2021 Gatlinburg Conference Symposium Submission

EXAMPLE

Symposium Title: Patient-Researcher Partnerships Across Rare Genetic Forms of NDD and ASD

Chair: Shafali Spurling Jeste[1] and Alycia Halladay[2],

Discussants: Wendy Chung[3]

Overview: Although Intellectual and Developmental Disabilities (IDDs) are not rare, a host of genetic etiologies have been identified over the last decade that cause IDDs and help to explain the vast heterogeneity of the condition. In fact, as better resolution genetic testing becomes the clinical gold standard in the evaluation of a child with either autism spectrum disorder (ASD) or IDD, a rapidly increasing number of children with specific genetic etiologies are identified. Each of these genetic syndromes is considered a rare disease (with prevalence rates ranging from 1/50,000 – 1/6,000), but taken together they account for up to ~15% of ASD and up to 40% of cases of IDD. Currently, there are over 30 patient advocacy groups (PAGs) that support these rare disease causes of IDDs, with a growth of about 5 a year. One area of focus for these PAGs has been clinical trial readiness, and these patient groups have made considerable efforts to address the challenges that undermine progress in clinical trial readiness, including (1) lack of comprehensive clinical characterization to define clinical endpoints for trials, (2) limited natural history studies, including registries, to understand the life course of the disease, especially at each end of the lifespan (infancy and adulthood) and (3) inadequate scalability of research methods, which, in turn, limits access to research to families across the world, (4) insufficient biomarker development for trials, (5) paucity of comprehensive and accessible resources about both clinical care and research for families, particularly those with new diagnoses who are navigating a somewhat obscure healthcare landscape, and (6) inadequate preclinical models that are informed by the clinical features of the conditions that, ultimately, will improve drug discovery and testing. This symposium will provide three perspectives and experiences (clinical researcher, PAG leadership, and neuroscientist) on the potential for partnerships between PAGS and researchers to advance clinical trial readiness across rare genetic disorders of IDDs. We will end with an introduction to group called AGENDA (Alliance for Genetic Etiologies of Neurodevelopmental Disorders and Autism) that seeks to convene leaders across rare disorder PAG's with clinicians and researchers to develop common approaches to solve the major gaps in the field of syndromic IDDs.

Paper 1 of 3

Paper Title: Clinical Research Partnerships with PAGs – Experiences from Dup15q Syndrome

Authors: Shafali Spurling Jeste[1], Charlotte Distefano[1] and Vanessa Vogel-Farley[4]

Introduction: As increasing number of children and adults with genetic causes for their IDD are identified, there is a growing opportunity for collaboration between syndrome specific patient advocacy groups (PAGs) and researchers, with the goal of gathering data from a larger cohort of individuals to better characterize clinical features, natural history of the condition and meaningful endpoints for trials. Duplications of chromosome 15q11.2-13.1 represent one of the most common copy number variants causing IDDs, and over the past 5 years, the Dup15q Alliance has partnered with researchers to develop methods to accelerate these clinical research efforts, with the primary goals

[1] University of California at Los Angeles
[2] Autism Science Foundation and Rutgers University
[3] Columbia University and Simons Foundation for Autism Research

[4] Dup15qAlliance

being the examination of: (1) properties of standardized assessments (both direct assessment and parent questionnaires) and their ability to capture heterogeneity in a condition characterized by severe ID and epilepsy; (2) cognitive and behavioral features of the syndrome, particularly as they may be influenced by epilepsy and genetic subtype; (3) features of the EEG biomarker that defines this condition. These goals can only be addressed with large sample sizes that are unable to be collected at individual research sites.

Methods: Researchers at UCLA created a team and developed a structured protocol to collect data at the biannual Dup15q syndrome family meetings (Orlando, 2015; Redondo Beach, 2017; Houston, 2019). Data collection included high density EEG (Orlando only), direct cognitive and behavioral assessments (Orlando and Redondo Beach), online parent questionnaires (all three meetings), and tutorials on uploading clinical EEG and neuroimaging data to a common portal (Houston). Other families that consented to participate in research who were unable to be tested at the meetings were provided remote links to a battery of online questionnaires, with detailed instructions on survey completion.

Results: Data from 90 individuals from the US and international locations (Europe, Middle East) have been collected through this process, with age range of 1-35. When focusing on the pediatric cohort (ages 2.5-18), the total sample size includes 62 children with behavioral data (Distefano et al, 2019 *in press*) and 41 children with usable EEG data (Saravanpandian, 2019, under review). Across all participants, there was a wide range of abilities. Although adaptive behavior was strongly associated with cognitive ability, adaptive abilities were higher on average than cognitive scores. Measures of autism symptoms were highly associated with cognitive ability, while parent report of challenging behavior was not. Several parent report measures, such as the CBCL and the SRS, gave limited data given their reliance on spoken language. Cognitive abilities were best captured by generation of ratio IQ scores (tested age / chronological age) rather than standard scores, given the low IQ scores of many participants. The EEG biomarker showed robust stability over time, scalability and variable relation to phenotype, most robustly in its relation to epilepsy status. Overall, families reported high satisfaction with the experience of engaging in research at family meetings and through remote assessments.

Discussion: The experience of directly partnering with PAGs and bringing research to the families has motivated ongoing studies to further improve the accessibility and scalability of research in rare disorders such as Dup15q syndrome. The challenge lies in balancing data quality with quantity, but as more PAG's are developed for specific genetic conditions, some common protocols and guidelines can be established to promote large scale research efforts that will ultimately accelerate the path to effective clinical trials for these conditions.

