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## Case Report

# Prenatal and postnatal evaluation of polymicrogyria with band heterotopia

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## ABSTRACT

The coexistence of band heterotopia and polymicrogyria is extremely rare though it has been reported in the presence of corpus callosum anomalies and megalencephaly. We present prenatal and postnatal MRI findings of a rare case of diffuse cortical malformation characterized by polymicrogyria and band heterotopia. Agenesis of the corpus callosum and megalencephaly were also noted. In addition, bilateral closed-lip schizencephaly was identified on postnatal MRI, which has not been previously reported with this combination of imaging findings. Polymicrogyria with band heterotopia can occur and can be diagnosed with fetal MRI. The coexistence of corpus callosum anomalies and megalencephaly comprises a rare phenotype that has been previously described, suggesting an underlying genetic abnormality.

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## Introduction

Subcortical band heterotopia, also known as double cortex syndrome, is characterized by bands of heterotopic gray matter between the ventricular wall and cortical mantle. The overlying cortex is usually normal or along the lissencephaly/pachygyria spectrum, and nearly, all affected patients are female [1]. The most common associated mutations identified are found in the *DCX* gene [2]. Subcortical band heterotopia with associated polymicrogyria is extremely rare, with only 4 previously reported cases in the literature [3–5]. We describe a unique case of subcortical band heterotopia with

polymicrogyria, agenesis of the corpus callosum, and bilateral closed-lip schizencephaly. We also describe the prenatal imaging findings, which have not been previously reported.

## Case report

A 25-year-old gravida 3 para 2 female with a single intrauterine gestation at 28 weeks and 5 days gestational age (GA) was referred to the Cincinnati Fetal Center for further evaluation of abnormal fetal ultrasound findings first noted at 22 weeks and 5 days GA. Reported abnormalities included a dilated third

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ventricle, and a follow-up fetal ultrasound at 26 weeks and 5 days GA suggested agenesis of the corpus callosum and cerebellar hypoplasia. This case report is Health Insurance Portability and Accountability Act compliant and did not require approval from the institutional review board.

The patient reported an otherwise uneventful pregnancy and was not exposed to any medications, alcohol, drugs, or tobacco during the pregnancy. There was no history of diabetes or hypertension. Alpha-fetoprotein tetra screen was low risk for open spinal dysraphism and trisomy 21, 18, and 13. Amniocentesis was offered but not performed. There was no history of consanguinity. While the couple has 2 healthy children together, pertinent family history includes a history of cerebral palsy in the patient's maternal cousin and a paternal grandmother who had an unspecified type of muscular dystrophy.

Fetal ultrasound performed at 28 weeks and 5 days GA revealed multiple abnormalities including absent cavum septum pellucidum, parallel configuration of the lateral ventricles, dilated third ventricle at 5 mm, and cerebellar hypoplasia with a transverse cerebellar diameter of 28.8 mm consistent with a 25-week and 6-day GA fetus (Fig. 1). Cisterna magna was upper limits of normal in size at 9.5 mm. The bowel was echogenic, and the neck was persistently hyperflexed during examination. There was question of mild hypotelorism with an intraocular diameter of 16 mm, consistent with a 24-week and 2-day GA fetus; however, binocular diameter was 43.6 mm consistent with a 27-week and 3-day GA fetus. Head circumference and biparietal diameter were normal in size for GA.

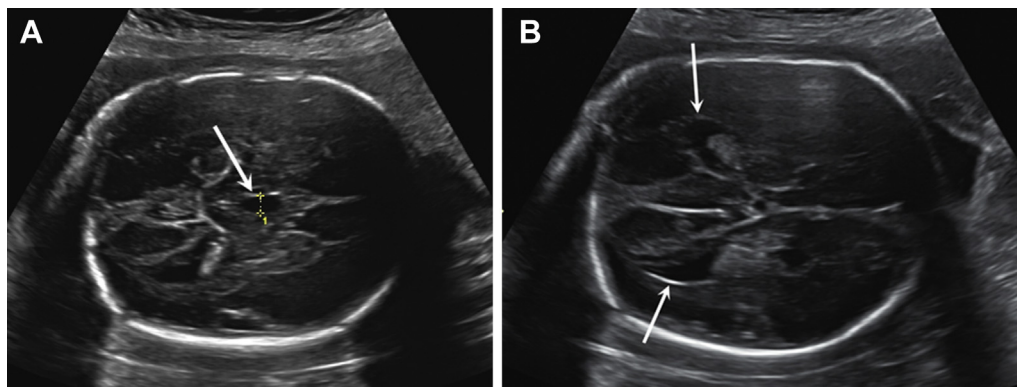
The patient had a fetal MRI performed in conjunction with the ultrasound on a 1.5T General Electric Signa (Milwaukee, WI) magnet. The gyral sulcal pattern was diffusely abnormal and was undersulcated for GA with abnormal asymmetric and shallow sulci. Bilateral deep gray matter-lined clefts in the parieto-occipital lobes were noted, not clearly reaching the ventricular walls. The signal of the supratentorial brain was abnormal as well-demonstrating bilateral hemispheric band heterotopia in a wavy “ribbon-like” pattern. The corpus callosum was completely absent with an enlarged high-riding third ventricle (Fig. 2). The cerebellum was hypoplastic with decreased transverse cerebellar diameter for GA at 26 mm. The cerebellar vermis was normal. The brainstem was hypoplastic with flattening of the anterior margin of the pons.

