw on your child and both parents if available
- We will do a cheek swab
- We may collect a tissue sample
- We will collect reports, MRI's and other test results and do a survey.

The genetic research

- We are using sequencing techniques to look for small changes in the DNA
- We are also trying to understand the spectrum of medical issues in PHACE syndrome and the natural history

Confirming results

- Confirm any changes found with a second method
- Continue to increase the size of the study to prove and confirm our findings
- For that reason specific results might not be shared with you

Congenital Cardiac, Aortic Arch, and Vascular Bed Anomalies in PHACE Syndrome (from the International PHACE Syndrome Registry)

Michelle L. Bayer, MD[a], Peter C. Frommelt, MD[a], Francine Blei, MD, MBA[b], Johannes M.P.J. Breur, MD, PhD[c], Maria R. Cordisco, MD[d], Ilona J. Frieden, MD[e], Deborah S. Goddard, MD[f], Kristen E. Holland, MD[a], Alfons L. Krol, MD[g], Mohit Maheshwari, MD[a], Denise W. Metry, MD[h], Kimberly D. Morel, MD[i], Paula E. North, MD, PhD[a], Elena Pope, MD, MSc[j], Joseph T. Shieh, MD, PhD[e], James F. Southern, MD, PhD[a], Orli Wargon, MD[k], Dawn H. Siegel, MD[a], and Beth A. Drolet, MD[a,*]

PHACE syndrome represents the association of large infantile hemangiomas of the head and neck with brain, cerebrovascular, cardiac, ocular, and ventral or midline defects. Cardiac and cerebrovascular anomalies are the most common extracutaneous features of PHACE, and they also constitute the greatest source of potential morbidity. Congenital heart disease in PHACE is incompletely described, and this study was conducted to better characterize its features. This study of the International PHACE Syndrome Registry represents the largest central review of clinical, radiologic, and histopathologic data for cardiovascular anomalies in patients with PHACE to date. Sixty-two (41%) of 150 subjects had intracardiac, aortic arch, or brachiocephalic vessel anomalies. Aberrant origin of a subclavian artery was the most common cardiovascular anomaly (present in 31 (21%) of 150 subjects). Coarctation was the second most common anomaly, identified in 28 (19%) of 150 subjects, and can be missed clinically in patients with PHACE because of the frequent association of arch obstruction with aberrant subclavian origin. Twenty-three (37%) of 62 subjects with cardiovascular anomalies required procedural intervention. A greater percentage of hemangiomas were located on the left side of the head and neck in patients with coarctation (46% vs 39%); however, hemangioma distribution did not predict the presence of cardiovascular anomalies overall. In conclusion, PHACE is associated with a high risk of congenital heart disease. Cardiac and aortic arch imaging with detailed assessment of arch patency and brachiocephalic origins is essential for any patient suspected of having PHACE. Longitudinal investigation is needed to determine the long-term outcomes of cardiovascular anomalies in PHACE. © 2013 Elsevier Inc. All rights reserved. (Am J Cardiol 2013;112:1948–1952)

Take home points:

- The most common finding is an abnormal position of the subclavian artery (21%)
- The 2nd most common finding is coarctation of the aorta (19%)
- Around 1/3 of these individuals needed an intervention

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Stroke in Children With Posterior Fossa Brain Malformations, Hemangiomas, Arterial Anomalies, Coarctation of the Aorta and Cardiac Defects, and Eye Abnormalities (PHACE) Syndrome: A Systematic Review of the Literature

Dawn H. Siegel, Kimberly A. Tefft, Teresa Kelly, Craig Johnson, Denise Metry, Patricia Burrows, Elena Pope, Maria Cordisco, Kristen E. Holland, Mohit Maheshwari, Phillip Keith, Maria Garzon, Christopher Hess, Ilona J. Frieden, Heather J. Fullerton and Beth A. Drolet

Stroke. 2012;43:1672-1674; originally published online March 22, 2012;
doi: 10.1161/STROKEAHA.112.650952
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

Stroke risk: Take home points:

- This study was both from the registry and a literature review
- We looked at all reported cases of stroke in PHACE
- We found 22 individuals with PHACE and stroke

Stroke. 2012 Jun;43(6):1672-4. Epub 2012 Mar 22.