References:

- DiStefano, C., Wilson, R., Hyde, C., Cook, E., Reiter, L. T., Thibert, T., et al. (in press). Behavioral characterization of dup15q syndrome: Towards meaningful endpoints for clinical trials. *American Journal of Medical Genetics*.
- Saravanpandian V, Frohlich J, Hipp J, Hyde C, Scheffler A, Golshani P, Cook E, Reiter L, Senturk D, Jeste SS. Properties of beat oscillations in dup15q syndrome. Under Review at *Journal of Neurodevelopmental Disorders. (2019)*
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Paper 2 of 3

Paper Title: The role of Patient Advocacy Groups in Promoting Research in IDDs – Perspectives from Patient Advocates.

Authors: Elizabeth Jalazo[5], Vanessa Vogel-Farley[6], Audrey Thurm[7], Jennifer Tjernagel[8], Ann Wheeler[9] and Melissa Raspa[10]

Introduction: The importance of understanding the natural history and clinical needs of patients with rare disorders cannot be understated, particularly as communities prepare for clinical trials of new exciting therapeutics. Without the critical information gathered from clinical data and longitudinal research endeavors the full potential of new therapeutics would be difficult, if not impossible to demonstrate. This talk will highlight different novel models of data collection and clinical consultation across multiple rare diseases associated with NDDs

Methods: This presentation will 1) Highlight the role of the Angelman and Dup15q communities in developing an international network of 15q-focused clinics, multiple natural history studies, patient registries and a handful of other important clinical research programs including a clinical research network, focused on outcomes for patients and their families; 2) Provide an overview of the planned development of this clinical research network and shared database including the vision for parent, clinician and researcher use as well as the management of multiple data sources. The benefits and potential challenges of this resource for the community will also be discussed. In addition to robust clinical data collection, the network serves to unify the clinical community and improve standardization of care for patients across the world; 3) Present a complementary model of registry data collection, Simons Searchlight which provides data collection and biorepository infrastructure for multiple rare disease groups to accelerate research discoveries. Finally, the presentation will: 4) introduce the use of a new model, called ECHO, to promote education of physicians regarding care standards which has leveraged the rising telehealth movement. The Phelan-McDermid community has utilized the ECHO model to empower local caregivers with the knowledge of academic experts through telementoring and e-learning to improve care of patients with PMS.

Results: All of these approaches have the goal of improving the care of neuropsychiatric disorders in our children and increasing the number of doctors who are equipped to handle these complex conditions. Lessons learned from these models and potential implementation strategies for other rare disorders will also be briefly covered.

Discussion: Newer technological approaches, including standardized natural history registries, combined phenotyping approaches with biosample collection, and telehealth networks provide infrastructure needed to promote improved clinical care. All of these efforts are driven, in part, by PAGs, who provide not just funding, but important patient-led expertise into the continued development and improvement of these approaches.

References: none

[5] University of North Carolina at Chapel Hill and Angelman Syndrome Foundation
[6] Dup15q Alliance
[7] National Institutes of Mental Health
[8] Simons Foundation Autism Research Initiative
[9] University of North Carolina at Chapel Hill and RTI
[10] RTI

Paper 3 of 3

Paper Title: Partnering with PAG's to Advance Preclinical Models of NDDs in Rare Genetic Disorders

Authors: Jill Silverman[11] and Kyle Fink[11]

Introduction: Forging definitive links between genetic alterations and behavioral impairments in preclinical models of rare genetic disorders associated with NDDs is challenging, however, these challenges are not insurmountable. Translational endpoints, including behavioral outcomes, are essential for studying mechanisms of NDDs and for developing therapeutic treatment strategies. Translational research on rare genetic disorder forms NDDs are strengthened by partnerships with patient advocacy groups (PAG)s, and these partnerships can take many forms.

Methods: This talk will highlight research that is closely driven through discussions with PAGs. The work presented is based on on defined genetic forms of NDDs including Angelman, Dup15q and CDKL5 syndromes based on regular consultation with corresponding PAGs. These discussions focus on 1) what research is the biggest priority for the majority of patients in organized disorder communities, 2) how research can be better disseminated to families over complex academic journal article sharing, 3) the limitations on academic translational research and how PAGs are required as advocates, partners, and liaisons and 4) defining the steps/hurdles from academic basic research to approved compound/therapeutic (the full pathway of translation). Methods used in these endeavors include cellular model systems, gene editing tools, delivery methods, preclinical in vivo models and translational outcomes of behavior and beyond.

Results: The presentation will demonstrate how pairing behavior with a physiological marker can corroborate and expand translational research and how these innovative measures can facilitate studies and better predict clinical success for ASD and neurodevelopmental disorders. The advent of robust gene editing methods (changing the DNA sequence) and epigenome editing methods (changing gene expression) offers the opportunity to develop therapeutic tools that can address the underlying genetic causes of diseases. Our team has developed methods to therapeutically target the DNA of genes implicated in disease. How such tools can be delivered clinically in a widespread, safe, and persistent manner to treat neurodevelopmental disorders remains a challenge. Combining molecular, cellular data with in vivo data will improve/advancement therapeutics to clinical trial.

Discussion: The next steps are to disseminate our academic partnership with one PAG as a model for others and share successes and failures of preclinical to clinical pipeline.

References: none

[11] University of California at Davis