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De Novo *GLI3* Pathogenic Variants May Cause Hypotonia and a Range of Brain Malformations Without Skeletal Abnormalities

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Abstract

Background: *GLI3* encodes a zinc finger transcription factor that plays a role in the sonic hedgehog pathway. Germline pathogenic *GLI3* variants are associated with Greig cephalopolysyndactyly and Pallister-Hall syndromes, two syndromes involving brain malformation and polydactyly.

Methods: We identified patients with pathogenic *GLI3* variants and brain malformations in the absence of polydactyly or other skeletal malformation.

Results: Two patients were identified. Patient #1 is a 4-year-old boy with hypotonia and global developmental delay. Brain MRI showed a focal cortical dysplasia, but he had no history of seizures. Genetic testing identified a de novo likely pathogenic *GLI3* variant: c.4453A>T, p.Asn1485Tyr. Patient #2 is a 4-year-old boy with hypotonia, macrocephaly, and global developmental delay. His brain MRI showed partial agenesis of the corpus callosum, dilatation of the right lateral ventricle, and absent hippocampal commissure. Genetic testing identified a de novo pathogenic *GLI3* variant: c.4236_4237del, p.Gln1414AspfsTer21. Neither patient had polydactyly or any apparent skeletal abnormality.

Conclusions: These patients widen the spectrum of clinical features that may be associated with *GLI3* pathogenic variants to include hypotonia, focal cortical dysplasia, and other brain malformations, in the absence of apparent skeletal malformation. Further study is needed to determine if *GLI3* pathogenic variants are a more common cause of focal cortical dysplasia or corpus callosum agenesis than presently recognized.

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Keywords

GLI3; Focal cortical dysplasia; Hypotonia; Agenesis of corpus callosum; Macrocephaly

Background

GLI3 (OMIM 165240) encodes GLI3, a zinc finger transcription factor that plays a role in the sonic hedgehog pathway. GLI3 is crucial for embryonic development, mediating anterior/posterior patterning during limb embryogenesis, thus determining digit number and morphogenesis.[1] Pathogenic *GLI3* variants are associated with different autosomal dominant inherited disorders including Greig cephalopolysyndactyly syndrome (GCPS) and Pallister-Hall syndrome (PHS).[2]

GCPS is typically characterized by ocular hypertelorism, macrocephaly, and preaxial or mixed preaxial and postaxial polydactyly with variable cutaneous syndactyly.[3] Patients with PHS may have mesoaxial or postaxial polydactyly, asymptomatic bifid epiglottis, and hypothalamic hamartoma or more severe findings such as laryngotracheal cleft and neonatal death.[4,5] PHS is usually caused by truncating *GLI3* variants in the middle third of the gene, while truncation variants in the proximal or distal third are associated with GCPS.[5,6] Pathogenic *GLI3* variants can also result in different forms of nonsyndromic polydactyly.[1]

Methods

We attempted to identify patients with pathogenic variants in *GLI3* and brain malformations without polydactyly using GeneMatcher.[7]

Results

Two patients were identified.

Patient #1

A 4-year-old boy had hypotonia and developmental delay. At age 7 months, he was able to roll supine to prone. At age 11 months, he was able to vocalize but was not truly babbling. He pulled to stand at 19 months and walked independently at 21 months. He had a severe expressive and a moderate receptive language delay. He had no events concerning for seizure. He was followed up by ophthalmologists for astigmatism and strabismus which was managed with patching. He did not have polydactyly or other apparent skeletal abnormalities. His neurologic examination was significant for marked hypotonia and hyporeflexia, both of which gradually improved with age.

Brain magnetic resonance imaging (MRI) at age 8 months identified only borderline small frontal lobes, but a follow-up study at age 35 months showed findings consistent with a focal cortical dysplasia in the left frontal lobe (Fig 1). Electroencephalography at age 3 years showed mild background slowing but no epileptiform abnormalities. Screening blood work including thyroid-stimulating hormone and creatine kinase was normal.

