**Symposium Title**: Multi-Method, Multi-Stakeholder Approaches to Advancing Research and Clinical Trial Readiness in Rare Neurogenetic Conditions: A Focus on ASXL-Related Disorders

**Chair**: Natasha N. Ludwig1,2 & Rujuta B. Wilson3

**Discussant**: Audrey Thurm4

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**Overview**: The identification of rare monogenic causes of neurodevelopmental disabilities has surged with advances in next-generation sequencing and broader access to genetic testing. This progress has paved the way for the development of novel disease-modifying therapies that address the root cause of these disorders rather than just managing symptoms. To prepare for patient-centered clinical trials that target meaningful outcomes for both patients and families, it is critical to bring together stakeholders, clinicians, and researchers to expand our understanding of the patient experience, natural history, genotype-phenotype relationships, and relevant biomarkers.

This symposium will explore multiple approaches to build a comprehensive knowledge base around three rare monogenic causes of neurodevelopmental disabilities—ASXL1, ASXL2, and ASXL3—collectively known as ASXL-Related Disorders (ASXL-RDs). These disorders are characterized by intellectual disability, autism spectrum disorder, severe motor impairments, and a range of medical complications including epilepsy, feeding difficulties, respiratory challenges, and vision impairment. Despite their clinical impact, current knowledge of ASXL-RDs is limited to case reports, underscoring the urgent need for richer data on patient experiences, natural history, and genotype-phenotype correlations, as well as the identification of biomarkers.

This symposium, chaired by Drs. Natasha Ludwig (neuropsychologist and sibling of an adult with ASXL3-RD) and Rujuta Wilson (behavioral child neurologist), will highlight multiple methods of qualitative and quantitative patient-experience, behavioral, and brain function data collection. These methods include focus-groups, measures of cognition, language, autism symptoms, motor function, and neurophysiological examination of brain functioning. The symposium will demonstrate how stakeholders—including researchers, clinicians, and patient families—are collaborating to meet shared research goals and ascertain clinically meaningful information about these rare genetic neurodevelopmental disorders. Featured speakers include Amanda Johnson, Executive Director of the ASXL Rare Research Endowment (ARRE) Foundation, Dr. Bianca Russell, PI of the UCLA ASXL Natural History Study (NHS), Sereen Wong, an Autism Science Foundation Fellow working with Dr. Wilson, and Dr. Abigail Dickinson, a neuroscientist. The presenters represent a diverse range of stakeholders and bring experience from longstanding research collaborations with multiple rare disease patient advocacy groups. Through these presentations, we aim to showcase how these partnerships have driven rich, multi-method data collection efforts for ASXL-RDs. Dr. Audrey Thurm will discuss how the information shared through this symposium can serve as a model for academics, clinicians, patient groups, and other stakeholders, demonstrating how successful collaboration can lay the groundwork for patient-focused data collection and clinical trial readiness.

**Paper 1 of 4**

**Paper Title**: The power of a multi-stakeholder steering committee in understanding family-centered research priorities in ASXL-related disorders

**Authors**: Amanda Johnson1

1. ASXL Rare Research Endowment Foundation

**Introduction**: Founded in 2018, the ASXL Rare Research Endowment (ARRE) Foundation is a small, family-led patient advocacy organization aiming to improve the quality of life for individuals living with ASXL-RDs through research and education. In 2022, the ARRE Foundation conducted a survey to assess family research priorities to help guide the development of the Foundation’s research strategic plan. This survey received 205 responses from affected families in 28 countries. The top three priority areas that emerged included GI-related symptoms, neurodevelopmental symptoms (specifically, cognition and communication), and behavioral dysregulation. Data and insights from this survey supported a collaboration between the ARRE Foundation and academic researchers to develop a multi-stakeholder project funded by a Eugene Washington PCORI Engagement Stakeholder Convening Award titled, “*Defining and Prioritizing Research Questions and Outcome Measures for ASXL-Related Disorders*.” The goal of the project was to a) engage caregivers, clinicians, and researchers in further defining the lived experience of families in the three research priority areas via focus groups and b) identify and prioritize specific research questions that are most important to families within these three areas.

