GENOTYPIC HETEROGENEITY IN GM1

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BACKGROUND

GM1 gangliosidosis is a fatal, ultra-rare neurodegenerative autosomal recessive disease caused by 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. GM1 is not included in public newborn screening and approved therapies are absent for affected individuals. As such, there are significant unmet needs.

METHODS

- Study population: Consented participants residing in US, UK, or Canada, with physician-confirmed diagnosis via documented genetic or enzymatic tests.
- Data: All available patient medical records were digitized with structured clinical data variables gathered by AllStripes trained clinical abstractors.
- Approach: De-identified study data were provided to the research investigator, who assigned GM1 subtypes based on medical and developmental history. *GLB1* variant classifications were sourced July 2024 [http://www.ncbi.nlm.nih.gov/clinvar/].

  (P) pathogenic, (LP) = likely-pathogenic, (VUS) = Variant of Uncertain Significance, conflicting = discrepant classifications among ClinVar submissions.

RESULTS

The dataset consisted of 26 participants. Categorized by GM1 subtype, 5 had Type 1 early infantile, 6 Type 2a late infantile,12 Type 2b juvenile, and 3 Type 2 unspecified. [TABLE 1] The majority of participants were male (62%) and resided in the US (81%). For the study sample, mean ages at symptom onset and diagnosis were 26.4 and 67.3 months, respectively, with variance as expected by type stratifications. Individual participant ages at symptom onset and diagnosis are shown in FIGURE 1. Most common symptoms at onset [TABLE 2, FIGURE 2] were those affecting motor, sensory, or cognitive functions. The *GLB1* genotypes (n=26) were heterogeneous (81% unique) with only 4 recurring [TABLE 3]; A total of 52 *GLB1* gene variants are reported in the dataset among 26 participants, distilled into 27 unique variants. 17/27 (63%) of the unique *GLB1* gene variants are seen only once [TABLE 4]. Of the unique variants, 86% were identified as pathogenic or likely pathogenic [FIGURE 3]. Developmental milestones achieved and lost were captured, but due to lack of standardized GM1 assessments, milestones are inconsistently reported. Case examples are provided in FIGURES 4a & b.

DISCUSSION

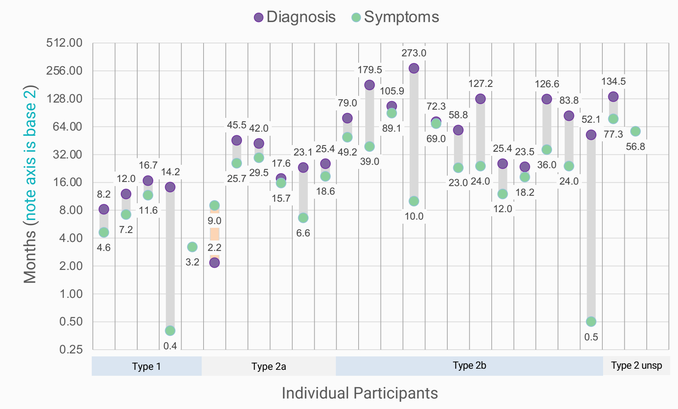
GM1 patients face significant diagnostic delays due to varied onset of symptoms and subtle changes in development that may occur with the later onset forms. Significant genetic heterogeneity was seen in this population, adding to the genetic knowledge of GM1. Reporting of GM1 genotype-phenotype data 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 impart prognosis for future patients.

TABLE 1. Participant Demographics (n=26)[1]

Characteristic	Type 1 (n=5)	Type 2a late infantile (n=6)	Type 2b juvenile (n=12)	Type 2 unspecified (n=3)	Total (n=26)
Gender					
Female	1	0	9	0	10 (38%)
Male	4	6	3	3	16 (62%)
Residence					
US	3	4	11	3	21 (81%)
Canada	1	2	0	0	3 (12%)
UK	1	0	1	0	2 (8%)
Vital Status					
Living	2	5	12	3	22 (85%)
Deceased	3	1	0	0	4 (15%)
Mean (Median) Age*					
at Symptom Onset	5.4 (4.6)	17.5 (17.2)	32.8 (24.0)	67.1 (67.1) n=2	26.4 (18.6) n=25
at Diagnosis	12.8 (13.1) n=4	26.0 (24.2)	100.6 (81.4)	134.5 (134.5) n=1	67.3 (45.5) n=23

