

Xu He  
Oana Caluseriu, MD  
Ratika Srivastava, MD  
Anne Marie Denny, MD  
Francois V. Bolduc, MD,  
PhD

*Neurol Genet*  
2016;2:e58; doi: 10.1212/  
NXG.000000000000058

## REVERSIBLE WHITE MATTER LESIONS ASSOCIATED WITH MUTANT *EHMT1* AND KLEEFSTRA SYNDROME

### OPEN

Kleefstra syndrome (KS; OMIM #610253), formerly known as the 9q subtelomeric deletion syndrome, is an autosomal dominant cause of intellectual disability (ID) characterized by hypotonia and facial dysmorphisms.<sup>1,2</sup> The cause of KS is attributed to haploinsufficiency of the euchromatin histone methyltransferase 1 (*EHMT1*) gene (OMIM \*607001) located at chromosome 9q34.3 (i.e., distal long arm of chromosome 9), either by microdeletion or point mutation. *EHMT1* encodes a histone H3 methyltransferase at position Lys-9 (H3K9).<sup>1–3</sup>

*EHMTs* (including *EHMT1*) form an evolutionarily conserved family that regulates neuronal activity via histone methylation and chromatin modification resulting in transcriptional control.<sup>2–5</sup> Several cases of *EHMT1*-negative patients exhibiting the KS phenotype with mutations in 4 functionally similar epigenetic regulator genes (*MBD5*, *MLL3*, *SMARCB1*, and *NRI13*) have been reported.<sup>3,4</sup> *EHMT1* knockout mice also display impaired fear conditioning, indicative of learning and memory defects.<sup>6</sup> Similar studies have also been demonstrated in *Drosophila*.<sup>5</sup>

Neuroimaging in patients with KS has not been consistently reported (table e-1 at [Neurology.org/ng](http://Neurology.org/ng)). In many cases, normal MRIs were noted, although white matter (WM) changes and corpus callosum hypoplasia have been observed. Of interest, differentiation in oligodendrocyte development, an important process in the myelination of the CNS, has been shown to be affected by epigenetic regulation.<sup>7</sup>

**Case report.** *Presentation.* The patient initially presented as a 20-month-old ambidextrous boy with global developmental delay and facial dysmorphic features, including midfacial hypoplasia, horizontal palpebral fissures, prominent lower lip, and upturned ear lobes, characteristic of KS. Pregnancy, perinatal, and family history were unremarkable. Developmental delay was first noticed at 8 months, and the patient did not sit independently until 12 months of age. He was found to have severely impaired gross motor skills with moderate impairment in language. Examination revealed 75th percentile for weight, length,

and head circumference. Cranium was abnormally shaped with right plagiocephaly. There were no focal anomalies on his neurologic examination.

*Follow-up.* By age 4 he could walk independently and sit on a tricycle. He was diagnosed with severe expressive speech delay and moderate receptive speech delay. Most of his communication came from signing and use of a Picture Exchange Communication System; he nonspecifically used the single word “mom.” He was very social with family and strangers alike. At age 7, he remained nonverbal.