**Method:** The collaborative project was co-led by the ARRE Foundation Executive Director and a clinician researcher with guidance from a steering committee of 15 stakeholders from multiple institutions/regions across the country called the Topic Group Team (TGT). The TGT included two parent-caregivers from each of the three ASXL-RDs, three outcomes measure experts, five clinical geneticists with expertise in ASXL-RDs, and two program/project experts. The TGT met monthly from March to June 2024 to develop a discussion guide for focus groups held in-person at the 2024 ASXL Family Conference in Baltimore, MD. TGT members were compensated and provided travel support to attend the conference; additionally, the project funded 21 needs-based scholarships to help ASXL families attend the conference to participate in the focus groups.

**Results:** 45 ASXL families attended the conference, including 13 TGT members. 40 parent-caregivers participated in 15 focus group sessions held over two days. Post-conference observations by the TGT included previously unidentified quality of life challenges and strong family engagement in research activities. Family respondents to a post-conference survey (N=21) had strong positive feedback about the focus groups including that they were a “therapeutic experience” and “offered rich conversations.” 44% of respondents suggested that the focus groups should be repeated at a future conference. Focus group recordings were transcribed and coded. Preliminary thematic analysis has revealed concerns around limited communication of needs/wants/pain as well as concerns around child safety, both of which spanned across the three priority areas. In depth-thematic analysis is ongoing and results will be presented.

**Discussion:** This project has cultivated a new structure and communication channels for ongoing collaboration between academic researchers, clinicians and the ASXL family community facilitated by the ARRE Foundation through the development of the TGT and beyond. Next steps involve generation of draft research questions based on the themes identified from the focus groups and sharing these draft research questions with the ASXL community to be prioritized via a survey in January 2025. Both the themes generated from the focus groups and research question prioritization survey results will inform the ARRE Foundation’s future investments in research and will guide future endpoint development for these rare disorders.

**References:** Johnson A, Badmaev L, Lopez J, Ordower D, Bichell TJ, Ludwig NN. Building a Research Roadmap for ASXL-related disorders: Determining family research priorities. Poster presented at: National Organization for Rare Disorders (NORD) Breakthrough Summit; October 17-19, 2022; Washington, DC.

**Paper 2 of 4**

**Paper Title**: Enhancing Research for Rare Neurogenetic Conditions: The Role of a Centralized Patient Registry and Collaborative Data Collection During the ASXL Family Conference

**Authors:** Bianca E. Russell1, Julia Sloan1, Rachel Northrup2, Jennea Franklin2, Isabella Capps2 & Natasha N. Ludwig2,3

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**Introduction:** Investigating rare neurogenetic conditions presents significant challenges, primarily due to small patient populations that hinder the achievement of robust sample sizes. Patient registries are invaluable for centralizing data collection, enabling more comprehensive research. The UCLA ASXL Natural History Study (NHS), initiated in 2018, has enrolled 137 families across five academic institutions as a multi-site study. Funded by the ASXL Rare Research Endowment (ARRE) Foundation, the NHS is guided by a diverse multi-stakeholder steering committee. To date, six studies have either emerged from or utilized the NHS framework, employing methodologies such as biospecimen collection, electroencephalogram, caregiver surveys, and remote interviews. However, performance-based neurodevelopmental assessments—crucial for understanding neurodevelopmental phenotypes and preparing for clinical trials—have yet to be conducted. This presentation will showcase a collaborative effort leveraging the NHS infrastructure and the ARRE Foundation’s 2024 ASXL Family Conference at Kennedy Krieger Institute (a NHS site) to collect rich neurodevelopmental data.

**Method:** Individuals with ASXL1-Related Disorders (ASXL-RDs) participated in data collection across three research initiatives during the Family Conference: The NHS/Biorepository, the ASXL-Behavioral Phenotyping Study, and the Chromatinopathies and Autism: Motor Phenotyping and Indicators of Neurodevelopment study. To streamline participant experience and minimize burden, the research teams collaborated extensively on data collection and data sharing through the NHS. Participants completed a pre-conference questionnaire to gauge interest in the studies, functioning level to support neurodevelopmental test selection, and logistical preferences to support planning and feasibility (e.g., optimal testing times, attention span). An additional 30-minute pre-conference meeting with families helped to illustrate the connectedness across the three studies, provided further instructions (e.g., what to bring, who should accompany the child to research sessions), and ensured that the study team was prepared to address individual participant requirements (e.g., sensory needs, behavioral supports). The ARRE Foundation provided feedback on all pre-conference surveys and meeting activities to support understanding and relevance for families and to maximize utility for the research team. The conference schedule allowed families to engage in five research sessions including assessment of cognition/communication (3 hours), neurological and motor function (1.5 hours), autism symptomatology (1.5 hours), cortical vision impairment (1.5 hours), and biospecimen collection (30 minutes), alongside caregiver questionnaires (~2 hours) over the four-day conference. Post-conference remote caregiver interviews of adaptive behavior (1.5 hours) and behavioral functioning (1.5 hours) were also conducted.

