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Biallelic variants in *GLE1* with survival beyond neonatal period

Running title: *GLE1* extended survival phenotype

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Biallelic pathogenic variants in *GLE1* cause Lethal Congenital Contracture Syndrome 1 (LCCS1, MIM#253310) and Congenital Arthrogryposis with Anterior Horn Cell Disease (CAAHD, MIM#611890) – previously Lethal Arthrogryposis with Anterior Horn Cell Disease. LCCS1 is characterised by severe joint contractures and skeletal muscle atrophy and is fatal *in utero*. CAAHD was initially thought to be a similar, slightly milder condition, with early neonatal fatality (1). More recently, six individuals with biallelic variants in *GLE1* and survival beyond age six months have been described (2–5).

We present three individuals with biallelic pathogenic/likely pathogenic variants in *GLE1,* and a fourth in whom we suspect it, with survival beyond infancy. Clinical features included joint contractures (3/4), hypotonia (3/4), scoliosis (2/4) and kyphosis (2/4) (Table 1). Individual 1 required home ventilation due to difficulties maintaining airway. Individual 4 developed alveolar hypoventilation during viral infections as a neonate, requiring nocturnal non-invasive ventilation. Individual 3 was last assessed age 41 years, demonstrating possible longer-term survival.

All individuals were recruited after routine genetics referral. Trio-based exome sequencing was performed for individuals 1 (Agilent SureSelect with Illumina HiSeq as part of the Wellcome Trust Deciphering Developmental Disorders (DDD) study) and 2 (SeqCap EZ Med Exome (Roche) and Illumina NextSeq550). Individual 3 had sequencing of a panel of 161 genes associated with arthrogryposis (MNG laboratories,

Atlanta, USA, www.mnglabs.com). Genome sequencing (Illumina HiSeq 4000) was performed for individual 4. All variants are according to transcript NM_001003722.1. All had normal chromosomal microarray testing, except individual 4, who had a 15q13.1 (pat) microduplication. All individuals had biallelic pathogenic or likely pathogenic variants in *GLE1*, except for individual 3, who has a c.433-15A>G variant (not maternally inherited; father unavailable for testing) with a c.1706 G>A(mat) (p.(Arg569His)) variant (Table 1). The c.433-15A>G variant is classified as a VUS, with equivocal *in silico* scores (CADD 8.2, DANN 0.62, MaxEnt -92.9% and NNSPLICE +188.1%). However, given its rarity (allele frequency 3.21e-5 on gnomAD, no homozygotes), phenotypic fit and known pathogenicity of p.(Arg569His) variant very likely *in trans*, this is thought likely to explain the patient's phenotype.

Including the six previously reported individuals with survival beyond six months age (2–5), we further define the emerging phenotypic spectrum associated with variants in *GLE1* and milder disease (Table 1). Totals given include only cases where a feature was reported. Polyhydramnios (2/5; 40%) and decreased fetal movements/contractures (3/5; 60%) were present antenatally. Most individuals (9/10; 90%) had feeding difficulties, with 5/9 (56%) requiring gastrostomy. Development was globally delayed in 7/10 (70%). It is possible language function may be less severely affected, given three individuals with delay can communicate with signing. Most had respiratory difficulties (9/10; 90%), with 4/10 (40%) requiring ventilation as

a neonate, and 2/10 (20%) requiring long-term ventilatory support. Other prominent features included hypotonia (7/10; 70%), muscle weakness/atrophy (5/10; 50%) and joint contractures (8/9; 89%).

Pathogenic variants in *GLE1* are largely missense, located throughout the gene and not associated with a particular functional domain. The nonsense variant in individual 1, and a frameshift variant reported by Smith *et al.* (2017) are the only truncating variants found to-date. The extended survival phenotype may be associated with hypomorphic variants. However, there may be additional genetic modifiers involved in the phenotypic variance associated with this gene. Also, medical intervention, for example long-term ventilation, may influence survival, regardless of the underlying genetic pathology.

