Neurodevelopmental Defects Due to Haploinsufficiency of *KMT2E*

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BACKGROUND

- The lysine-specific methyltransferase 2E (*KMT2E/MLL5*) gene codes for a KMT2 family of proteins that specifically methylate the Lysine-3 of the H4 histone via their SET domains. However, KMT2E lacks a functional SET domain.
- Other KMT2 genes such as *KMT2A, KMT2B,* and *KMT2D* are known to cause neurodevelopmental disorders in humans when mutated.
- Initial reports of *de novo* truncating variants affecting *KMT2E* involved only three patients: one with intellectual disability, macrocephaly and possible developmental regression but no seizures (Iossifov, 2012); another with intellectual disability, speech regression, seizures, but normal growth parameters (Dong, 2014) and the DECIPHER patient #263273 with intellectual disability, delayed speech, ataxia, visual and hearing impairment, and focal seizures.
- Recently, over 30 patients with neurodevelopmental deficits with *de novo* mostly truncating mutations in *KMT2E* were reported. Some common features of these patients were intellectual disability, macrocephaly, autism, gastrointestinal abnormalities, and epilepsy (O'Donnell-Luria, 2019).
- Here we present three patients (2 new and 1 previously published) with similar features all of who had truncating mutations in *KMT2E* of whom one had inherited the mutation from a mildly affected parent. This is the first report of an inherited pathogenic mutation in *KMT2E*.

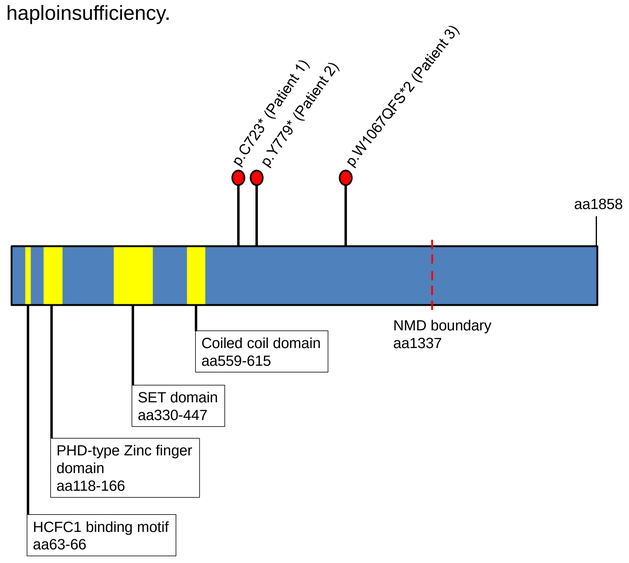
METHODS

- Trio-based diagnostic whole exome sequencing was performed on the proband and relatives as previously described [Farwell KD, *et al*. (2014) *Genet Med* **17**(7):578-586] with the exception of the capture reagent used which was IDT xGen Exome Research Panel V1.0. Approximately 97% of each individual's exome was covered at 20X or higher.
- Population frequency cutoffs for variant filtering included 0.1% for dominant, 1% and 0.2% for recessive characterized and uncharacterized genes, respectively, and 0.2% for incomplete penetrance models. The latter model included variants that are found in the Human Gene Mutation Database (HGMD), those that cause truncations such as frameshift, nonsense, and canonical splice, and those found in known imprinted disorder-causing genes. Population databases used were 1000 Genomes Project, Exome Sequencing Project (ESP), and Exome and Genome Aggregation Consortia (ExAC and gnomAD, respectively).