**Results:** A total of 29 participants (ages 1 to 26 years, M=9.44) with diverse functional abilities (15 non-verbal, 8 non-ambulatory) were enrolled. All individuals, except one, attended the conference with more than one caregiver. Cognitive assessments were successfully conducted for all participants (n=16 Bayley Scales of Infant and Toddler Development, Fourth Edition, n=6 Differential Abilities Scale, Second Edition, n=7 Wechsler Abbreviated Scale of Intelligence, Second Edition). 28 neuro/motor exams, 21 cortical vision impairment assessments, and 23 autism assessments (n=18 Autism Diagnostic Observation Schedule, Second Edition, n=5 Autism Observation Scale for Infants) were completed. All but one family completed the caregiver questionnaires by the end of the conference, and nearly all participated in the two post-conference interviews within 3 months. Feedback from a post-conference survey indicated a highly positive research experience, with an average rating of 5.53 (1=low to 6=high). Positively, the event also led to an increase in NHS participants (n=15). All data was fed back into the NHS to promote comprehensive characterization on each participant, which is important for clinical trial readiness. Notably, this has resulted in longitudinal adaptive functioning data in the NHS for 7 individuals with ASXL1-RD, illustrating the power and potential of data sharing over time through a centralized data repository in rare neurogenetic conditions.

**Discussion:** This presentation will illustrate the successful collaboration between the ARRE Foundation, UCLA, and the Kennedy Krieger Institute, highlighting the logistics and strategic planning that facilitated this data collection model. Key considerations, including challenges faced and solutions implemented, will be discussed, along with lessons learned regarding the unique needs of participants (e.g., attention span and how this impacted feasibility of data collection). This collaborative approach will not only advance our understanding of ASXL-RDs and help the community prepare for clinical trials, but also serves as a scalable framework for future research in other rare neurogenetic conditions.

**Paper 3 of 4**

**Paper Title**: Multi-modal approach to evaluate motor function and autism symptoms in ASXL conditions

**Authors**: Sereen Wong[[1]](#footnote-1), Sonia Tran2, Laura Dinh2, Jina Song2, Jessica Le2, Sitaram Vangala3, Nicole McDonald4, Rujuta B. Wilson1

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**Introduction**: ASXL 1, 2, and 3 are a group of homologous genes that each cause a distinct neurodevelopmental disorder1-2. However, central to these three conditions are a range of motor impairments, including hypo and hypertonia, delayed and atypical gait, intellectual disability and autism symptoms3. These conditions are representative of many genetic neurodevelopmental disorders (genetic NDDs) that have similar presentations. Our previous pilot work in ASXL conditions and other genetic NDDS has indicated the limitations in current standardized assessments of motor, with many individuals achieving “floor” effects due to the cognitive level needed to understand how to complete necessary testing items. Additionally, well-established autism spectrum disorder (ASD) screening and diagnostic assessments require individuals to be ambulatory, a milestone that is often achieved after 2 years of age in ASXL conditions and other genetic NDDs. These are important considerations for using tools that can best ascertain variation in motor abilities and autism symptoms in these conditions. Here we present a multi-method approach, including in-person and remote methods, to evaluate motor function and autism symptoms in a representative sample of individuals with ASXL conditions. Ultimately these data can lead to better characterization of motor impairments, autism symptoms, and the relationship of these domains in genetic NDDs. This information is critical to inform clinical monitoring, diagnosis, and the development of outcome measures for burgeoning natural history studies and therapeutic trials in these conditions.