Stroke risk: Take home points:

- Narrowing or absence of at least 1 major artery in the brain or neck was reported in 19 of 20 of the cases of stroke
  - 15 had 2 major vessels involved.
- Aortic arch anomalies were reported in 13 of 22 individuals.

Stroke. 2012 Jun;43(6):1672-4. Epub 2012 Mar 22.

Stroke in children with PHACE yndrome: a systematic review of the literature.

- Having a small or missing major cerebral artery increases risk for stroke, especially if more than one vessel is involved.
- Coarctation of the aorta also leads to a higher risk

NIH Public Access
Author Manuscript
J Invest Dermatol. Author manuscript; available in PMC 2014 April 01.

Published in final edited form as:
J Invest Dermatol. 2013 March ; 133(3): 677–684. doi:10.1038/jid.2012.367.

Copy Number Variation analysis in 98 individuals with PHACE syndrome

DH Siegel[1], JTC Shieh[2], EK Kwon[3], E Baselga[4], F Blei[5], M Cordisco[6], WB Dobyns[7], K Duffy[8], MC Garzon[9], DL Gibbs[10], JF Grimmer[11], SJ Hayflick[12], AL Krol[13], PY Kwok[14], R Lorier[15], A Matter[15], S McWeeney[16], D Metry[17], S Mitchell[18], E Pope[19], J Santoro[3], DA Stevenson[20], PB Toydemir[21], B Wilmot[16], E Worthey[22], IJ Frieden[23], BA Drolet[1], and U Broeckel[22]

[1]Departments of Dermatology and Pediatrics, Medical College of Wisconsin, Milwaukee, WI

[2]Department of Pediatrics, University of California, San Francisco, San Francisco, CA

[3]Department of Dermatology, Medical College of Wisconsin, Milwaukee, WI

[4]Department of Dermatology, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain

[5]Department of Hematology and Oncology, Vascular Birthmark Institute of New York, New York, NY

[6]Department of Dermatology, Hospital de Pediatria JP Garrahan, Buenos Aires, Argentina

[7]Departments of Pediatrics and Neurology, University of Washington, Seattle, WA

[8]Department of Radiology, Medical College of Wisconsin, Milwaukee, WI

[9]Departments of Dermatology and Pediatrics, Columbia University, Columbia, NY

[10]Department of Bioinformatics and Computational Biology, Oregon Health & Science University, Portland, OR

[11]Departments of Surgery and Otolaryngology, University of Utah, Salt Lake City, UT

[12]Departments of Molecular and Medical Genetics, Pediatrics, and Neurology, Oregon Health & Science University, Portland, OR

[13]Departments of Dermatology and Pediatrics, Oregon Health & Science University, Portland, OR

[14]Department of Cardiovascular Research, University of California, San Francisco, San Francisco, CA

[15]Department of Human and Molecular Genetics, Medical College of Wisconsin, Milwaukee, WI

[16]Department of Biostatistics, Oregon Health & Science University, Portland, OR

Corresponding Author: Dawn H. Siegel, MD, Department of Dermatology, Medical College of Wisconsin, 8701 Watertown Plank

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Copy Number Variation- Take home points

- Copy number variation is having a missing piece or an extra piece of a chromosome. Sometimes this can be the cause of a disease.
- There were no rare copy number changes that occurred in more than one subject.