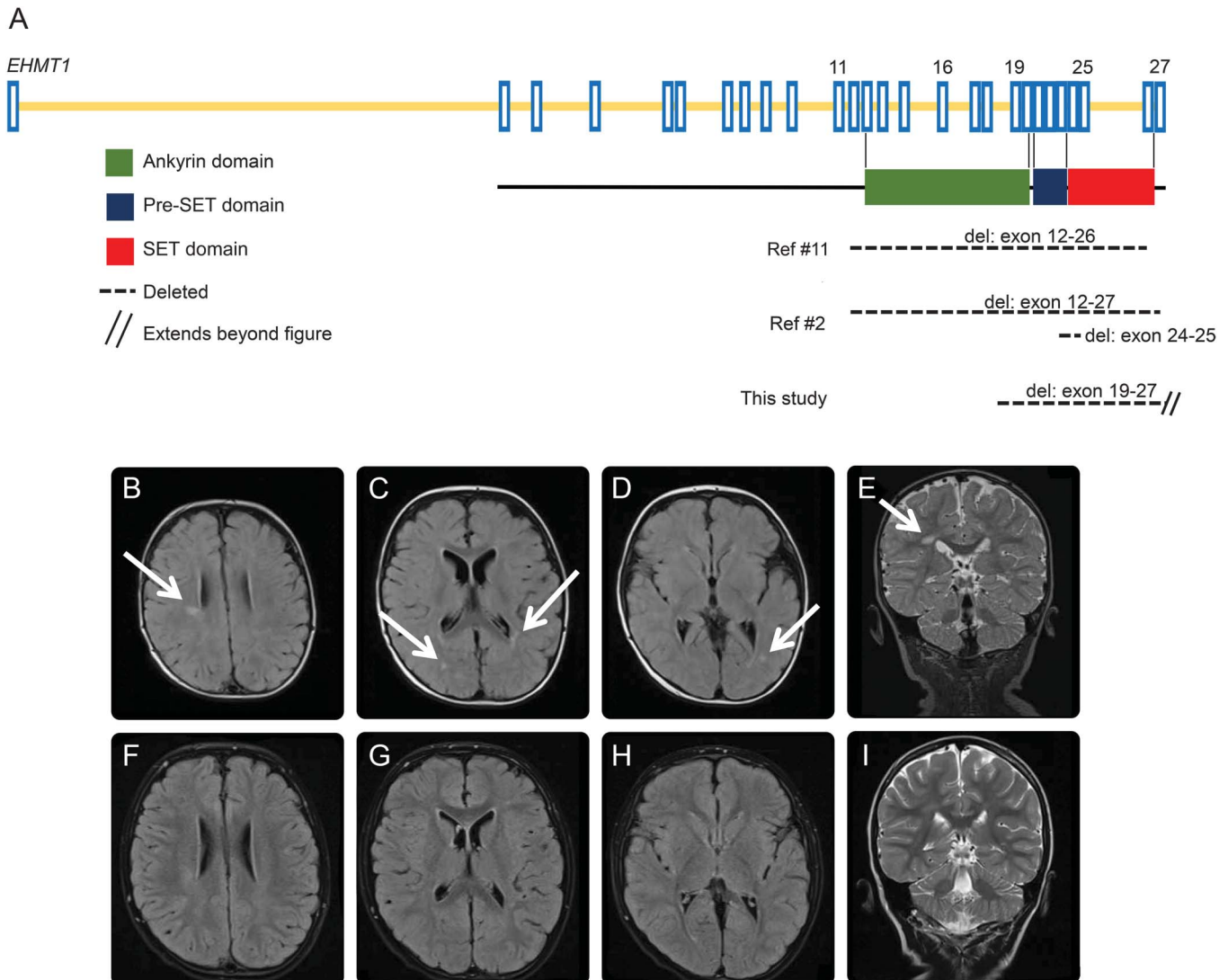
*Investigations.* Using chromosomal microarray analysis, a 60,654-bp interstitial deletion spanning the distal long arm of chromosome 9 (9q34.3) from nucleotide position 139,816,260 to 139,876,914 (NCBI36/Hg18) was reported. Parental testing was negative, indicative of a de novo lesion. Consent for publication was obtained from the parents. This deletion led to loss of the last 9 exons (i.e., exons 20–28) of the *EHMT1* gene, affecting the pre-SET and SET domains, as well as the last repeats of the ankyrin motif (figure, A). At 2 years, he had a brain MRI showing several T2 and fluid-attenuated inversion recovery hyperintensities in periventricular WM, bilaterally seen at various levels (figure, B–E). Of interest, a repeat MRI of the brain at age 6 showed marked reduction or resolution of the previously identified WM abnormalities (figure, F–I).