**Method**: Data were collected as a part of an ongoing study on chromatin-modifying conditions at UCLA and in conjunction with the ASXL-Behavioral Phenotyping Study at Kennedy Krieger Institute. Autism symptoms were measured by the Autism Observation Scale for Infants [AOSI] (n =5, Mage = 26.8 months, SDage = 15.12), the Autism Diagnostic Observation Schedule, 2nd Edition [ADOS-2] (n =14, Mage = 90.14 months, SDage = 34.85), and remotely using the Childhood Autism Rating Scale, 2nd Edition [CARS-2] (n=3, Mage = 43 months, SDage = 13.9). Developmental level was evaluated by the Bayley Scales of Infant and Toddler Development, 4th Edition [Bayley-IV] (n=6, Mage =79 months, SDage =34.01), the Mullen Scales of Early Learning [MSEL] (n=2, Mage = 43 months, SDage = 29.7), the Differential Abilities Scale, 2nd Edition [DAS-II] (n=4, Mage=78.5 months, SDage = 17.41), or the Wechsler Abbreviated Scale of Intelligence, 2nd Edition [WASI-II] (n=2, Mage =126.5 months, SDage = 3.54). Developmental quotients (DQs) were calculated to compare scores across measures. Motor function was measured using the Vineland Adaptive Behavior Scale, 3rd Edition [VABS-III] (n=16, Mage = 45.75 months, SDage = 18.96). The Protokinetics Zeno Pressure sensor walkway was used to evaluate quantitative measures of gait in ambulatory individuals. Participants used a spontaneous self-paced gait and walked at least 4 trials across the 16-foot walkway. Gait trials were averaged and here we present spatiotemporal gait variables of pace and variability, two measures shown to be atypical in other genetic NDDs. As a preliminary analysis, we examined the association of gait variables to developmental quotient (DQ), adjusting for age. We hypothesized that greater gait variability, lower step length and velocity would be associated with lower DQ scores.

**Results**: Total scores on the AOSI ranged from 12-21. On ADOS-2 and CARS-2, 16 individuals met cut-offs for ASD, with one child scoring in the non-spectrum range. The ADOS-2 Calibrated Severity Scores (CSS) ranged from 3 to 10 and developmental quotients ranged from 5 to 107. There was a significant association between lower DQ and higher gait variability (p=0.016) and nearing significance for higher DQ and higher step length (p=0.086). There was a non-significant positive relationship between higher velocity and higher DQ (p=0.104).

**Discussion**: Our results indicate that a range of ASD screening and diagnostic tools, cognitive assessments, and motor assessments need to be utilized when studying heterogenous manifestations of genetic NDDs. The ADOS-2, a well-established diagnostic measure of ASD, is not valid for use in non-ambulatory individuals. Our team holds expertise in ASD diagnosis and the use of tools outside of typical chronological age ranges, thus we utilized the AOSI to observe autism symptoms through direct tasks for non-ambulatory individuals when it was developmentally appropriate to be utilized. Based on ADOS-2 and CARS-2, 16 out of 17 individuals met clinical cut-offs for ASD, highlighting the prevalence of ASD symptoms in these ASXL conditions, along with potential over-estimation of autism in this cohort based with currently available measures. The large range of DQ scores indicate that ASXL genetic mutations have differential impact on cognition. Lastly, we were able to ascertain granular aspects of gait quality from 14 individuals and as hypothesized found that aspects of gait are related to developmental level. Establishing appropriate measures to evaluate motor function, autism symptoms, and developmental level in these conditions is necessary to inform accurate phenotypes, diagnosis, and clinical management. In addition to this data, at the time of the symposium, our team will discuss limitations and strengths of utilizing different ASD and motor assessments in this population. We will also include the interpretation of ASD diagnoses using a combination of direct standardized assessment, validated caregiver interviews using the Autism Diagnostic Interview-Revised, and a wholistic view of the individual rather than reliance on single diagnostic assessments.