[1]*Age at Symptom Onset recorded for 25 participants and Age at Diagnosis recorded for 23 participants.*
**Age in Months.*

FIGURE 1. Age (Months) at Symptom Onset & Diagnosis[1, 2]



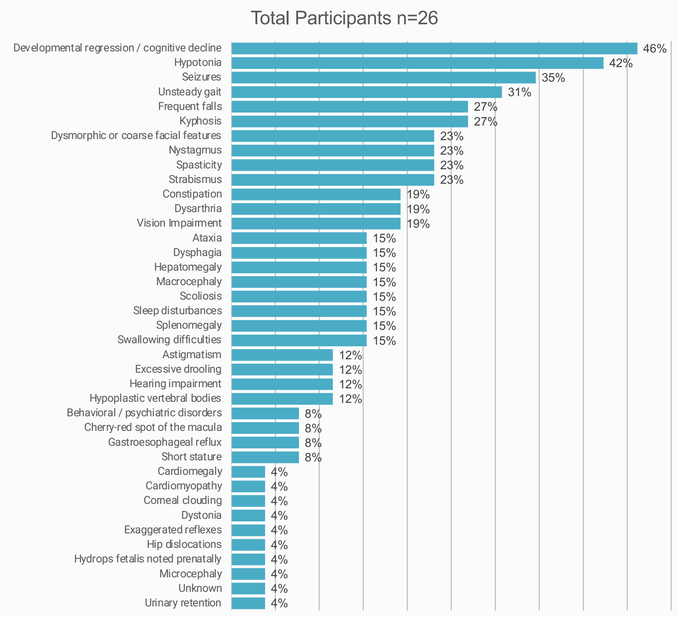
[2]Participants (3) classified as Type 2 unspecified had did not have sufficient information for categorization. 1 participant with Type 1 was diagnosed prior to onset of clinical signs due to prior affected sibling (orange).

TABLE 2. Participant Symptoms/Signs by Category at GM1 Onset (n=26)

GM1 Type	Bony Abnormalities	Cognitive	GI System	Motor	Other^	Sensory	Hypotonia
Type 1			√	√	√		√
	√		√	√	√	√	√
		√	√		√		√
			√	√	√	√	
					√	√	√
Type 2a late infantile		√	√	√	√		√
	√	√		√			
				√	√		√
	√	√		√	√	√	√
				√	√	√	
Type 2b juvenile				√		√	
	√	√	√	√	√		
	√	√		√	√		
	√	√	√	√	√		√
	√	√			√	√	
	√			√	√		
				√		√	
				√	√	√	
				√		√	√
	√	√		√	√		√
		√	√	√			
			√	√	√		
Type 2 unspecified		√		√			
		√		√	√	√	√
				√			
Total	9	12	9	22	18	11	11

Each row represents an individual participant (n=26). *^Other includes multiple symptom categories such as micro/macrocephaly, hepato/splenomegaly, strabismus, sleep disturbances, splenomegaly, excessive drooling, & short stature.*

FIGURE 2. Symptoms & Signs Observed at GM1 Onset



Participants may have more than one clinical sign or symptom recorded at onset of GM1.

TABLE 3. Participant *GLB1* Genotypes

Allele 1	Allele 2	No. Participants
c.601C>T (p.Arg201Cys)	c.601C>T (p.Arg201Cys)	3
c.481T>G (p.Trp161Gly)	c.602G>A (p.Arg201His)	2
c.622C>T (p.Arg208Cys)	c.602G>A (p.Arg201His)	2
c.931G>A (p.Gly311Arg)	c.602G>A (p.Arg201His)	2
c.1038G>C (p.Lys346Asn)	c.557A>C (p.Glu186Ala)	1
c.1233+1G>A (intronic)	c.959C>G (p.Ala320Gly)	1
c.1667T>C (p.Phe556Ser)	c.601C>T (p.Arg201Cys)	1
c.1733A>G (p.Lys578Arg)	c.601C>T (p.Arg201Cys)	1
c.1733A>G (p.Lys578Arg)	c.75+2dupT (intronic)	1
c.191A>G (p.Tyr64Cys)	c.442C>T (p.Arg148Cys)	1
c.380G>A (p.Cys127Tyr)	c.602G>A (p.Arg201His)	1
c.442C>A (p.Arg148Ser)	c.1442G>A (p.Gly481Glu)	1
c.442C>T (p.Arg148Cys)	c.319T>C (p.Phe107Leu)	1
c.464T>G (p.Leu155Arg)	arr[GRCh37]3p22.3(33106426_33110558)x1	1
c.464T>G (p.Leu155Arg)	c.464T>G (p.Leu155Arg)	1
c.574T>C (p.Tyr192His)	c.442C>A (p.Arg148Ser)	1
c.602G>A (p.Arg201His)	c.1051C>T (p.Arg351Ter)	1
c.622C>T (p.Arg208Cys)	c.841C>T (p.His281Tyr)	1
c.765G>C (p.Gln255His)	c.931G>A (p.Gly311Arg)	1
c.841C>T (p.His281Tyr)	c.808T>G (p.Tyr270Asp)	1
c.967C>G (p.Lys493Asn)	c.1479G>T (p.Pro323Ala)	1
Total Participants		**26**

