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Original Article

Leveraging a Sturge-Weber Gene Discovery: An Agenda for Future Research

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ABSTRACT

Sturge-Weber syndrome (SWS) is a vascular neurocutaneous disorder that results from a somatic mosaic mutation in GNAQ, which is also responsible for isolated port-wine birthmarks. Infants with SWS are born with a cutaneous capillary malformation (port-wine birthmark) of the forehead or upper eyelid which can signal an increased risk of brain and/or eye involvement prior to the onset of specific symptoms. This symptom-free interval represents a time when a targeted intervention could help to minimize the neurological and ophthalmologic manifestations of the disorder. This paper summarizes a 2015 SWS workshop in Bethesda, Maryland that was sponsored by the National Institutes of Health. Meeting attendees included a diverse group of clinical and translational researchers with a goal of establishing research priorities for the next few years. The initial portion of the meeting included a thorough review of the recent genetic discovery and what is known of the pathogenesis of SWS. Breakout sessions related to neurology, dermatology, and ophthalmology aimed to establish SWS research priorities in each field. Key priorities for future development include the need for clinical consensus guidelines, further work to develop a clinical trial network, improvement of tissue banking for research purposes, and the need for multiple animal and cell culture models of SWS.

Keywords: Sturge-Weber syndrome, GNAQ, somatic mutation, port-wine birthmark, glaucoma, seizures

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Introduction

The National Institutes of Health (NIH) sponsored a workshop on April 19-20 in Bethesda, Maryland, that convened a diverse group of clinical and translational researchers with a goal of discussing and agreeing on a research agenda for the next few years. The need for this workshop was highlighted by the recent discovery of the somatic mosaic mutation in *GNAQ* that is responsible for both isolated port-wine birthmarks (PWBs) and Sturge-Weber syndrome (SWS).[1] This discovery underlies the need to develop new collaborations and to set focused research priorities for the optimal use of resources. The Organizing Committee (see list of participants at the end of this article in Appendix) envisioned a workshop that focused on the recent updates and gaps in our knowledge in a multidisciplinary fashion and with an approach that would encourage the participation of attendees, trainees, and young investigators. The morning session of the first day featured a series of talks designed to provide the participants with a brief review of the salient features of SWS and an overview of what is now known about the somatic mutation in *GNAQ* and the pathogenesis of SWS. By bringing together translational researchers and clinician researchers already involved with SWS and those with expertise in other biomedical fields related to these molecular pathways, the workshop enabled novel interactions and discussions around SWS.

During the afternoon of the first day the participants attended breakout sessions in neurology, ophthalmology, or dermatology. Presentations were followed by a 90-minute discussion by attendees of the session, moderated by the chair with the goal of identifying several main priorities to bring to the group. The results of the breakout sessions were presented by the session chairs the following day and discussed by the entire group. The priorities identified by all three groups were identified, and the steps required to address these research priorities were discussed. The workshop ended with a session on the steps required to move clinical drug trials forward for the discovery of new and effective treatments for SWS. E-mail discussions, which followed the meeting and are summarized here, were centered on the four research priorities identified: clinical consensus, Clinical Trials Network, tissue banking, and animal and cell culture model development. Here, we present a summary of the proceedings from this workshop and of the discussions that followed.

SWS and GNAQ

SWS has long been suspected to result from a somatic mutation.[2,3] In 2013 a somatic nonsynonymous single-nucleotide variant (c.548G→A, p.Arg183Gln) in *GNAQ* was identified.[1] This R183Q mutation is associated with most of the SWS tissue and isolated PWB samples tested. The *GNAQ* gene codes for the protein Gαq, which is part of the trimeric G protein (guanine nucleotide–binding protein) associated with a subset of the G-protein–coupled receptors. When activated by the G-protein–coupled receptor ligand, Gαq binds GTP and releases GDP, dissociates from the trimeric protein complex, and activates downstream pathways. Hydrolysis of GTP to GDP and reassociation of the trimeric G protein with the GPRC result in inactivation of these pathways.[4] The R183Q mutation in *GNAQ* is predicted to result in a protein with impaired autohydrolysis of activated Gαq and therefore impaired inactivation of Gαq. The current understanding and data suggest that the mutation results in hyperactivation of downstream pathways, which include RAS-MEK-ERK, Hippo-Yap,[5] and, indirectly, mTOR (Fig 1). Some evidence of this constitutive hyperactivation of downstream pathways has been demonstrated in cells transiently transfected with the R183Q mutation.[1] In uveal melanocytes the R183Q and the Q209L mutation in *GNAQ* results in uveal melanoma.[5]

This new knowledge holds promise for targeted treatments aimed at blocking these overactivated pathways, and this workshop was focused on identifying the most pressing goals for SWS research.

From the breakout sessions

Neurology

The neurology breakout session focused on three main areas: (1) the clinical difficulties surrounding the diagnosis of brain involvement, (2) the need to identify the optimal windows for effective treatment, and (3) the practical application of the discovery of the somatic mutation in *GNAQ* to the treatment of the neurological involvement in SWS. Research has demonstrated that magnetic resonance imaging (MRI) with gadolinium contrast may be necessary to diagnose SWS and that postcontrast flair and susceptibility weighted imaging can aid in the sensitivity of this imaging.[7,8] Even so, MRI still lacks sensitivity in very young patients, and this remains a diagnostic issue. Electroencephalography (EEG) and quantitative EEG have both demonstrated promise as biomarkers to aid in the timing of neuroimaging.[9] However, these studies and the precise timing of MRI for the optimal diagnosis of SWS brain involvement require further investigation. The natural history of SWS is highly variable, and most published studies are either cross-sectional or short-term longitudinal studies over a few years. Two factors, the extent of brain involvement and the age of seizure onset, have been identified as predictive of neurological outcome and epilepsy severity.[10,11] In addition, the presence of epilepsy and frequency of seizures have been correlated with greater risk for a variety of intellectual, behavioral, and mood concerns.[12] Additional studies are required to better stratify patients into risk groups.

Furthermore a better understanding of how the mutation results in SWS vascular malformations could aid in the development of new treatments. It would also help our understanding of the optimal timing of treatment. Biomarker development will require access to brain, skin, and eye tissue and to blood and urine. One topic area