In summary, we present evidence for survival beyond the neonatal period in individuals with biallelic *GLE1* variants, with a phenotype including joint contractures, hypotonia, muscle weakness and respiratory insufficiency.

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Table Legend

Table 1. Clinical features of individuals with biallelic GLE1 variants in this series. Variants according to genome build GRCh37 and transcript NM_001003722.1. gnomAD (https://gnomad.broadinstitute.org/) accessed 23.7.20. +reported by Nousiainen *et al*(1). nd - not documented, yr - years, ACMG – American College of

Medical Genetics, OFC – occipitofrontal head circumference, EEG – electroencephalogram, NCS - nerve conduction studies, EMG – electromyography

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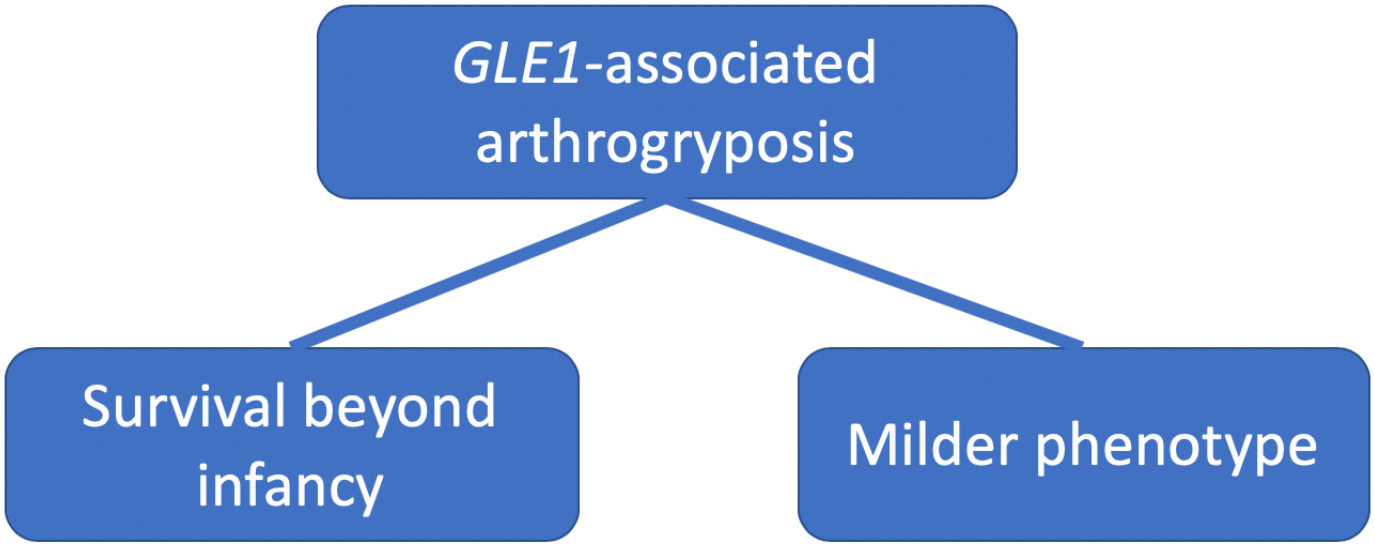
Conflicts of Interest

Nothing to declare.

Data Availability

The data that support the findings of this study are openly available in DECIPHER (https://decipher.sanger.ac.uk) and LOVD (http://gle1.lovd.nl).