An autism/intellectual disability gene panel trio (GeneDx) identified a de novo heterozygous missense *GLI3* variant (c.4453A>T, p.Asn1485Tyr), classified as “likely pathogenic” by American College of Medical Genetics and Genomics criteria.[8] This variant is absent in the Genome Aggregation Database and predicted damaging by Polyphen-2 (score 0.997). MutationTaster predicts the change to be disease causing due to changes to protein and possible splice site changes. The Grantham score is 143, indicating a “moderately radical” amino acid change.

The patient was recruited to the Neurodevelopmental Disorders Database/Biobank, approved by the McGill University Health Centre Research Ethics Board (2018-3937). The patient’s parents gave informed written consent.

Patient #2

A 4-year-old boy presented with hypotonia, macrocephaly, and global developmental delay. He sat at 8 months and walked at 17 months. Fine motor and language development were both also delayed. Babbling started at 12 months. He had autistic features per parent report. He had no events concerning for seizure. On examination, he was nondysmorphic, but head circumference was 3.5 standard deviations above the mean. He did not have polydactyly or any apparent skeletal abnormalities.

Brain MRI at 3 years showed partial agenesis of the corpus callosum, with dysgenesis of the posterior body and hypoplasia of the splenium, absent hippocampal commissure, mildly dilatated right lateral ventricle, and mildly diminished white matter volume (Fig 2). Trio whole-exome sequencing revealed a novel de novo frameshift pathogenic *GLI3* variant, c.4236_4237del, p.Gln1414AspfsTer21. For this patient, sequencing and analysis were provided by the Broad Institute of MIT and Harvard Center for Mendelian Genomics.

Discussion

These patients expand the phenotypic spectrum of *GLI3*-related disorders to include hypotonia, macrocephaly, and focal cortical dysplasia, without obvious skeletal abnormalities. Until now, germline pathogenic *GLI3* variants have previously been reported only with different syndromes associated with polydactyly.

As a missense change, Patient #1’s variant is located distal to all previously published *GLI3* pathogenic missense variants, which may explain the phenotypic differences observed. Nearly all published *GLI3* pathogenic variants have been predicted to lead to premature truncation, with the location of truncation being predictive of whether the resultant phenotype is GCPS or PHS.[5] Patient #2’s variant was also novel but predicted to result in truncation in the C-terminal region of the protein, more typical of what has been previously published in association with GCPS; however, the patient did not have any apparent skeletal abnormalities. He did, however, have partial agenesis of the corpus callosum, which has been reported in patients with GCPS with similar variants.[9]

Although germline *GLI3* pathogenic variants have thus far only been reported in association with polydactyly, somatic truncation *GLI3* pathogenic variants are a recognized cause of

nonsyndromic hypothalamic hamartoma, the characteristic brain malformation in PHS.[10,11] Patients with PHS due to *GLI3* truncating pathogenic variants may have hypoplasia of the corpus callosum, further emphasizing that GLI3 dysfunction may have broader effects on brain development beyond hypothalamic hamartoma.[9]

Taken together, the molecular and clinical findings in our two patients demonstrate that germline *GLI3* pathogenic variants can produce a wider spectrum of neurodevelopmental phenotypes than previously thought, which may occur in the absence of polydactyly or other skeletal abnormalities. Both our patients had significant hypotonia, but it is unclear if this was related to the brain malformations observed or if this is an indication that *GLI3* pathogenic variants cause a more widespread cerebral dysfunction than is appreciated on brain MRI. Further study is needed to determine the precise molecular mechanisms by which these brain malformations occur and whether *GLI3* is a common cause of focal cortical dysplasia or corpus callosum agenesis.

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Conflict of interest:

Dr. Myers holds or has held research funding from Savoy Foundation, Dravet Canada, Research Institute of the McGill University Health Centre, Citizens United for Research in Epilepsy (439534), Koolen-de Vries Foundation, Liam Foundation, and Fonds de Recherches du Québec – Santé; he is also a site principal investigator for the studies by LivaNova, GeneTx, and Ionis. The other authors report no conflicts of interest.

