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Mutations of *KIF5C* cause a neurodevelopmental disorder of infantile-onset epilepsy, absent language, and distinctive malformations of cortical development

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Abstract

The clinical diagnosis of malformations of cortical development (MCDs) is often challenging due to the complexity of the brain malformation by neuroimaging, the rarity of individual malformation syndromes, and the rapidly evolving genetic landscape of these disorders facilitated with the use of Next Generation Sequencing (NGS) methods. While the clinical and molecular diagnosis of severe cortical malformations, such as classic lissencephaly, is often straightforward, the diagnosis of more subtle and complex types of cortical malformations, such as pachygyria and polymicrogyria (PMG), can be more challenging due to limited knowledge regarding their genetic etiologies. Here, we report two individuals with the same *de novo KIF5C* mutation who present with subtle malformations of cortical development, early onset epilepsy and significant neurodevelopmental and behavioral issues including absent language. Our data, combined with the limited literature on *KIF5C* mutations, to date, support that *KIF5C* mutations are associated with a neurodevelopmental disorder characterized by infantile onset epilepsy, and subtle but recognizable types of brain malformations. We also show that the spectrum of *KIF5C* mutations is narrow, as five out of the six identified individuals have mutations affecting amino acid Glu237. Therefore, the identification of the clinical and neuroimaging features of this disorder may strongly facilitate rapid and efficient molecular diagnosis.

Keywords

KIF5C; intellectual disability; epilepsy; cortical dysplasia

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INTRODUCTION

With the advent of Next Generation Sequencing (NGS) methods, a growing number of genes are being identified in association with a wide spectrum of complex developmental brain disorders (Barkovich et al. 2012). The diagnosis of severe cortical malformations, such as classic lissencephaly, is often achievable clinically by the identification of characteristic neuroimaging abnormalities, which facilitates a more targeted molecular testing strategy (Guerrini and Dobyns 2014). However, more complex cortical malformations continue to pose challenges from a diagnostic perspective due to variability of the neuroimaging features of the brain malformation, and/or rarity of individual types of malformations. Examples of such malformations include polymicrogyria (PMG), variable types of pachygyria, and more subtle forms of cortical dysplasia. The *KIF5C* gene was identified recently in 2013 as a rare cause of cortical malformations variably characterized by regional or focal pachygyria with or without microcephaly, with only four children identified to have mutations of this gene, to date (Jamar et al. 2014; Poirier et al. 2013; Willemsen et al. 2014; Cavallin et al. 2016). Here we report two children with brain malformations, infantile onset epilepsy, and neurodevelopmental issues due to the same *de novo* mutation *KIF5C*. By adding our patients to the four previously reported individuals, we show that mutations of this gene are associated with a distinctive neurodevelopmental syndrome characterized by infantile-onset epilepsy and subtle but distinctive brain malformations recognizable by neuroimaging.

MATERIALS AND METHODS

Patients were enrolled in the Developmental Brain Disorders Research Program at Seattle Children's Research Institute, with IRB approval. The investigators reviewed all clinical, neuroimaging and molecular data. Molecular analysis was performed through clinically available targeted next generation commercial panels consisting of >1000 genes associated with epilepsy, intellectual disability and autism using the Agilent Clinical Research Exome kit. Sequencing was performed using the Illumina sequencing system with 2×100 bp paired-end reads.

RESULTS

The neuroimaging and clinical features of our two patients, along with the previously published *KIF5C* mutation-positive individuals, are summarized in Table 1.

Patient 1 (LR16-416)

This boy was born to consanguineous (first cousin) parents of Pakistani ancestry. He was born full-term via vaginal delivery following an uncomplicated pregnancy and labor. Birth weight was 3.03 kg (25–50th percentile for age and gender). He is the eldest of three siblings (a girl and two boys). The proband presented with poor feeding initially requiring nasogastric tube supplementation, global developmental delays, and diffuse hypotonia. He had seizure-like events at age one month characterized by head drop, generalized body stiffness, and widening of the eyes lasting a few seconds to one minute. Multiple electroencephalograms (EEGs) performed between 15 months and 12 years of age showed multifocal abnormalities mainly consisting of spike and waves discharges. With the use of

anti-epileptic medications, he had partial seizure control until age three and became free of overt clinical seizures allowing for steady, slow developmental progress from age 3 to 12 years. Other medical issues included bilateral congenital hip dysplasia surgically corrected with bilateral femoral varus osteotomies, and left Dega innominate osteotomy complicated by Superior Mesenteric Artery Syndrome.

