CLINICAL REPORT

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KIAA2022 Nonsense Mutation in a Symptomatic Female

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Mutations in the *KIAA2022* gene have been implicated in non-syndromic X-linked intellectual disability. Thus far, all carrier females reported have been unaffected and genotype–phenotype correlations have not been described. Herein, we report a de novo *KIAA2022* nonsense mutation in a 17-year-old female with short stature, microcephaly, severe intellectual disability, poor speech, epilepsy, and autistic behavior. X-inactivation pattern is normal suggesting that the mutation is causing the phenotype. This report contests the current view that *KIAA2022* mutations only affect males, which has implications for testing and genetic counseling. © 2015 Wiley Periodicals, Inc.

Key words: *KIAA2022*; X-linked; intellectual disability; X-inactivation; epilepsy; autism

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INTRODUCTION

Hemizygous mutations in the *KIAA2022* gene are associated with non-syndromic X-linked intellectual disability (ID). The phenotypic spectrum includes moderate to severe ID with autistic features, poor or absent speech, epilepsy, and mild facial dysmorphisms [Van Maldergem et al., 2013]. Thus far, all reported males with *KIAA2022* mutations are symptomatic while all reported females are asymptomatic. Herein, we present a female with a de novo *KIAA2022* nonsense mutation who displays the characteristic phenotype of an affected hemizygous male. To our knowledge, this case represents the first symptomatic female with a *KIAA2022* mutation reported to date. X-inactivation studies were normal, suggesting that the mutation could be causing the phenotype.

CLINICAL REPORT

The patient was initially evaluated at 16 years of age for ID, refractory epilepsy, and short stature. She was the product of a 23-year-old gravida 4 para 3 mother and a 34-year-old father. The pregnancy was notable only for increased fetal movement. She was born full term with no complications and normal growth parameters. She sat at 6 months and walked at 1–1.5 years. Concerns initially arose at 12 months, when she developed abnormal blinking episodes. At 18 months, she experienced what the family described as difficulty walking, after having had already acquired this milestone. She was diagnosed with hypotonia and epilepsy at that time. Despite numerous antiepileptic medications (carbamazepine, divalproex sodium, topiramate, lamotrigine, lacosamide, levetiracetam, rufinamide, clobazam, lacosamide, and clorazepate) her epilepsy was poorly controlled, and she experienced multiple seizures per day. Types of seizures included absence, atonic drop, tonic, and generalized tonic clonic seizures. At 9 years old, a vagal nerve stimulator was placed but her seizures persisted. From age 13 to 16 years, there was an increase in seizure frequency and intensity. At age 17, a corpus callosotomy was performed with vast improvement in seizure frequency. At the time of this report, she continues taking multiple antiepileptic agents, including lacosamide, clorazepate, and lamotrogine and continues to seize once per day. Her vocabulary consists of only two words which she learned at age 2. She is not toilet trained and not able to indicate wants. She has repetitive behaviors, aggression, and hyperactivity. She has three healthy siblings and no family history of seizures or ID.

On physical exam, height is −4 SD from the mean, weight is −3 SD from the mean, and head circumference is −2 SD from the mean. There is thick coarse hair, narrow forehead, prominent nasal bridge, brachydactyly, bilateral 5th finger clinodactyly, and a single transverse palmar crease on the right hand (Figs. 1 and 2). Skin exam demonstrates a café-au-lait macule on the right hip accompanied by inguinal freckling on that side only. She has repetitive movements and rocking. She will not stay seated unless held by her

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FIG. 1. Frontal and profile views of the proband demonstrate thick, coarse hair, bitemporal narrowing, and prominent nasal bridge without other dysmorphic features. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga].

parents. She speaks in occasional single words and follows simple commands. Tone, strength, muscle bulk, sensation, and deep tendon reflexes are all normal. She walks unassisted and reaches and grasps for objects without dysmetria or tremor.