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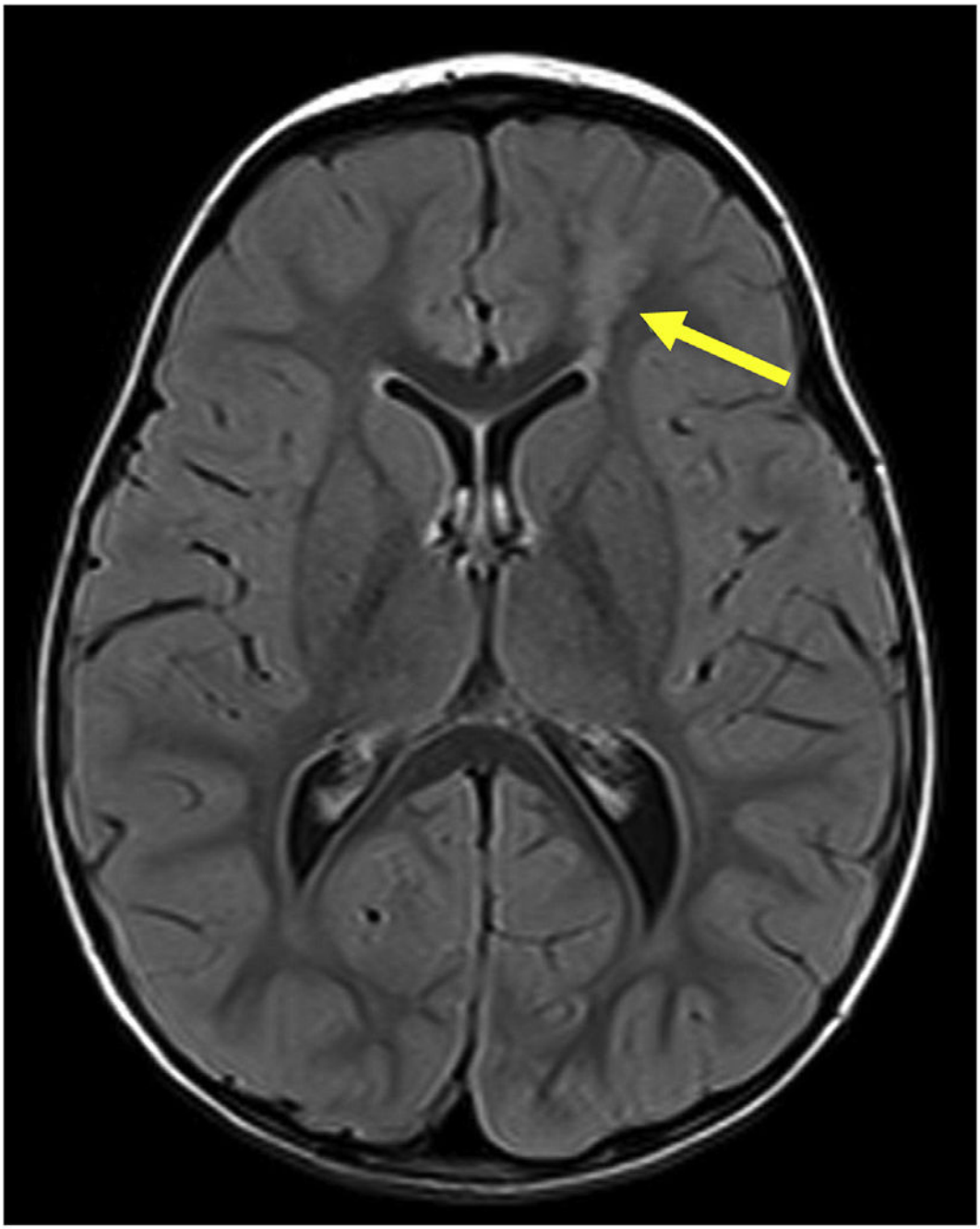

FIGURE 1.
Brain MRI of Patient #1 at age 35 months: Axial fluid-attenuated inversion recovery image shows a hyperintensity in the left frontal region (arrow). The appearance is consistent with a focal cortical dysplasia, most likely type II. MRI, magnetic resonance imaging.

