Neuroradiological Findings In Children With Genetic Variants In *KIF11*

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INTRODUCTION

Pathogenic *KIF11* variants are associated with a rare autosomal dominant disorder characterized by microcephaly, chorioretinopathy, lymphedema of the lower extremities, and intellectual disability (MCLID)[1,2]. This syndrome is well-described in the literature, but very limited information has been published about the spectrum of neuroradiological findings associated with this gene (e.g. abnormal gyral pattern, optic nerve atrophy, and vermian atrophy[3,4]), despite similar genes in the same kinesin family as *KIF11* being linked to a wide spectrum of brain malformations. Here, we aim to build upon the reported phenotypes. Therefore, we have assembled a cohort of 4 patients with known disease-causing *KIF11* variants who have been identified to have neuroanatomical abnormalities and expand the phenotypic spectrum of *KIF11*.

BACKGROUND

Abnormal cellular microtubule (MT) assembly and dysfunction can lead to significant developmental anomalies. Neurologically, such aberrant function can affect neuronal proliferation, maturation, dendritization, and migration[5-7], in turn producing a spectrum of associated manifestations, including microcephaly, polymicrogyria, pachygyria, and heterotopias[8-10]. Kinesin family (KIF) proteins associate with MTs to traffic intracellular cargoes, control cilia function, and regulate mitosis[11,12]. 45 *KIF* genes are expressed ubiquitously in eukaryotic cells, though some isoforms are solely expressed by neurons[13]. Pathogenic *KIF* variants have been linked to multiple neurologic and systemic congenital anomalies. The phenotypic spectrum of these conditions, referred to collectively as 'kinesinopathies,' can present as ciliopathies, progressive neurodegeneration, ophthalmologic complications, epilepsy, language delay, and intellectual disability[14–17]. While all 45 *KIF* genes are ontologically related, many kinesinopathies demonstrate distinct neurologic and systemic phenotypes (Table 1).

Table 1. Phenotypic spectrum of representative kinesinopathies in human studies and animal models.

Gene	Clinical Presentation Overview	Neurologic Manifestations (Humans)	Animal Model Neurologic Manifestations (Animal Models)
KIF1A	Progressive encephalopathy with developmental delay, hypotonia, and spastic paraparesis[16]	Progressive cerebral and cerebellar atrophy[16]	Marked neuronal degeneration, decreased synaptic vesicle density, and premature death (Mouse)[18]
KIF1C	Hereditary spastic paraplegias (predominantly lower extremities) with ataxia and dystonic tremors[19]	Hypomyelinating leukoencephalopathy with cerebral and upper cervical cord atrophy[20]	Demyelinating plaques, oligodendrocyte hypertrophy, and actin accumulation (Charolais bovine breed knockout)[21]
KIF5C	Early-onset epilepsy and absent language/language delay[15]	Simplified gyral pattern (anterior>posterior), thin corpus callosum, and vermian atrophy[22]	Decreased brain size, motor > sensory neuron depletion (Mouse)[23]
KIF14	Microcephaly, short stature, strabismus, microphthalmia, intellectual disability, ADHD[24]	Simplified frontal gyral pattern, cerebellar hypoplasia, partial agenesis of corpus callosum, and optic nerve hypoplasia[24]	Decreased brain size, small optic nerves, hypomyelination, and disrupted cytoarchitecture. Death before weaning (Mouse knockout)[25]

METHODS

Four patients with confirmed pathogenic variants in *KIF11* were identified through the Neurogenetics Clinic at UPMC Children's Hospital of Pittsburgh. Retrospective chart review was performed to record data on clinical and neuroradiological phenotypes. Magnetic resonance imaging (MRI) T1 and T2 images were obtained on 1.5T and 3T scanners, results were reviewed independently, then detailed analysis was performed by a pediatric neuroradiologist (SS). Patients (or parents if <18 years old) provided signed consent to participate in a Neurogenetics research registry or Case Report/Case Series related to *KIF11* clinical findings. This study was approved by the University of Pittsburgh Institutional Review Board as exempt secondary research.