Brain imaging demonstrates no structural brain abnormality prior to the corpus callosotomy surgery. Video electoencephalogram prior to the corpus callosotomy surgery demonstrated frequent clinical and electrographic seizures suggestive of both multifocal and generalized epilepsy. Specific features included bursts or runs of rhythmic generalized slow-frequency epileptiform activity, with an occasional maximum over the bi-frontal or central leads, associated with clinical staring, blinking, and decreased responsiveness. Another primary seizure type involved runs of generalized fast frequency epileptiform activity, often maximal over the left occipital area, typically associated with clusters of brief clinical head drops. In addition, intermittent interictal epileptiform discharges were seen independently over the left and right temporal/frontotemporal areas, as well as in a generalized distribution with an occasional bi-frontal, left frontal, or right frontal maximum. Metabolic studies, including plasma amino acids, urine organic acids, plasma and urine creatine and guanidinoacetate, total plasma homocysteine, and cerebrospinal fluid amino acid analyses were normal.



FIG. 2. Proband's right hand demonstrates brachydactyly, 5th finger clinodactyly, and single transverse palmar crease. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga].

Comprehensive chromosomal microarray analysis (Kleberg Cytogenetics Laboratory CMA + HR + SNP, version 10.1) demonstrates a 0.113 Mb copy number loss at 7p22.3 in a non-disease associated region (GRCh37/hg19 Assembly: minimum interval 2076135–2189398; maximum interval 2065241–2207938). The asymptomatic father also carries this variation. Whole exome sequencing was performed clinically by Baylor College of Medicine Medical Genetics Laboratory using whole exome sequencing version 2. Analysis was based on phenotypic data provided including delayed motor milestones, delayed speech, intellectual disability, hypotonia, seizure disorder (cryptogenic generalized epilepsy), short stature, failure to thrive, skin anomalies (single large café-au-lait on right leg, inguinal freckling), short stubby fingers, clinodactyly of 5th finger, and single palmar crease. A heterozygous c.964C>T, p.R322X (NM_001008537) pathogenic variant in the *KIAA2022* gene was detected. Sanger sequencing analysis of this region in the parental samples did not detect the variant, suggesting that the change arose de novo in this patient. There were no other

pathogenic variants or likely pathogenic variants in disease genes related to the clinical phenotype. Variants of unknown clinical significance in genes associated with autosomal dominant inheritance included a heterozygous variant in the *ADAR* gene (NM_001111:c.1024G>T, p.D342Y) inherited from her asymptomatic father and a heterozygous variant in the *GPR98* gene (NM_032119:c.7582C>T, p.P2528S) inherited from her asymptomatic mother. Other variants of unknown clinical significance were found in genes associated with autosomal recessive inheritance. All of these variants were heterozygous, and none were found in genes in the region of her copy number loss. Analysis of the Androgen Receptor locus performed at Greenwood Genetics Laboratory demonstrated a random X-inactivation pattern (73:27).

DISCUSSION

KIAA2022 is located on Xq13.3 and thus far has appeared to cause symptomatology only in males. In 2013, Van Maldergem et al. described four unrelated families with mutations in the *KIAA2022* gene. In all reported families, the mutation was inherited from a female. All males with the mutation (n = 9) were symptomatic while all females harboring the mutation (n = 9) were asymptomatic. All affected males had ID, which varied from mild to profound, poor or absent speech, and strabismus. They all learned to walk, but most were delayed in acquiring this milestone with the oldest acquisition at 4 years. Most patients had seizures, autistic features, including repetitive movements and rocking, and lack of sphincter control. Height was typically two standard deviations below the mean and microcephaly was present in half. Mutations included an X-chromosome inversion with breakpoint in exon 1; a 70 kb microduplication containing exon 1; and two frameshift mutations (c.186delC and c.3597dupA) resulting in premature stop codons [Van Maldergem et al., 2013]. In the family with the X-chromosome inversion, one of the two obligate female carriers was evaluated and found to have a skewed X-inactivation pattern but remained asymptomatic [Cantagrel et al., 2004]. Kuroda et al. [2015] recently reported two more cases of *KIAA2022* mutations found in males with similar symptomatology including hypotonia, delayed development, autistic behavior, poor or absent speech, and height at least two SD below the mean. One patient had microcephaly. Similar dysmorphic features found in both patients included upswept hair, narrow forehead, downslanting eyebrows, long nose, hypoplastic alae nasi, thin lips, open mouth, and large ears. Both had de novo nonsense mutations in the coding region of exon 3 (c.2113C>T, p.Q705X and c.964C>T, p.R322X) [Kuroda et al., 2015]. The second of these variants is the variant detected in the presented case.