Original Article

Molecular Syndromology

Mol Syndromol 2013;4:114–118
DOI: 10.1159/000343489

Invited and accepted: August 20, 2012
by M. Vikkula
Published online: November 16, 2012

X Chromosome-Inactivation Patterns in 31 Individuals with PHACE Syndrome

C.T. Sullivan[a] S.L. Christian[a] J.T.C. Shieh[c] D. Metry[d] F. Blei[e] A. Krol[f]
B.A. Drolet[g] I.J. Frieden[b] W.B. Dobyns[a, b] D.H. Siegel[f]

[a]Center for Integrative Brain Research, Seattle Children's Research Institute, and [b]Departments of Pediatrics and Neurology, University of Washington, and Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, Wash., [c]Division of Medical Genetics, Department of Pediatrics and Institute for Human Genetics, University of California San Francisco, San Francisco, Calif., [d]Department of Dermatology and Pediatrics, Texas Children's Hospital, Houston, Tex., [e]Vascular Birthmark Institute of New York, St. Luke's Roosevelt Hospital, New York, N.Y., [f]Department of Dermatology, Oregon Health and Science University, Portland, Oreg., [g]Department of Dermatology and Pediatrics, Medical College of Wisconsin, Children's Hospital of Wisconsin, Milwaukee, Wisc., USA

X Inactivation take home points

- Females have 2 copies of the X chromosome.
- To make sure there is not an overdose of one of the genes, one of the two copies is turned off in each cell
- An example of X inactivation is the Brindle coat color in Boxer dogs. The fur pigmentation gene is X-linked, and depending on which copy of the X chromosome each cell chooses to leave active, either an white, brown or black coat color results.

X Inactivation take home points

- To protect the patient from disease, sometimes the X chromosome can be preferentially inactivated to protect against the disease.
- No pattern of X inactivation was found in the PHACE cohort
- Conclusion: We do not think X inactivation plays a role in the cause of PHACE syndrome

Studies that have been generated from the registry:

Congenital cardiac, aortic arch, and vascular bed anomalies in **PHACE** syndrome (from the International **PHACE** Syndrome Registry). Bayer ML, Frommelt PC, Blei F, Breur JM, Cordisco MR, Frieden IJ, Goddard DS, Holland KE, Krol AL, Maheshwari M, Metry DW, Morel KD, North PE, Pope E, Shieh JT, Southern JF, Wargon O, **Siegel** DH, Drolet BA. Am J Cardiol. 2013 Dec 15;112(12):1948-52. doi: 10.1016/j.amjcard.2013.08.025.

X Chromosome-Inactivation Patterns in 31 Individuals with **PHACE** Syndrome. Sullivan CT, Christian SL, Shieh JT, Metry D, Blei F, Krol A, Drolet BA, Frieden IJ, Dobyns WB, **Siegel** DH. Mol Syndromol. 2013 Mar;4(3):114-8. doi: 10.1159/000343489. Epub 2012 Nov 16.

Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Drolet BA, Frommelt PC, Chamlin SL, Haggstrom A, Bauman NM, Chiu YE, Chun RH, Garzon MC, Holland KE, Liberman L, MacLellan-Tobert S, Mancini AJ, Metry D, Puttgen KB, Seefeldt M, Sidbury R, Ward KM, Blei F, Baselga E, Cassidy L, Darrow DH, Joachim S, Kwon EK, Martin K, Perkins J, **Siegel** DH, Boucek RJ, Frieden IJ.Pediatrics. 2013 Jan;131(1):128-40. doi: 10.1542/peds.2012-1691.

Copy number variation analysis in 98 individuals with **PHACE** syndrome. **Siegel** DH, Shieh JT, Kwon EK, Baselga E, Blei F, Cordisco M, Dobyns WB, Duffy KJ, Garzon MC, Gibbs DL, Grimmer JF, Hayflick SJ, Krol AL, Kwok PY, Lorier R, Matter A, McWeeney S, Metry D, Mitchell S, Pope E, Santoro JL, Stevenson DA, Bayrak-Toydemir P, Wilmot B, Worthey EA, Frieden IJ, Drolet BA, Broeckel U. J Invest Dermatol. 2013 Mar;133(3):677-84. doi: 10.1038/jid.2012.367.