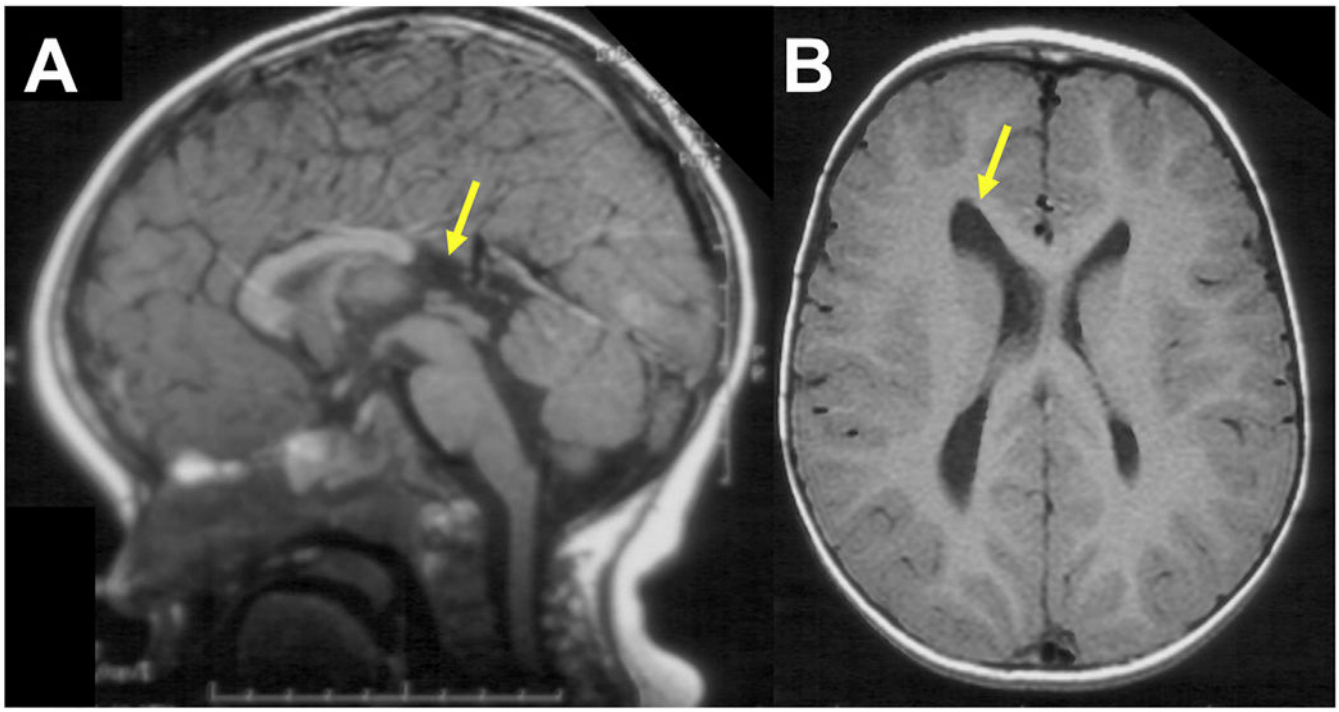

FIGURE 2.

Brain MRI of Patient #2 at age 23 months: (A) Sagittal T1-weighted midline image shows dysgenesis of posterior body of corpus callosum and absent splenium (arrow). (B) Axial T1-weighted image shows decreased white matter volume and dilatation of the right lateral ventricle (arrow). The patient also had absent hippocampal commissure (not shown). MRI, magnetic resonance imaging.