The presented patient's phenotype is consistent with the phenotype described in males with hemizygous *KIAA2022* mutations, including severe ID, poor speech, hypotonia as a child, seizures, repetitive movements, persistent rocking, hyperactivity, head size 2 SD below the mean, and height more than two SD below the mean. Like affected males, she has mild dysmorphisms only, specifically bitemporal narrowing. She has a single transverse palmar crease not reported in other males, but reflective of hypotonia reported in most cases. Seizure types found in this patient, including generalized tonic clonic, absence, and atonic seizures, have been reported in affected males. To our knowledge, this patient is the first reported symptomatic female with a *KIAA2022* mutation. Her mutation is a nonsense mutation that has recently been described in an affected male. We hypothesize that this mutation is responsible for her symptoms as WES and CMA did not elucidate other causes, the mutation is de novo and pathogenic, and her phenotype matches those of reported males.

With increased clinical experience and gain of knowledge on the molecular level, terminology for X-linked disorders has changed from X-linked dominant and X-linked recessive to X-linked [Dobyns et al., 2004; Dobyns, 2006]. Many cases of X-linked diseases exist which are fully penetrant and more severe in hemizygous males; but have some penetrance in females as well. Typically heterozygous females are less severely affected than hemizygous males. Reasons for females to have a more severe phenotype resembling that of hemizygous males include having only one X chromosome or skewed X-inactivation. X-inactivation is typically a random process wherein most of the genes on one X are silenced, resulting in equalization of dosage of these genes in males and females [Van den Veyver, 2001]. As the process is random, it is expected that females have about 50% of each X inactivated, much like flipping a coin. Skewed X-inactivation can occur for several reasons, including stochastic effects, positive or negative selection, and inherited mutations or epigenetic mutations affecting the genes responsible for X-inactivation [Van den Veyver, 2001]. Regardless of the reason, in a female with either skewed X-inactivation or monosomy X, the genotype more closely resembles that of a hemizygous male, explaining the phenotypic similarity to an affected male. Conversely, the presented patient has a severe phenotype similar to hemizygous males yet her chromosomal microarray and X-inactivation studies demonstrate that she has two X chromosomes and a normal X-inactivation pattern.

There are several proposed reasons to explain why the presented patient displays the severe phenotype of hemizygous males, while demonstrating normal female chromosomal compliment with normal X-inactivation pattern. As this mutation has not been previously described in a female, one proposed explanation is that the mutation itself may be enough to cause severe symptomatology in a female. However, mechanistic reasons for this are unclear. The exact function of the *KIAA2022* gene product is not well described but is thought to have a major role in neuron development and brain function [Cantagrel et al., 2009]. Previously described *KIAA2022* mutations found in asymptomatic females are thought to result in premature stop codons, similar to the presented patient's mutation. However, the presented patient's mutation differs in that the mutation is downstream from others described. Perhaps the stop codon is downstream enough to allow the gene product to be made, resulting in interference with normal gene product or other cellular processes. Or perhaps this mutation in conjunction with the presented patient's specific X-inactivation pattern (73:27), although not categorized as "skewed," is enough to demonstrate effect. As there is a report of an asymptomatic carrier female with a different mutation (X-chromosome inversion with breakpoint in exon one of *KIAA2022*) who demonstrated skewed X-inactivation, the threshold amount of X-inactivation skewing may be mutation specific. It is also possible that the presented patient is mosaic

and has either skewed X-inactivation or monosomy X in the brain, which is not being detected in the blood. In that case, the genotype in her brain cells would be similar to hemizygous males, explaining the indistinguishable phenotype. Another possibility is that her second copy of the *KIAA2022* gene has a variant that was not detected by whole exome sequencing or chromosomal microarray. Further studies, including RNA and protein function studies would be helpful in elucidating the effect of this mutation.

This report demonstrates that *KIAA2022* mutations may cause disease in females. This finding has important implications for genetic counseling and patient selection for genetic testing. Further studies would be helpful in elucidating the factors that cause females with *KIAA2022* mutations to be symptomatic.

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