Propranolol use in **PHACE** syndrome with cervical and intracranial arterial anomalies: collective experience in 32 infants. Metry D, Frieden IJ, Hess C, **Siegel** D, Maheshwari M, Baselga E, Chamlin S, Garzon M, Mancini AJ, Powell J, Drolet BA. Pediatr Dermatol. 2013 Jan-Feb;30(1):71-89. doi: 10.1111/j.1525-1470.2012.01879.x. Epub 2012 Sep 20

Candidate locus analysis for **PHACE** syndrome. Mitchell S, **Siegel** DH, Shieh JT, Stevenson DA, Grimmer JF, Lewis T, Metry D, Frieden I, Blei F, Kayserili H, Drolet BA, Bayrak-Toydemir P. Am J Med Genet A. 2012 Jun;158A(6):1363-7. doi: 10.1002/ajmg.a.35341.

Stroke in children with posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities (**PHACE**) syndrome: a systematic review of the literature. **Siegel** DH, Tefft KA, Kelly T, Johnson C, Metry D, Burrows P, Pope E, Cordisco M, Holland KE, Maheshwari M, Keith P, Garzon M, Hess C, Frieden IJ, Fullerton HJ, Drolet BA. Stroke. 2012 Jun;43(6):1672-4. doi: 10.1161/STROKEAHA.112.650952.

Cervical and intracranial arterial anomalies in 70 patients with **PHACE** syndrome. Hess CP, Fullerton HJ, Metry DW, Drolet BA, **Siegel** DH, Auguste KI, Gupta N, Haggstrom AN, Dowd CF, Frieden IJ, Barkovich AJ. AJNR Am J Neuroradiol. 2010 Nov;31(10):1980-6. doi: 10.3174/ajnr.A2206 .

Risk for **PHACE** syndrome in infants with large facial hemangiomas. Haggstrom AN, Garzon MC, Baselga E, Chamlin SL, Frieden IJ, Holland K, Maguiness S, Mancini AJ, McCuaig C, Metry DW, Morel K, Powell J, Perkins SM, **Siegel** D, Drolet BA. Pediatrics. 2010 Aug;126(2):e418-26. doi: 10.1542/peds.2009-3166. Epub 2010 Jul 19.

Consensus Statement on Diagnostic Criteria for **PHACE** Syndrome. Metry D, Heyer G, Hess C, Garzon M, Haggstrom A, Frommelt P, Adams D, **Siegel** D, Hall K, Powell J, Frieden I, Drolet B; **PHACE** Syndrome Research Conference. Pediatrics. 2009 Nov;124(5):1447-56. doi: 10.1542/peds.2009-0082.

A comparison of disease severity among affected male versus female patients with **PHACE** syndrome. Metry DW, **Siegel** DH, Cordisco MR, Pope E, Prendiville J, Drolet BA, Horii KA, Stein SL, Frieden IJ.J Am Acad Dermatol. 2008 Jan;58(1):81-7.

Pending publications:

- Dental anomalies in PHACE syndrome
- Speech and Swallow Issues in PHACE syndrome

Ongoing and future studies

- The Spectrum of Headaches in PHACE
- The Spectrum of Brain Anomalies in PHACE
- Cardiac Surgery in PHACE
- Health Supervision Guidelines
- Prenatal risk factors for the Development of PHACE

Thank you to all of the families who are participating in this study!

Thank you to our funders and support organizations!

phace syndrome™ community

American Skin Association

NOVA

NIAMS
National Institute of Arthritis and Musculoskeletal and Skin Diseases
NATIONAL INSTITUTES OF HEALTH

Greater Milwaukee Foundation

DF

PeDRA Pediatric Dermatology Research Alliance