**References:** Russell BE, Kianmahd RR, Munster C, Yu A, Ahad L, Tan WH. Clinical findings in 39 individuals with Bohring-Opitz syndrome from a global patient-driven registry with implications for tumor surveillance and recurrence risk. *Am J Med Genet A*. 2023;191(4):1050-1058. doi:10.1002/ajmg.a.63125

Schirwani S, Albaba S, Carere DA, et al. Expanding the phenotype of ASXL3-related syndrome: A comprehensive description of 45 unpublished individuals with inherited and de novo pathogenic variants in ASXL3 [published correction appears in Am J Med Genet A. 2023 Jan;191(1):310. doi: 10.1002/ajmg.a.62993]. *Am J Med Genet A*. 2021;185(11):3446-3458. doi:10.1002/ajmg.a.62465

Ayoub MC, Anderson JT, Russell BE, Wilson RB. Examining the neurodevelopmental and motor phenotypes of Bohring-Opitz syndrome (ASXL1) and Bainbridge-Ropers syndrome (ASXL3). *Front Neurosci*. 2023;17:1244176. Published 2023 Nov 6. doi:10.3389/fnins.2023.1244176

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**Paper Title**: Quantitative EEG Reveals Atypical Spectral Profiles in ASXL1-Related Disorder

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**Introduction**: Electroencephalogram (EEG) is a powerful tool for analyzing atypical developmental trajectories in neurodevelopmental disorders like ASXL1-Related Disorder (ASXL1-RD). By capturing patterns of neural oscillations, EEG provides insights into circuit functions essential for higher-order cognitive processes, including memory, attention, and executive function. As such, EEG metrics can track the functional organization of neural circuits and detect deviations from typical developmental trajectories. This study examines oscillatory characteristics extracted from EEG data in children with BOS to understand age-related trends in spectral profiles and their relationships with behavioral measures.

**Method:** EEG data were collected from 26 children diagnosed with ASXL1-RD, with an average age of 7.07 years (SD = 3.90; range = 1.17–14.92). Participants were identified through the UCLA Natural History Study (NHS) and were geographically distributed across the United States and Canada. Pathogenicity of variants was confirmed with methylation signature data for inclusion. EEG recordings, conducted in participants' homes using a 21-channel clinical montage, included standard clinical protocols with hyperventilation, photic stimulation, and rest. Task-free periods were used to examine resting-state EEG, with data filtered (1–50 Hz) and inspected to remove artifacts. EEGs were reviewed for clinical features. Spectral power was extracted across canonical frequency bands (delta, theta, alpha, beta, and gamma) within frontal, central, and occipital regions, and peak alpha frequency (PAF) was calculated as the dominant frequency within the alpha range (6–12 Hz). Multiple linear regression models were used to examine relationships between EEG metrics, age, and neurodevelopmental abilities (i.e., Developmental Profile, Fourth Edition Cognitive Scale; Vineland Adaptive Behavior Scales, Third Edition Parent/Caregiver Interview). Data collected through this study was shared back with the NHS.

**Results**: 50% of participants had a history of epilepsy and 100% demonstrated clinical abnormalities (i.e., 77% generalized slowing, 69% focal spikes, 62% excessive beta activity, 35% generalized spike-wave discharges, 15% notched delta pattern, and 4% hypsarrhythmia). Findings characterize spectral profiles across canonical frequency bands and brain regions, revealing both typical and atypical developmental patterns. Age-related decreases in delta power were observed, as expected, but over 50% of participants displayed significant increases in beta power, diverging from typical trajectories. Additionally, only 60% of participants exhibited a clear alpha peak, lower than expected for this age range. We also present analyses examining associations between spectral characteristics and neurodevelopmental abilities.

**Discussion**: Our findings reveal distinct EEG spectral profiles in individuals with ASXL1-RD, reflecting typical and atypical spectral characteristics. For instance, we observed age-related decreases in delta power, aligning with patterns seen in typical development. However, we also noted a significant absence of a clear alpha peak in many participants (~40%), where a consistent alpha peak would typically be expected across this age range. Additionally, many participants exhibited increased beta power, and we saw age-related increases in beta power, a pattern that may indicate evolving disruptions in neural circuit function with age. These spectral differences provide valuable insights into neural circuit variations that may shape developmental trajectories in ASXL1-RD and other neurodevelopmental disorders. For instance, elevated beta power is similarly observed in conditions like Dup15q and Fragile X syndrome, suggesting potential converging mechanisms. Understanding these shared pathways could illuminate the underlying processes driving atypical brain development across different conditions. In this context, examining spectral profiles offers a basis for more targeted insights into the mechanisms through which brain development is altered in ASXL1-RDs and how these neural differences relate to complex behavioral trajectories.

1. Prestige Institute of Learning [↑](#footnote-ref-1)