TABLE 1. CLINICAL FEATURES OF 3 FEMALE PATIENTS WITH TRUNCATING *KMT2E* MUTATIONS

PATIENT #	1	2	3 (patient #19 in O'Donnell-Luria, 2019)
Variant	*KMT2E* NM_182931.2 c.2169T>A p.C723*	*KMT2E* NM_182931.2 c.2337C>A p.Y779*	*KMT2E* NM_182931.2 c.3198_3234DEL37 p.W1067QFS*2
Inheritance	Inherited from affected mother	*De novo*	Not maternal but father unavailable for testing
Age last assessed	10y 6mo	4y	7y 5mo
Ethnicity	Caucasian	Caucasian	Caucasian
Pertinent family history	Mother received help in school from 6th grade to high school. Maternal uncle has ADHD and required special ed. Father had difficulty in school, especially math, but did not receive special ed. Paternal aunt had septal defect which was surgically repaired.	None	None
BIRTH			
Gestational age	n/a	39 weeks	35
Birth weight	n/a	2.67 kg (-1.44 SD)	3.29 (+2 SD)
Birth length	n/a	48.3 cm (-0.51 SD)	48.3 cm (+1 SD)
Birth head circumference	n/a	n/a	Noted to have a large head
GROWTH			
Height (and SD) at most recent assessment	132.6 cm (-1.31 SD)	100.5 cm (-0.24 SD)	139.7 cm (+2.61 SD)
Weight (and SD) at most recent assessment	29 kg (-1.23 SD)	15.6 kg (-0.17 SD)	31.07 kg (+1.17 SD)
Head circumference (and SD) at most recent assessment	53.4 cm (+0.7 SD)	51.4 cm (+1.15 SD)	55.9 cm (+3.4 SD)
Growth abnormalities	None	High head circumference (90 percentile) but not quite macrocephalic; Has squamous craniocynostosis	Macrocephaly and tall stature
NEUROLOGICAL			
Intellectual disability	Mild (IQ=54)	Concern for cogntive skills	Yes
Developmental delay	Yes	Yes	Yes; regression seen at 7mo
Age - 1st walked	n/a	n/a	17mo
Age - 1st words	n/a	n/a	11mo then lost speech; again at 23mo; sentences at 3y
Speech/language development	Receives speech therapy	Expressive speech delay	Delayed
Seizures	No	No	No
Tone	Mildly decreased	Mixed but mostly decreased tone	Low
Autism/behavioral issues	Hyperactive, attention problems, occasional temper tantrums	None	None
Other neurologic findings	None	Static encephalopathy	None
Brain MR imaging, age	Not done	Yes (4y 8mo)	Yes (6y 1mo)
Brain MRI abnormalities	n/a	Bilateral foci of subependymal nodular gray matter heterotopia	Subepindemyal cysts in lateral ventricles
EEG abnormalities (age)	Not done	Not done	Not done
OTHER ORGANS			
Ocular features	None	Previous history of nearsightedness that resolved	Horizontal nystagmus
Dysmorphic features	Deep-set eyes with allergic shiners, right frontal upsweep, mildly cupped ears, slightly overfolded and crumpled helices, small upturned nose, mildly tented upper lip, mild retrognathia, pointed chin, dental crowding	Asymmetric face, upslanted eyes	Tall forehead, frontal bossing, superficial blood vessels on nose, two café-au-lait spots, deep set eyes, flattened posterior helix (same as mother), Cupid's bow, malar flattening, underbite, prominent jaw, dental malocculusion, poor enamel
Palate anomalies	None	n/a	High arched
Cardiovascular problems	Tetralogy of Fallot diagnosed at 6 months (repaired surgically); ECHO showed a large subaortic ventricular septal defect (VSD) with minimal overriding by large aortic root and severe right ventricular flow tract obstruction at pulmonic valve level and subpulmonic area	None	None
Gastrointestinal problems	None	Neonatal feeding difficulties involving a disorganized suck which eventually improved	None
Urogenital/kidney anomalies	None	None	None
Skeletal abnormalities	Mild scoliosis without vertebral anomalies on spinal X-ray,swan necking of the fingers with mild hypermobility of the small joints	None	Slight pectus excavatum, bilateral 4th and 5th finger clinodactyly
Other findings	Recurrent otitis media	Congenital torticollis, abnormal winde-based gait, nasolacrimal duct obstruction, frequent ear infections and otitis media	Ear tubes, diastasis recti at birth as well as a midline hernia, clumsy with balance issues, two cafe-au-lait macules, heavy sweating that "smelled like old beer" from birth to about 4y
Other genetic findings	Array-CGH revealed a 176kb deletion of 17q25.3 that is paternally inherited and not thought to be clinically significant	None	None
Previous normal tests	Karyotype; 22q FISH; FMR1 repeat test; Hepatic function panel; Renal ultrasound; Congenital Heart Disease panel of *GATA4, NKX2-5, JAG1*	Karyotype; SNP microarray; Craniosynostosis multi-gene sequencing and del/dup panel	Microarray, Fragile X, MPS screen, urine organic and amino acids, bone age, Echocardiogram, abdominal ultrasound, Leukocyte enzyme screen for Krabbe and Metachromatic Leukodystrophy

FIGURE 1. Schematic of the full length KMT2E protein showing locations of variants identified in the current patient cohort as well as the various annotated domains. Transcripts with truncating variants that add a new stop codon prior to the nonsense-mediated decay (NMD) boundary are expected to be degraded and result in haploinsufficiency.



TAKE HOME POINTS

- We report 2 new patients with truncating mutations in *KMT2E*
- Our report confirms a previous report that truncating mutations in *KMT2E* cause neurodevelopmental defects (O'Donnell-Luria, 2019).
- We present the first report of a pathogenic mutation in *KMT2E* that was inherited from a mildly affected parent, thereby expanding its inheritance spectrum

REFERENCES

Dong S, *et al*. (2014) *Cell Rep* **9**(1): 16-23.

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