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Patient ID	Individual 1 [DECIPHER ID 301225]	Individual 2	Individual 3	Individual 4	Smith et al. (2017)	Said et al. (2017)	Said et al. (2017)	Tan et al. (2017)	Cerino et al. (2020)	Cerino et al. (2020)
Gender	M	M	F	M	M	M	F	F	M	
***GLE1* variant 1**	c.397C>T	c.1706G>A	c.1706G>A	c.1790G>A	c.100-7_100-3delTCTCT c.1882-2A>G	c.2078C>T	c.1706G>A	c.1808G>T	c.1808G>T	c.1808G>T
Predicted protein change	p.(Arg133*)	p.(Arg569His)+	p.(Arg569His)+	p.(Gly597Asp)	p.(Asp34_Lys107 del)	p.(Ser693Phe)	p.(Arg569His)	p.(Arg603Leu)	p.(Arg603Leu)	p.(Arg603Leu)
gnomAD allele frequency/homo zygotes	Absent/0	2.51e-4/0	2.51e-4/0	7.96e-6/0	-	-	-	-	-	-
ACMG pathogenicity criteria	V - PVS1, PM2, PP3	IV - PM3, PP2, PP3, PP4, PP5	IV - PM3, PP2, PP3, PP4, PP5	IV - PM2, PM3, PP3, PP4	-	-	-	-	-	-
***GLE1* variant 2**	c.1790G>A	c.2006T>A	c.433-15A>G	c.1790G>A	c.1882-2A>G	c.2078C>T	c.1750C>T	c.1997G>T	c.1808G>T	c.1808G>T
Predicted protein change	p.(Gly597Asp)	p.(Ile669Lys)	IVS3-15A>G	p.(Gly597Asp)	p.Val238_Asnfs*2	p.(Ser693Phe)	p.(Arg584Trp)	p.(Gly666Val)	p.(Arg603Leu)	p.(Arg603Leu)
gnomAD allele frequency/homo zygotes	7.96e-6/0	1.59e-5/0	3.21e-5/0	7.96e-6/0	-	-	-	-	-	-
ACMG pathogenicity criteria	IV - PM2, PM3, PP3, PP4	IV - PM1, PM2, PM3, PP2, PP4	III-PM2,PM3	IV - PM2, PM3, PP3, PP4	-	-	-	-	-	-
Parents consanguineous	No	No	No	No	No	No	No	No	Yes	Yes
Ethnicity	European	European	French-Canadian White	European	European	European/Maltese	European	European/ Native American	Flemish	Flemish
Gestation at birth (weeks)	39	40+5	38	39	38	38	41	36	41	39
Age last assessed	3.5yr	1 year	41 years	2yr 3mo	12yr	5yr	Died age 4yr	2yr 2 mo	6yr 10 mo	4yr
Height (centile)	9th	50th	2nd	0.4th	nd	nd	nd	2nd	<0.4th	0.4th-2nd
Weight (centile)	9th-25th	50th	50th	2nd-9th	nd	nd	nd	75th-91st	0.4th	0.4th
OFC (centile)	50th	50th	50th	2nd	<0.4th	nd	nd	2nd	2nd-9th	2nd
Prenatal findings	Bilateral talipes	Polyhydramnios	Nil	Decreased fetal movements	Polyhydramnios, contractures	nd	nd	nd	nd	nd
Resuscitation at birth	Yes	No	No	No	Yes	Yes	No	Yes	No	No