On last assessment at age 13 years, seizures were well controlled. His weight was 40.2 kg (20th percentile), length was 152.9 cm (25th percentile), and occipito-frontal circumference (OFC) was 53.2 cm (10–25th percentile). Facial examination revealed a few subtle dysmorphic features including synophrys, laterally prominent ears, prominent nasal bridge and a relatively large mouth (Figure 1, A–B). Spinal examination revealed scoliosis. Neurological examination showed a delayed non-verbal boy with limited mobility (using a wheelchair). He was unable to walk independently, but stood for short periods of time with the use of a gait trainer. Fine motor skills were delayed with inability to hold objects. He was non-verbal and exhibited several stereotypic movements including teeth grinding, thumb sucking, rocking behavior, and repetitive hand movements. He frequently smiled and made appropriate eye contact, but did not follow commands. He had increased oral secretions and dysphagia requiring a liquid diet. He was enrolled in special education in 7th grade, primarily consisting of physical, occupation, speech, and functional therapy multiple times per week.

Brain magnetic resonance imaging (MRI) at age one and three years showed several abnormalities including subtle irregularity of the cortical gray-white matter junction suggestive of dysgyria, with a thick cortex in the frontal, parietal lobes and perisylvian regions (thickness ~9.9 mm). Other abnormalities include mildly thin corpus callosum (genu, body and splenium), mild ventriculomegaly, and mildly small cerebellar vermis with subtle foliar dysplasia (Figure 1, C–D). The patient underwent multiple genetic and metabolic tests, which were inconclusive. Testing for epilepsy genes through a targeted NGS panel of 1148 genes (GeneDx EpiXpanded panel) identified a *de novo* heterozygous mutation in *KIF5C* (NM_004522.2, c. 709G>A, p.Glu237Lys).

Patient 2 (LR17-160)

This girl is of Vietnamese non-consanguineous ancestry. She was born full-term via vaginal delivery following an uncomplicated pregnancy. Birth weight was 3.34 kg (25–50th percentile). She is the youngest child of two healthy siblings (a girl and a boy). At age three months, she presented with global developmental delays, spasticity and apparent microcephaly. On examination, further signs included eye fixation, constipation, and a red, scaly rash covering her cheeks, scalp, arms, legs, and trunk. Early onset epilepsy occurred at three months, with seizures being predominantly febrile. At age six months, she developed afebrile seizures including staring spells. She has continued to have seizures since, and has been on and off oxcarbazepine since age six years. An awake EEG at age 13 months was normal.

On last assessment at age 11 years, growth measurements were as follows: weight was 30.4 kg (10th percentile), length was 145 cm (44th percentile), and OFC was 49 cm (3.5 standard deviations below the mean). Facial examination revealed a few subtle dysmorphic facial

features including low sloping forehead, apparent prognathism, relatively large mouth with downturned corners, mildly arched eyebrows and mildly high-arched palate (Figure 1, E–F). Neurological examination showed a delayed non-verbal girl. She could independently ambulate but her gait was unsteady and mildly wide-based. She had axial and appendicular hypotonia. She did not have a pincer grasp, did not point and required assistance with all self-care skills. Her speech and language development were severely delayed as well, with increased oral secretions. She was non-verbal with limited social skills. She also had several behavioral problems include self-injurious behavior, aggression, impulsivity, and pica. She was receiving Applied Behavior Analysis (ABA) therapy in addition to physical therapy and speech therapy at her elementary school. Other medical issues included persistent nocturnal enuresis. She had a tonsillectomy and adenoidectomy at five years of age due to obstructive sleep apnea.

Brain MRI at age ten months showed cortical dysgyria in the frontal and mesio-frontal regions with undersulcation and simplification of the gyral pattern, thin and mildly dysplastic corpus callosum, mild ventriculomegaly and mildly increased extra-axial space (Figure 1, G–H). She underwent multiple genetic and metabolic tests that were all inconclusive. Testing for epilepsy genes through a targeted NGS of 1387 genes (GeneDx EpiXpanded panel) identified a *de novo* heterozygous mutation in *KIF5C* (NM_004522.2, c.709G>A, p.Glu237Lys).

DISCUSSION

KIF5C is a member of the kinesin family of proteins that have critical roles in the developing brain including transport of intracellular material along microtubules (Hirokawa et al., 2009). Mutations of several members of the kinesin family of genes have been shown to cause developmental brain disorders (Supplementary Table). Our data, combined with the literature, establish that mutations of *KIF5C* cause a neurodevelopmental disorder characterized by infantile-onset epilepsy, neurobehavioral issues including absent speech/ language development, and a distinctive spectrum of brain malformations (Table 1).