The patient was counseled that the fetus had a severe neuronal migrational disorder with expected severe developmental impairments, intractable epilepsy, and shortened life span. A male neonate was delivered at 39 weeks and 1 day GA via uncomplicated spontaneous vaginal delivery. The infant was initially doing well clinically and was discharged home on day of life 2. The infant underwent outpatient MRI of the brain at 6 weeks of age on a 3T Phillips Ingenia (Best, the Netherlands) magnet which revealed extensive neuronal migrational anomalies including bilateral diffuse polymicrogyria, band heterotopia, and nodular gray matter heterotopias in the hemispheric white matter. Bilateral closed-lip schizencephalic clefts were identified in the parietal lobes. There was effacement of the hemispheric sulci suggesting megalencephaly. Complete agenesis of the corpus callosum, including absence of the anterior commissure and hippocampal commissure, was identified (Fig. 3). T1 hyperintense ectopic neurohypophyseal tissue was also suspected near the median eminence.

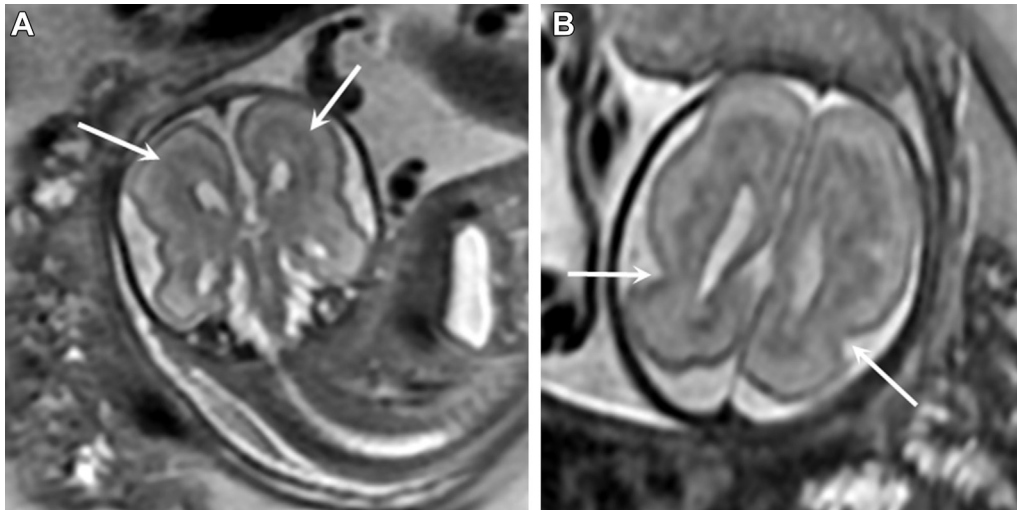
The infant underwent initial neurologic evaluation at 2 months of age at which time physical examination was notable for macrocephaly and was otherwise unremarkable. The infant later presented for inpatient evaluation at 7 months of age with seizures, developmental delay, and failure to thrive. The infant underwent genetics evaluation which included a pediatric neurology region of interest panel with deletion/duplication analysis (Claritas Genomics, Cambridge, MA). Initial region of interest gene panel was negative including mutations involving DCX, ARX, and RELN; however, the complete report later revealed a heterozygous pathogenic variant in DOK7. Whole exome sequencing was offered though to date has not yet been performed.