17 (65%) of genotypes are unique and observed in only 1 participant. Only 4 genotypes are recurring and seen in more than one participant.

TABLE 4. Observed *GLB1* Variants

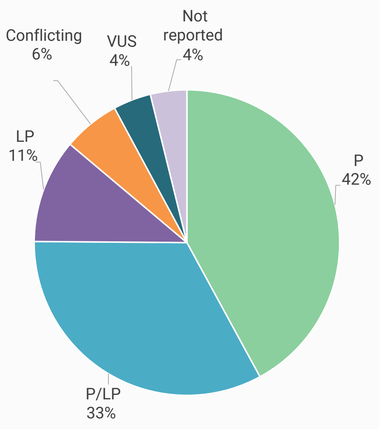
Unique Variants (n=27)	Variant Classification[1]	Molecular Consequence	Times Observed (n= 52)
c.601C>T (p.Arg201Cys)	P/LP	Missense	8
c.602G>A (p.Arg201His)	P	Missense	8
c.464T>G (p.Leu155Arg)	P	Missense	3
c.622C>T (p.Arg208Cys)	P	Missense	3
c.931G>A (p.Gly311Arg)	P	Missense	3
c.442C>T (p.Arg148Cys)	P/LP	Missense	2
c.442C>A (p.Arg148Ser)	P/LP	Missense	2
c.481T>G (p.Trp161Gly)	Conflicting	Missense	2
c.841C>T (p.His281Tyr)	P	Missense	2
c.1733A>G (p.Lys578Arg)	P/LP	Missense	2
c.191A>G (p.Tyr64Cys)	Conflicting	Missense	1
c.319T>C (p.Phe107Leu)	LP	Missense	1
c.380G>A (p.Cys127Tyr)	LP	Missense	1
c.557A>C (p.Glu186Ala)	LP	Missense	1
c.574T>C (p.Tyr192His)	VUS	Missense	1
c.75+2dupT (intronic)	P	Splice donor	1
c.765G>C (p.Gln255His)	LP	Missense	1
c.808T>G (p.Tyr270Asp)	P/LP	Missense	1
c.959C>G (p.Ala320Gly)	Not reported	Not reported	1
c.967C>G (p.Lys493Asn)	VUS	Missense	1
c.1038G>C (p.Lys346Asn)	P/LP	Missense	1
c.1051C>T (p.Arg351Ter)	P	Nonsense	1
c.1233+1G>A (intronic)	P/LP	Splice donor	1
c.1442G>A (p.Gly481Glu)	P	Missense	1
c.1479G>T (p.Pro323Ala)	LP	Missense	1
c.1667T>C (p.Phe556Ser)	LP	Missense	1
arr[GRCh37]3p22.3(33106426_33110558)x1			1

[1]*GLB1* variant classifications http://www.ncbi.nlm.nih.gov/clinvar. *GLB1* CNV variant classification not reported.

Two variants were identified in all 26 participants, totaling 52 variants and distilled into 27 unique variants. 17/27 (63%) variants are observed only once.