The six *KIF5C* mutation-positive individuals, including the two published in this report, all had cortical brain malformations that can be conservatively classified as a cortical dysplasia (or dysgyria), and ranged in appearance from a thick to disorganized microgyric cortex, suggestive of pachygyria or polymicrogyria, respectively; although the quality of the imaging data was suboptimal for some of the previously reported individuals to fully assess the appearance of the cortical gyral pattern. Importantly, the pattern of distribution of the cortical dysplasia in *KIF5C* mutation-positive children is distinctive as it appears to be frontal (including mesio-frontal) in five out of the six reported individuals. Interestingly, these five individuals all had mutations involving amino acid Glu237, with four individuals harboring the same p.Glu237Lys mutation. The cortical gyral pattern in one previously reported individual was distinct with a posterior– (rather than anterior–) predominant distribution, under-sulcation of the cortex and a thick subcortical band heterotopia (SBH) (Jamuar et al. 2014). This individual had a different mutation downstream of Glu237 (p.Ala268Ser). These data suggest that *KIF5C* mutations involving amino acid Glu237 may

be associated with a more consistent phenotype than other mutations, with possible preliminary genotype-phenotype correlations (Table 1).

In a few reported patients, the cortical dysplasia was overall mild (Poirier et al. 2013), and in some patients, the cortical gyral pattern appeared irregular with possible microgyri suggestive of PMG. Both patients reported in our study had mild cortical dysplasia involving predominantly the frontal and mesio-frontal regions (Figure 1). Other notable MRI features in all six *KIF5C* mutation-positive children include mild ventriculomegaly (seen in 5/6 patients), a thin and dysplastic corpus callosum (5/6 patients), and cerebellar abnormalities (seen only in patient LR16-416 who had mild cerebellar vermis hypoplasia with subtle foliar dysplasia). Furthermore, one previously-reported patient had a single periventricular nodular heterotopia (Cavallin et al. 2016).

Therefore, the key features of *KIF5C* related disorders, to date, appear to include the following: (1) cortical malformation variably classified as dysplasia that can resemble pachygyria or PMG, with simplification of the gyral pattern, (seen in 6/6 patients), and a characteristic pattern of distribution that is anterior-predominant, including frontal and mesio-frontal in individuals with mutations of Glu237, (2) variable other brain MRI features including callosal and cerebellar abnormalities that can be subtle or mild (seen in 5/6 patients), (3) early infantile onset epilepsy (seen in 4/6 patients), (4) severe intellectual disability with absent speech and language development (seen in 4/6 patients), and (5) abnormal stereotypic movements along with several neurobehavioral issues including aggression and self-injurious behavior (seen in 3/6 patients).

The Glu237Lys mutation identified in our two patients is located within the microtubule-binding domain of the gene and, therefore, appears to be highly recurrent (Cavallin et al., 2016). The p.Glu237Lys mutation has been identified to be *de novo* in four individuals, with no sibling recurrence. The fifth *KIF5C* mutation-positive family consisted of four affected individuals (all boys) who had cortical dysplasia and microcephaly, with limited imaging data as three boys died *in utero*. These siblings had a different substitution at the same amino acid position in *KIF5C*, p.Glu237Val, presumed to be due to maternal germline mosaicism (Poirier et al. 2013). The sixth patient had a distinct *de novo* mutation (p.Ala268Ser) that also lies within the microtubule-binding domain. (Jamuar et al. 2014). As mentioned previously, the distribution of the cortical malformation of this patient was also distinct from the other mutation-positive children as it was posterior-, rather than anterior-, predominant in distribution with subcortical band heterotopia (SBH). Therefore, all in all, the molecular spectrum of *KIF5C* related disorders appears to be narrow with a recurrent mutation affecting amino acid Glu237, and with all mutations clustered within the microtubule binding domain of the protein. Mutations of *KIF5C* have been shown to cause Kinesin proteins to lose their ability to hydrolyze ATP and lead to a non-functional motor domain (Padzik et al. 2016). Mutations of the amino acid Glu237 have been shown to affect the binding ability of these microtubule proteins to their targets, protein folding and ATP hydrolysis (Poirier et al., 2013; Cavallin et al., 2016).