RESULTS

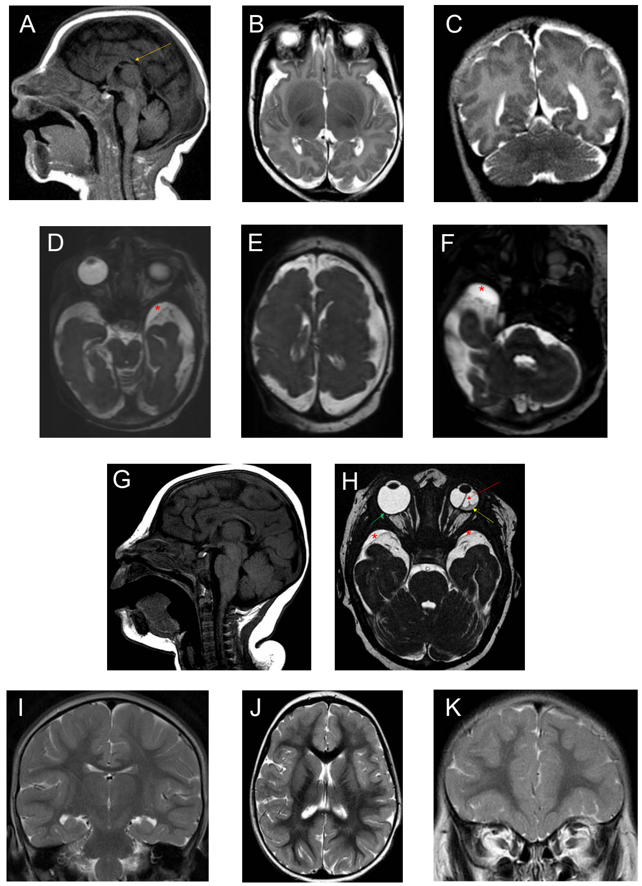

Figure 1. Neuroradiological findings in four patients with *KIF11* variants. Select images from magnetic resonance imaging studies are shown. Sagittal images shown are T1-weighted and axial and coronal images are T2-weighted. Patient 1 (A, B, C) demonstrated microcephaly (A), hypoplastic splenium of the corpus callosum (A, orange arrow), and parietal and occipital lobe polymicrogyria (B,C) . Patient 2 (D, E, F) was found to have microcephaly (D), a simplified gyral pattern (D, E), hypertrophied choroid plexi (E), and bilateral middle cranial fossa arachnoid cysts (D, F denoted by *). Patient 3 (G, H) had microcephaly and simplified gyral pattern (G) with right globe posterior staphyloma (green arrow), left globe persistent hyperplastic primary vitreous (PHPV, red arrow), microphthalmia, retinal detachment (yellow arrow), and bilateral subdural collections (H, denoted by *). Patient 4 (I, J, K) had bilateral hippocampal malrotation (J) and abnormal gyral pattern with prominent sulci and smooth gyri (J,K).

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KIF11 FUNCTION/VARIANT MAP

- Homotetramer crosslinks anti-parallel MTs and produces a bipolar spindle (required for mitosis)[25]
- Transports secretory vesicles from the Golgi apparatus to the cell surface[26]
- Influences axonal length and dendritic shape in developing and mature neurons[27]

Figure 2. Exon diagram of the pathogenic variants in the *KIF11 gene* found in our patient cohort. Created with BioRender.com

CLINICAL PHENOTYPES OF COHORT

Table 2. Clinical presentations of patients confirmed with pathogenic *KIF11* variants represented in this neuroradiological case series.

Patient	Clinical Phenotype
1	Microcephaly, mild developmental delay, hyperopia of both eyes, and a conjunctival cyst of the right eye
2	Microcephaly, familial exudative vitreoretinopathy, exotropia and nystagmus of left eye, and mild developmental delay
3	Microcephaly, chorioretinal atrophy, "coloboma" in right eye, traction retinal detachment in left eye, infantile nystagmus syndrome, microphthalmia, and bilateral myopia
4	Familial exudative vitreoretinopathy, short stature, submucous cleft palate, hyperopia of both eyes, and hypertrichosis

CONCLUSIONS/FUTURE DIRECTIONS

1. Patients with *KIF11* variants have evidence of abnormalities in developmental neuronal proliferation and migration
2. Neuroradiological findings are in alignment with typical findings of other *KIF* orthologs
3. Continue clinical neurodevelopmental follow-up to gauge significance of neurologic anomalies in overall clinical prognosis

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