## Discussion

Subcortical band heterotopia with associated polymicrogyria is an extremely rare combination of neuroimaging findings with only 4 previously reported cases in the literature. Two of these cases were described to also have agenesis of the corpus callosum and macrocephaly in association with EML1 mutation [5]. The third case



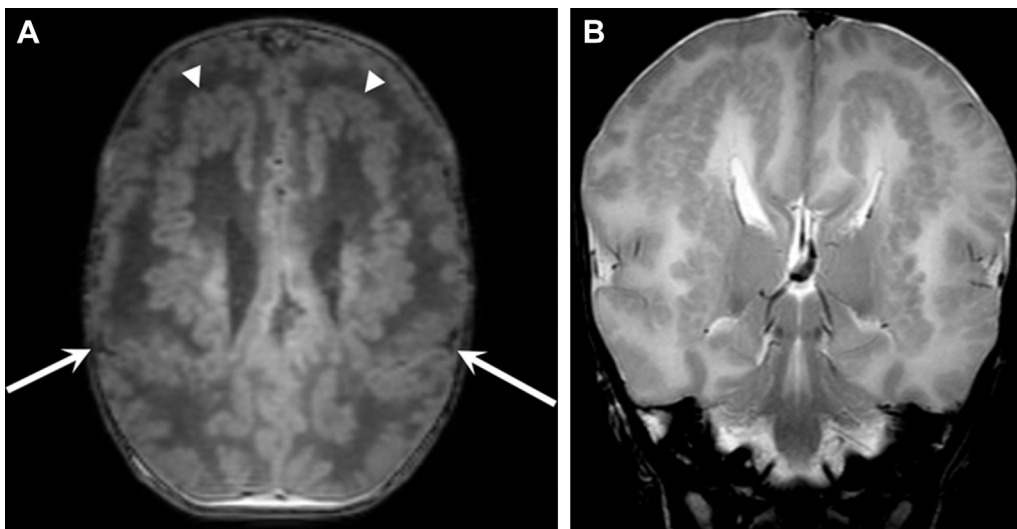
**Fig. 1** – Axial images through the brain from fetal US at 28 weeks and 5 days GA. There is a mildly dilated third ventricle (arrow) and absence of the cavum septum pellucidum (A). There is also a parallel configuration of the lateral ventricles with colpocephaly (arrows) (B), and no portion of the corpus callosum is identified. GA, gestational age; US, ultrasound.



**Fig. 2** – Fetal MRI T2-SSFSE images of the fetal brain at 28 weeks and 5 days GA. On the coronal image (A), there is absence of the corpus callosum, band heterotopia (arrows), and diffuse undersulcation with shallow Sylvian fissures. Axial image (B) shows the same findings along with parallel configuration of the lateral ventricles and deep gray matter-lined parieto-occipital clefts (arrows), which in retrospect are closed-lip schizencephalic clefts though on fetal MRI, the extension to the ventricular lining is difficult to discern. GA, gestational age.

described a female patient with megalencephaly and callosal hypoplasia, though no pathogenic mutations were identified despite whole exome sequencing [4]. The fourth case described a female patient with callosal dysgenesis; however, this patient was microcephalic, and although no genetic testing was performed, this patient was the only child of consanguineous parents. Three of the 4 previously reported patients had macrocephaly, like our patient. All 4 patients had callosal agenesis/dysgenesis and were reported to have a clinical presentation of seizures during the first year of life, also like our patient.

Our case of band heterotopia with polymicrogyria is unique in several ways. For one, we describe the prenatal ultrasound and fetal MRI findings, which have not been previously described. We demonstrate that diffuse polymicrogyria on the postnatal MRI can have the appearance of undersulcation or lissencephaly on fetal MRI. Second, unlike previously reported cases, our case has the additional finding of bilateral closed-lip schizencephaly. Third, our patient is male, which is unusual as nearly all band heterotopia patients are female. Finally, our patient demonstrated a heterozygous pathogenic variant in the *DOK7* gene.



**Fig. 3** – Axial T1-SPGR (A) and coronal T2-FSE (B) from postnatal MRI at 6 weeks of age. Axial image (A) demonstrates extensive polymicrogyria involving the cerebral hemispheres with polymicrogyric band heterotopia (arrowheads). There is also bilateral closed-lip schizencephaly (arrows). Coronal image (B) shows many of the same findings including complete agenesis of the corpus callosum.

*DOK7* gene mutations have been previously described as an autosomal recessive cause of congenital myasthenic syndromes. While this finding is of unclear significance in our patient, as this mutation has not been previously described in association with neuronal migrational disorders and *DOK7*-related congenital myasthenia is autosomal recessive, it appears likely that this is not the main cause of the brain malformation in this case [6]. The cause remains uncertain at this time. Other potential causes of both polymicrogyria and schizencephaly include disruptions of normal development related to viral illness, hypoxic ischemic injury, or other environmental factors [7]. Mosaic mutations limited to the central nervous system should also be considered. These are quite difficult to investigate in a living patient and may not be demonstrated even with detailed evaluation.

We conclude that band heterotopia with polymicrogyria, though rare, can occur and like our case has been previously described with coexisting anomalies of the corpus callosum and megalencephaly. We describe a unique case in a male patient with bilateral closed-lip schizencephaly and prenatal neuroimaging findings which have not been previously described. An underlying genetic abnormality is suspected; however, further studies are warranted to establish the exact cause.

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