In summary, we report the fifth and sixth children with *KIF5C* mutation, to date. Both individuals presented with a distinctive clinical picture characterized by frontal predominant

cortical dysplasia, with subtler callosal, cerebellar and ventricular abnormalities. Our study adds to the previous limited literature on *KIF5C* related disorders and establishes that this spectrum constitutes a severe neurodevelopmental disorder characterized by variable brain malformations, early onset epilepsy, absent language and speech development, and neurobehavioral issues. Clinical and neuroimaging recognition of these features, along with the narrow mutational spectrum of *KIF5C* related disorders to date, will facilitate more efficient clinical and molecular diagnosis of affected individuals in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Barkovich AJ, Guerrini R, Kuzniecky RI, Jackson GD, Dobyns WB. A developmental and genetic classification for malformations of cortical development: update 2012. *Brain*. 2012; 135:1348–1369. [PubMed: 22427329]
- Cavallin M, Hubert L, Cantagrel V, Munnich A, Boddaert N, Vincent-Delorme C, Cuvellier JC, Masson C, Besmond C, Bahi-Buisson N. Recurrent *KIF5C* mutation leading to frontal pachygyria without microcephaly. *Neurogenetics*. 2016; 17:79–82. [PubMed: 26384676]
- Guerrini, Renzo, Dobyns, William B. Malformations of cortical development: clinical features and genetic causes. *The Lancet Neurology*. 2014; 13:710–726. [PubMed: 24932993]
- Hirokawa N, Noda Y, Tanaka Y, Niwa S. Kinesin superfamily motor proteins and intracellular transport. *Nat Rev Mol Cell Biol*. 2009; 10(10):682–696. [PubMed: 19773780]
- Jamuar SS, Lam AT, Kircher M, D’Gama AM, Wang J, Barry BJ, Zhang X, Hill RS, Partlow JN, Rozzo A, Servattalab S, Mehta BK, Topcu M, Amrom D, Andermann E, Dan B, Parrini E, Guerrini R, Scheffer IE, Berkovic SF, Leventer RJ, Shen Y, Wu BL, Barkovich AJ, Sahin M, Chang BS, Bamshad M, Nickerson DA, Shendure J, Poduri A, Yu TW, Walsh CA. Somatic mutations in cerebral cortical malformations. *N Engl J Med*. 2014; 371:733–743. [PubMed: 25140959]
- Padzik A, Deshpande P, Hollos P, Franker M, Rannikko EH, Cai D, Prus P, Magard M, Westerlund N, Verhey KJ, James P, Hoogenraad CC, Coffey ET. *KIF5C* S176 Phosphorylation Regulates Microtubule Binding and Transport Efficiency in Mammalian Neurons. *Front Cell Neurosci*. 2016; 10:57. [PubMed: 27013971]
- Poirier K, Lebrun N, Broix L, Tian G, Saillour Y, Boscheron C, Parrini E, Valence S, Pierre BS, Oger M, Lacombe D, Genevieve D, Fontana E, Darra F, Cances C, Barth M, Bonneau D, Bernadina BD, N’Guyen S, Gitiaux C, Parent P, des Portes V, Pedespan JM, Legrez V, Castelnau-Ptakine L, Nitschke P, Hieu T, Masson C, Zelenika D, Andrieux A, Francis F, Guerrini R, Cowan NJ, Bahi-Buisson N, Chelly J. Mutations in *TUBG1*, *DYNC1H1*, *KIF5C* and *KIF2A* cause malformations of cortical development and microcephaly. *Nat Genet*. 2013; 45:639–647. [PubMed: 23603762]
- Willemsen MH, Ba W, Wissink-Lindhout WM, de Brouwer AP, Haas SA, Bienek M, Hu H, Vissers LE, van Bokhoven H, Kalscheuer V, Kasri N Nadif, Kleefstra T. Involvement of the kinesin family members *KIF4A* and *KIF5C* in intellectual disability and synaptic function. *J Med Genet*. 2014; 51:487–494. [PubMed: 24812067]

Figure 1.

Clinical photographs and brain MRI images of our two *KIF5C* mutation-positive patients.

A–B, facial photographs of patient LR16-416 showing a low-sloping forehead, prominent nose with a high nasal bridge, relatively large mouth, prognathism, and synophrys. **C–D**, T1-weighted mid-sagittal (C) and T2-weighted axial (D) brain MRI image of patient LR16-416 at age 3 years showing a mildly thin corpus callosum, subtle irregularity of the cortical gray-white matter junction suggestive of dysgyria with a thick cortex in the frontal lobes and perisylvian regions. The lateral and third ventricles were mildly enlarged. The cerebellar vermis was mildly small with subtle foliar dysplasia. **E–F**, facial photographs of patient LR17-160 showing relatively large mouth, prognathism and mildly arched eyebrows. **G–H**, T1-weighted mid-sagittal (G) and T2-weighted axial (I) brain MRI image of patient LR17-169 at age 10 months showing a thin corpus callosum, mild ventriculomegaly with mildly increased extra-axial space, and bilateral frontal and mesial cortical dysgyria characterized by undersulcation and simplification of the gyral pattern in those regions (arrows).

