Title:

De novo Mutations of *KIAA2022* in Females Cause Epileptic Encephalopathy

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Description:

Introduction: The X-chromosome gene *KIAA2022* encodes a protein of unknown function, which is highly expressed in postmitotic neurons in the fetal and adult brain and has been suggested to play an important role in early brain development. Hemizygous loss-of-function mutations in*KIAA2022* have been previously reported in male patients with X-linked intellectual disability and other variable features including mild non-specific dysmorphic features, muscular hypotonia, autistic features, and epilepsy. Carrier females in these families are unaffected with random X-inactivation patterns and normal *KIAA2022* expression levels. While the male *KIAA2022* phenotype is well established, little is known about the phenotype of female patients. Here, we report 11 new female patients with heterozygous *de novo* loss-of-function mutations of *KIAA2022*.

Methods: We evaluated whole genome sequencing, whole exome sequencing, and NGS panel data of individuals with neurodevelopmental disorders and epilepsy to identify female patients with *de novo* mutations in *KIAA2022*. One patient was diagnosed after array CGH indicated a microdeletion disrupting *KIAA2022.* X chromosome inactivation and *KIAA2022* RNA expression studies were performed where possible.

Results: We identified 11 previously unreported female patients, all with *de novo* loss-of-function mutations in *KIAA2022*. Refractory generalized epilepsy with onset in infancy or early childhood was present in 9/11 (81.8%) patients. Myoclonic seizures were a predominant seizure type, seen in 8/9 (88.9%) patients. Other seizure types included absence (7/9; 77.8%), generalized tonic-clonic (6/9; 66.7%), atonic (4/9; 44.4%), and tonic seizures (4/9; 44.4%). Status epilepticus was reported in 3/9 (33.3%) patients with epilepsy. Cognitive outcomes ranged from mild to severe intellectual disability. All but one patient had limited speech and language skills. Autism or autistic features were noted in 6/11 (54.5%) patients. Behavioral problems including aggression, hyperactivity, and ADHD were identified in 8/11 patients (72.7%). X chromosome inactivation studies revealed a random inactivation pattern in 6/7 patients (85.7%), but a ratio of 0:100 in 1/7 (14.3%)*KIAA2022* RNA expression studies showed detectable but decreased expression in 4/5 patients (80.0%) and absent RNA expression in the patient with 100% skewed X-inactivation. The patient with 100% skewing and absent expression did not have seizures and had a phenotype more consistent with affected males, including severe generalized hypotonia, microcephaly, postnatal growth restriction, and mild dysmorphic facial features. In comparison to previously described affected males, females with *KIAA2022* encephalopathy do not show the distinct phenotype characterized by severe intellectual disability, microcephaly, growth restriction, and dysmorphic facial features as seen in most males. However, refractory generalized seizures consistent with epileptic encephalopathy were a prominent feature in affected females.

Conclusion: *De novo* loss-of-function mutations in *KIAA2022* in females cause a distinctive phenotype characterized by refractory myoclonic epilepsy, mild to severe intellectual disability, autistic features, and behavioral disturbances. This phenotype is in contrast to the male phenotype which is characterized by more severe intellectual disability and dysmorphic features. The mechanisms that may underlie the female phenotype may

be haploinsufficiency or cellular interference, due to a mosaic cell population expressing both mutant and wild type cells. Random X-chromosome inactivation patterns, both in affected and unaffected carrier females, suggest that other factors explain the strongly reduced expression in symptomatic females.

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