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1 **Biallelic variants in *GLE1* with survival beyond neonatal period**

2

3 Running title: *GLE1* extended survival phenotype

4

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33 Keywords: *GLE1*, Arthrogyrosis, Lethal Congenital Contracture Syndrome 1,
34 Congenital Arthrogyrosis with Anterior Horn Cell Disease, Lethal Arthrogyrosis
35 with Anterior Horn Cell Disease

36

37 Biallelic pathogenic variants in *GLE1* cause Lethal Congenital Contracture Syndrome
38 1 (LCCS1, MIM#253310) and Congenital Arthrogryposis with Anterior Horn Cell
39 Disease (CAAHD, MIM#611890) – previously Lethal Arthrogryposis with Anterior
40 Horn Cell Disease. LCCS1 is characterised by severe joint contractures and skeletal
41 muscle atrophy and is fatal *in utero*. CAAHD was initially thought to be a similar,
42 slightly milder condition, with early neonatal fatality (1). More recently, six
43 individuals with biallelic variants in *GLE1* and survival beyond age six months have
44 been described (2–5).

45

46 We present three individuals with biallelic pathogenic/likely pathogenic variants in
47 *GLE1*, and a fourth in whom we suspect it, with survival beyond infancy. Clinical
48 features included joint contractures (3/4), hypotonia (3/4), scoliosis (2/4) and kyphosis
49 (2/4) (Table 1). Individual 1 required home ventilation due to difficulties maintaining
50 airway. Individual 4 developed alveolar hypoventilation during viral infections as a
51 neonate, requiring nocturnal non-invasive ventilation. Individual 3 was last assessed
52 age 41 years, demonstrating possible longer-term survival.

53

54 All individuals were recruited after routine genetics referral. Trio-based exome
55 sequencing was performed for individuals 1 (Agilent SureSelect with Illumina HiSeq
56 as part of the Wellcome Trust Deciphering Developmental Disorders (DDD) study)
57 and 2 (SeqCap EZ Med Exome (Roche) and Illumina NextSeq550). Individual 3 had
58 sequencing of a panel of 161 genes associated with arthrogryposis (MNG laboratories,
59 Atlanta, USA, www.mnglabs.com). Genome sequencing (Illumina HiSeq 4000) was
60 performed for individual 4. All variants are according to transcript NM_001003722.1.
61 All had normal chromosomal microarray testing, except individual 4, who had a

62 15q13.1 (pat) microduplication. All individuals had biallelic pathogenic or likely
63 pathogenic variants in *GLE1*, except for individual 3, who has a c.433-15A>G variant
64 (not maternally inherited; father unavailable for testing) with a c.1706 G>A(mat)
65 (p.(Arg569His)) variant (Table 1). The c.433-15A>G variant is classified as a VUS,
66 with equivocal *in silico* scores (CADD 8.2, DANN 0.62, MaxEnt -92.9% and
67 NNSPLICE +188.1%). However, given its rarity (allele frequency 3.21e-5 on
68 gnomAD, no homozygotes), phenotypic fit and known pathogenicity of
69 p.(Arg569His) variant *very likely in trans*, this is thought likely to explain the
70 patient's phenotype.

71

72 Including the six previously reported individuals with survival beyond six months age
73 (2–5), we further define the emerging phenotypic spectrum associated with variants in
74 *GLE1* and milder disease (Table 1). Totals given include only cases where a feature
75 was reported. Polyhydramnios (2/5; 40%) and decreased fetal
76 movements/contractures (3/5; 60%) were present antenatally. Most individuals (9/10;
77 90%) had feeding difficulties, with 5/9 (56%) requiring gastrostomy. Development
78 was globally delayed in 7/10 (70%). It is possible language function may be less
79 severely affected, given three individuals with delay can communicate with signing.
80 Most had respiratory difficulties (9/10; 90%), with 4/10 (40%) requiring ventilation as
81 a neonate, and 2/10 (20%) requiring long-term ventilatory support. Other prominent
82 features included hypotonia (7/10; 70%), muscle weakness/atrophy (5/10; 50%) and
83 joint contractures (8/9; 89%).

84

85 Pathogenic variants in *GLE1* are largely missense, located throughout the gene and
86 not associated with a particular functional domain. The nonsense variant in individual

87 1, and a frameshift variant reported by Smith *et al.* (2017) are the only truncating
88 variants found to-date. The extended survival phenotype may be associated with
89 hypomorphic variants. However, there may be additional genetic modifiers involved
90 in the phenotypic variance associated with this gene. Also, medical intervention, for
91 example long-term ventilation, may influence survival, regardless of the underlying
92 genetic pathology.

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

96

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113 congenital form resembling congenital myopathy. Mol Genet Genomic Med.
114 2020.

115

116 **Table Legend**

117

118 Table 1. Clinical features of individuals with biallelic GLE1 variants in this series.

119 Variants according to genome build GRCh37 and transcript NM_001003722.1.

120 gnomAD (<https://gnomad.broadinstitute.org/>) accessed 23.7.20. +reported by

121 Nousiainen *et al*(1). nd - not documented, yr - years, ACMG – American College of

122 Medical Genetics, OFC – occipitofrontal head circumference, EEG –

123 electroencephalogram, NCS - nerve conduction studies, EMG – electromyography

124

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129 PMID: 25533962 or www.ddduk.org/access.html for full acknowledgement

130

131 **Conflicts of Interest**

132

133 Nothing to declare.

134

135 **Data Availability**

136

137 The data that support the findings of this study are openly available in DECIPHER

138 (<https://decipher.sanger.ac.uk>) and LOVD (<http://gle1.lovd.nl>).

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