Abstract for WORLD 2025
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Title: Genotypic heterogeneity in GM1

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Background: GM1 gangliosidosis is a fatal, ultra-rare neurodegenerative disease caused by a deficiency or functional impairment in the ß-galactosidase enzyme (encoded by the *GLB1* gene) that leads to buildup of GM1 gangliosides, multi-organ dysfunction, developmental delay, and regression. Limited information is known on natural history and genotypic diversity. There are no approved therapies for GM1, highlighting the significant unmet need.

Methods: De-identified data were obtained from consenting participants in the AllStripes GM1 real-world data study. Data were provided to the research investigator and subtypes further assigned based on medical and developmental history. *GLB1* variant and clinical analyses were performed.

Results: The dataset consisted of 26 participants categorized by GM1 subtype: 6 Type 1 early infantile, 5 Type 2a late infantile; 12 Type 2b juvenile, and 3 Type 2 unspecified. Twenty-one patients reside in the US, 3 in Canada and 2 in the UK. Average age of diagnosis is 0.89 yrs for Type 1, 4 years for Type 2a, and 8.38 years for Type 2b. Developmental milestones achieved and lost were captured, but due to lack of standardized GM1 assessments, milestones are inconsistently reported. The *GLB1* genotypes (n=26) are heterogeneous (85% unique) with only 3 recurring; 16/26 (62%) of the unique *GLB1* gene variants are seen only once.

Discussion: GM1 patients face significant diagnostic delays due to varied onset of symptoms and subtle changes in development that may occur with the later onset forms. Significant genetic heterogeneity was seen in this population, adding to the genetic knowledge of GM1. Reporting of GM1 genotype-phenotype data with clinical and biochemical evidence is critical to aid in variant classification, timely diagnosis, and support genome-based and newborn screening studies. Further, a comprehensive database is needed to correlate genotype-phenotype and subtype classifications to the natural progression of the disease and impart prognosis for future patients.