FIGURE 3. Variant Classification

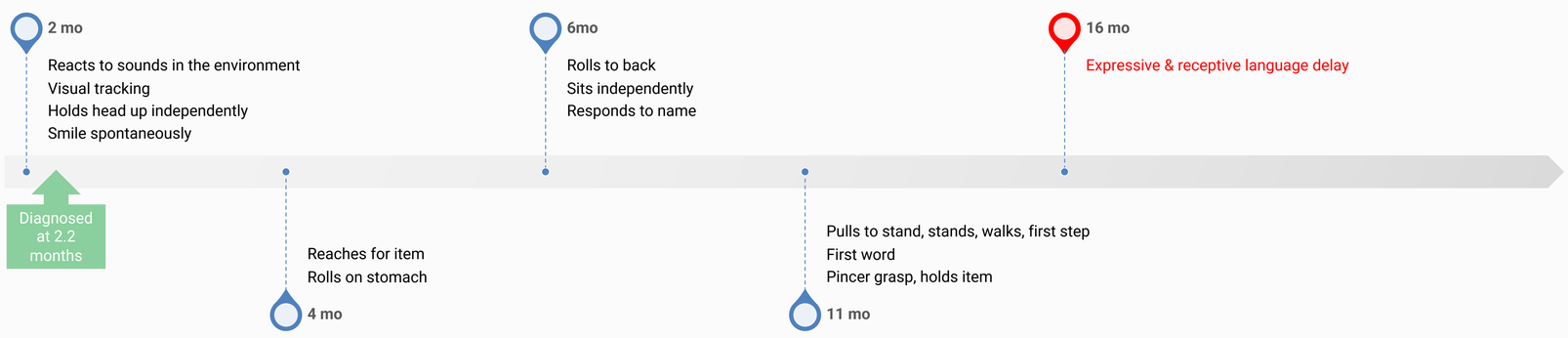
Classification of *GLB1* variants in this dataset.



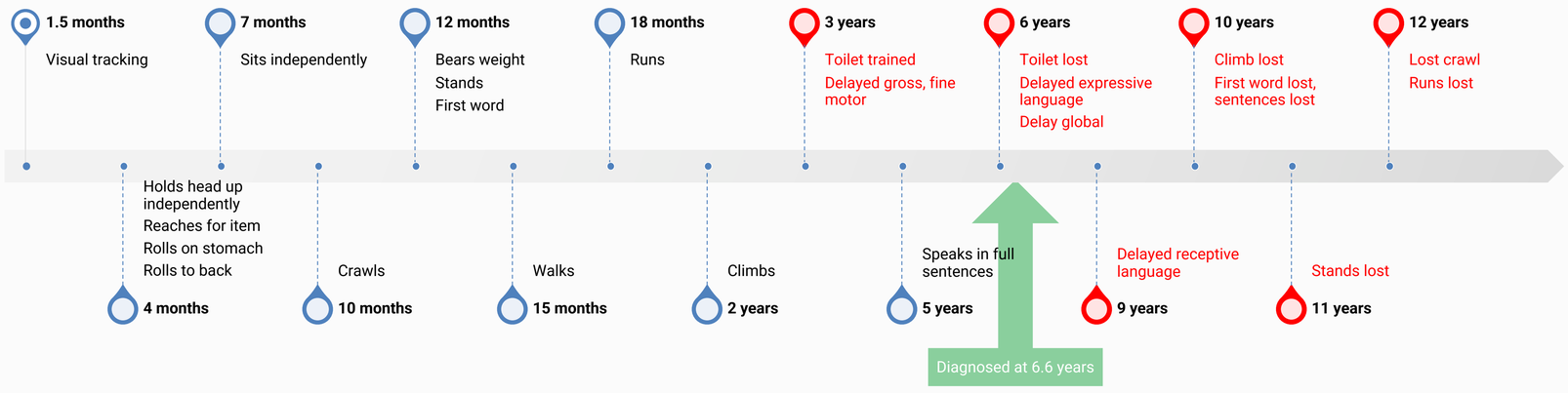
Denominator is total variants observed, n=52. 86% of variants observed are disease-associated (P, LP classifications).

FIGURE 4. DIAGNOSIS JOURNEY AND DEVELOPMENTAL TIMELINE FOR EARLY VS LATE DIAGNOSIS

4a. Developmental Timeline of Participant with Affected Sibling and Presymptomatic Diagnosis of Type 2a Late Infantile GM1



4b. Developmental Timeline of Participant with Symptomatic Diagnosis of Type 2B Juvenile GM1



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