Table 1

Reported individuals with *KIF5C* mutations (N = 6, including the two individuals reported in this study)

Data	Poirier et al., 2013 (Patient P20) *	Willmsen et al., 2014 (Patient 2)	Cavallin et al., 2015 (Patient 3)	Jamuar et al., 2014 (LIS-6801)	Patient 1 (LR16-416)	Patient 2 (LR17-160)
Gender	Male	Female	Male	Female	Male	Female
Age last assessed	1 month	15 years	7 years	ND	13 years	11 years
Last OFC SD (age)	[ND, MIC]	[ND, MIC]	+0.5 SD (7y)	ND	-1.5 SD (13y)	-2 SD (11y)
Seizures	+	+	-	ND	+	+
Seizure onset	1 month	6 months	NA	ND	1 month	3 months
Seizure types	Clonic	ND	NA	ND	Generalized epilepsy	Febrile, GTC
Epilepsy severity	Treated with carbamazepine	ND	NA	ND	Intractable	Intractable
Tone abnormalities	Spastic quadriplegia	Mild hypotonia	ND	ND	Spastic quadriplegia	Hypotonia
Behavioral problems	ND	Stereotypic hand movements	Stereotypic hand movements, inappropriate laughter	ND	Stereotypic hand movements	Self-injurious behavior, aggression, impulsivity
ID	ND	Severe ID, non-verbal, walked with support at age 9-10 years	Severe delays, non-verbal	ND	Non-verbal, non-ambulatory	Non-verbal, ambulatory
Dysmorphic facial features	ND	Apparent MIC	ND	ND	+	+
Other notable medical problems	IUGR, severe arthrogryposis	Severe auto mutilation	Auto mutilation	ND	Static encephalopathy, bilateral hip dysplasia, SMA5	Pica, nocturnal enuresis
Age at brain MRI scan	7 days	15 years	5.5 years	ND	1 year, 3 years	10 months
Cortical abnormalities	PMG-pachygyria (F, PS)	Pachygyria (mesio-F)	Pachygyria (F), 1 PVNH	Subcortical pachygyria/SBH (posterior)	Mild pachygyria (mesio-F)	Mild pachygyria (mesio-F)
Ventriculomegaly/hydrocephalus	+, VMEG	-	+, VMEG	+, VMEG	+, mild VMEG	+, mild VMEG
Cerebellar abnormalities **	-	-	-	-	Mild CBVH, subtle foliar dysplasia	-
Callosal abnormalities	Thin	-	Thin, dysplastic	Thin, dysplastic	Thin	Thin
Testing method	ND	Trio based WES	Trio based WES	Targeted panel	Targeted NGS panel	Targeted NGS panel
cDNA	c.710A>T	c.709G>A	c.709G>A	c.805G>T	c.709G>A	c.709G>A
Amino acid	p.Glu237Val	p.Glu237Lys	p.Glu237Lys	p.Ala268Ser	p.Glu237Lys	p.Glu237Lys

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Data	Poirier et al., 2013 (Patient P20) *	Willemssen et al., 2014 (Patient 2)	Cavallin et al., 2015 (Patient 3)	Jamuar et al., 2014 (LIS-6801)	Patient 1 (LR16-416)	Patient 2 (LR17-160)
Inheritance	*See notes	De novo	De novo	NA	De novo	De novo

Notes:

* This child is a member of a family of four affected boys, all with reported brain malformations and microcephaly. The three other affected siblings died *in utero*. All four maternal siblings were found to have the p.Glu237Val *KIF5C* mutation by segregation analysis suggestive of maternal germline mosaicism.

** Limited brain images for several patients.

Abbreviations: CBVH, cerebellar vermis hypoplasia; CC, corpus callosum; CTX, cortex; F, frontal; ID, intellectual disability; MIC, microcephaly; ND, no data; PMG, polymicrogyria; PS, perisylvian; SD, standard deviations; SMAS, superior mesenteric artery syndrome; VMEG, ventriculomegaly.

KIF5C transcript ID: NM_004522.2.