
Article:
Yates, T.M., Campeau, P.M., Ghoumid, J. et al. (6 more authors) (2020) Biallelic variants in GLE1 with survival beyond neonatal period. Clinical Genetics, 98 (6). pp. 622-625. ISSN 0009-9163

https://doi.org/10.1111/cge.13841

Biallelic variants in *GLE1* with survival beyond neonatal period

Running title: *GLE1* extended survival phenotype

T. Michael Yates[1], Philippe M. Campeau[2], Jamal Ghoumid[3], Maria Kibaek[4], Martin J. Larsen[5], Thomas Smol[6], Sami A Albaba S[7], Jens Michael Hertz[5], Meena Balasubramanian[8,9].

1. MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK
2. Department of Pediatrics, Sainte-Justine Hospital, University of Montreal, Montréal, Canada
3. CHU Lille, Clinique de Génétique Guy Fontaine, F-59000, Lille, France
4. Department of Pediatrics, Odense University Hospital, Odense, Denmark
5. Department of Clinical Genetics, Odense University Hospital, Odense, Denmark
6. CHU Lille, Institut de Génétique Médicale, F-59000, Lille, France
7. Sheffield Diagnostic Genetics Service, Sheffield Children's NHS Foundation Trust, Sheffield, UK
8. Sheffield Clinical Genetics Service, Sheffield Children's NHS Foundation Trust, UK
9. Academic Unit of Child Health, Department of Oncology & Metabolism, University of Sheffield, UK

Corresponding Author

Dr Meena Balasubramanian

Sheffield Clinical Genetics Service, Sheffield Children's NHS Foundation Trust, Western Bank, Sheffield, UK, S10 2TH

meena.balasubramanian@nhs.net

Keywords: GLE1, Arthrogryposis, Lethal Congenital Contracture Syndrome 1, Congenital Arthrogryposis with Anterior Horn Cell Disease, Lethal Arthrogryposis with Anterior Horn Cell Disease

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.

References

1. Nousiainen HO, Kestilä M, Pakkasjärvi N, Honkala H, Kuure S. Mutations in mRNA export mediator GLE1 result in a fetal motoneuron disease. Nat Genet. 2008;40(2):155–7.
2. Smith C, Parboosingh JS, Boycott KM, Bönnemann CG, Mah JK, Lamont RE, et al. Expansion of the GLE1-associated arthrogryposis multiplex congenita clinical spectrum. Clin Genet. 2017;91(3):426–30.
3. Said E, Chong JX, Hempel M, Denecke J, Soler P, Strom T, et al. Survival beyond the perinatal period expands the phenotypes caused by mutations in GLE1. Am J Med Genet Part A. 2017;173(11):3098–103.
4. Tan QKG, McConkie-Rosell A, Juusola J, Gustafson KE, Pizoli CE, Buckley AF, et al. The importance of managing the patient and not the gene: expanded

phenotype of GLE1-associated arthrogryposis. Cold Spring Harb Mol case Stud. 2017;3(6):1–10.

5. Cerino M, Di Meglio C, Albertini F, Audic F, Riccardi F, Boulay C, et al. Extension of the phenotypic spectrum of GLE1-related disorders to a mild congenital form resembling congenital myopathy. Mol Genet Genomic Med. 2020.

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

Acknowledgments

The DDD study presents independent research commissioned by the Health Innovation Challenge Fund [grant number HICF-1009-003]. This study makes use of DECIPHER (http://decipher.sanger.ac.uk), which is funded by Wellcome. See Nature PMID: 25533962 or www.ddduk.org/access.html for full acknowledgement

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).