Feeding difficulties	Gastrostomy	Sucking problems due to weakness	Swallowing difficulties as neonate	Nasogastric feeding required in first few months	Gastrostomy	Gastrostomy	Gastrostomy	Gastrostomy	Thickened feed	Nil
Respiratory	Ventilation as neonate, bilateral vocal cord palsy, tracheostomy and home ventilation due to difficulties maintaining airway. Hyoscine patch due to large volume secretions.	Recurrent severe respiratory infections first six months life	Obstructive apneic events in neonatal period only. Restrictive lung disease secondary to severe kyphoscoliosis.	Alveolar hypoventilation with hypercapnia during viral infections as neonate - required nocturnal non-invasive ventilation.	Ventilation as neonate, nocturnal BiPAP via tracheostomy since four months age	Ventilation as neonate, oxygen dependent, recurrent infection	Recurrent infection requiring ventilation, prolonged weaning	Repeated apnoeas, increased secretions requiring ventilation as neonate. Mild left bronchomalacia	Nil	Respiratory arrest due to swallowing disorder
Neurological	Hypotonia, seizures	Hypotonia, generalised weakness with reduced facial expression. Brisk reflexes.	Proximal lower extremity weakness	Severe congenital hypotonia	Severe hypotonia Facial diplegia, bulbar weakness	Truncal hypotonia, hypertonia limbs, decreased muscle bulk	Truncal hypotonia, dystonia, seizures	Hypotonia, muscle weakness	Peroneal muscle atrophy, patellar hyperreflexia	Patellar hyperreflexia
Development	Globally delayed. Sitting unsupported at 3.5yr, using Makaton sign language	Globally delayed. Sitting unsupported 9 month.	Mild fine motor delay, resolved. Now working in a high-functioning administrative role requiring advanced accounting skills.	Mild delay	Globally delayed.	Globally delayed.	Globally delayed.	Globally delayed.	Globally delayed	Motor delay
Dysmorphic facies	Upturned nose, 'cupid bow' mouth, bilateral low-set ears, metopic ridging	Micrognathia, high-arched palate, short neck	At birth: short nose, hypoplasia alae nasi, short philtrum, vertical dimple on chin.	nd	Microcephaly, severe myopia, myopathic, facial diplegia	Prominent forehead, downslanting palpebral fissures, tent-shaped mouth, prominent frenulum, micrognathia, low-set ears	nd	Prominent forehead, depressed nasal bridge, low-set ears, excess nuchal folds	High anterior hairline, downslanted palpebral fissure, smooth philtrum, microretrognathia	nd
Hands	Clenched	Single palmar crease bilat.	Residual 5th finger camptodactyly. Small feet. Mild	Contractures	Contractures	Bilateral camptodactyly, adducted thumbs	nd	Clenched, ulnar deviation	Clenched, adducted thumbs	nd

			2-3 toe cutaneous syndactyly.							
Joints	Multiple contractures, particularly legs and fingers	No contractures	Distal arthrogryposis. Beighton score 4/9	Contractures knees and elbows	Multiple contractures	Multiple contractures	nd	Multiple contractures	Multiple contractures	Multiple contractures
Skeletal	Scoliosis	Slight kyphosis	Short stature, Short and clubbed feet. Severe kyphoscoliosis requiring several surgical interventions.	Pes planus, Asthenic kyphosis	Scoliosis	nd	nd	nd	Short stature	Thoracolumbar kyphosis
MRI brain	Few foci white matter high T1 signal left hemisphere consistent with microhaemorrhage or white matter injury of prematurity.	Normal	nd	Bilateral hypertrophic olivary nuclei	Diffuse cerebral atrophy, prominent CSF spaces and dilated ventricles	Immature cortical folding pattern and myelination	Generalised volume loss, small brainstem, and atrophic superior colliculi	Mild hypoxic ischaemic encephalopathy attributed to apnoeic event	Normal	nd
EEG	nd	Normal	nd	Normal	Diffuse background slowing with right frontocentral epileptogenic discharges	Normal	Depressed activity	nd	nd	nd
NCS	nd	nd	nd	Normal	Diffuse motor axonopathy	nd	nd	nd	nd	Nd
EMG	nd	nd	nd	Normal	Neurogenic recruitment	Neuropathic	nd	Normal	Myogenic pattern with neurogenic component	nd
Histopathology	nd	nd	nd	Homogeneous atrophy of all muscle fibres with predominance of type 1 fibres (90%)	Muscle biopsy non-specific paucity of muscle	nd	nd	nd	Nonspecific	nd
Other	Conductive hearing loss.	nd	Secundum atrial septal defect	nd	nd	nd	nd	nd	Hypermetropia	Hypermetropia