**Discussion.** KS is a recognized cause of syndromic ID associated with *EHMT1* mutations. WM abnormalities have been reported previously on MRIs of patients with KS. Available neuroimaging data (table e-1) suggest that WM lesions are frequent brain abnormalities observed in KS. However, serial imaging has not been reported systematically for most of these patients.

There is growing evidence in recent years for the role of epigenetic temporal changes that affect structural brain changes in relation to neurodevelopmental phenotypes (i.e., Rett syndrome, autism spectrum disorder). The SET domain is responsible for histone methylation in humans,<sup>8</sup> and conditional ablation of *Ehmt1* in postnatal mouse forebrain neurons causes a reduction in euchromatic H3K9 methylation and upregulation of neuronal and non-neuronal genes. Transition from electrically active to myelinating oligodendrocytes requires H3K9 methylation. It remains unclear whether this is *EHMT1* dependent.

Supplemental data  
at [Neurology.org/ng](http://Neurology.org/ng)

**Figure** Genetic deletion and MRI changes with *EHMT1* deletion



(A) *EHMT1* gene is represented (top) with its numbered exon regions (merged into Hg19 assembly). The *EHMT1* protein includes 3 important functional domains: (1) ankyrin domain, (2) pre-SET domain, and (3) SET domain. Previously published deletions restricted to the functional domains are identified. (B–I) MRI of the brain of the patient described in this study. (B–D) Axial MRI fluid-attenuated inversion recovery images of the brain with arrows pointing toward anomalies noted at 2 years of age. (E) Coronal T2 image of the brain also showing anomalous white matter signal. (F–I) Similar sequences on MRI at 6 years of age showed marked reduction of the hyperintense T2 signal in the region of the white matter anomalies previously seen at 2 years of age.

The ankyrin domain, a second motif deleted in our patient, may also be associated with myelination, in addition to its role in proliferation and migration.<sup>9</sup> Some isoforms of ankyrin localize to the junction between myelinated sheets.<sup>10</sup> Our study illustrates that in addition to its role in neuronal proliferation, *EHMT1* may regulate myelination development and suggests a value in serial imaging in patients with KS.

*From the Department of Pediatrics (X.H., R.S., A.M.D., F.V.B.), Neuroscience and Mental Health Institute (F.V.B.), and Department of Medical Genetics (O.C., F.V.B.), University of Alberta, Edmonton, Alberta, Canada.*

*Author contributions: Xu He: acquisition of data, analysis, manuscript preparation. Oana Caluseriu: data analysis, supervision, manuscript preparation. Ratika Srivastava: acquisition of data, manuscript preparation. Anne Marie Denny: revision of the*

*manuscript for important intellectual content. Francois V. Bolduc: acquisition of data, analysis, manuscript preparation, supervision.*

*Study funding: No targeted funding reported.*

*Disclosure: The authors report no disclosures. Go to Neurology.org/ng for full disclosure forms. The Article Processing Charge was paid by the authors.*

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*Received November 5, 2015. Accepted in final form January 22, 2016.*

*Correspondence to Dr. Bolduc: fbolduc@ualberta.ca*

1. Kleefstra T, Brunner HG, Amiel J, et al. Loss-of-function mutations in euchromatin histone methyl transferase

- 1 (EHMT1) cause the 9q34 subtelomeric deletion syndrome. *Am J Hum Genet* 2006;79:370–377.
2. Willemsen MH, Vulto-van Silfhout AT, Nillesen WM, et al. Update on Kleefstra syndrome. *Mol Syndromol* 2012;2:202–212.
3. Kleefstra T, Kramer JM, Neveling K, et al. Disruption of an EHMT1-associated chromatin-modification module causes intellectual disability. *Am J Hum Genet* 2012;91:73–82.
4. Balemans MC, Kasri NN, Kopanitsa MV, et al. Hippocampal dysfunction in the Euchromatin histone methyltransferase 1 heterozygous knockout mouse model for Kleefstra syndrome. *Hum Mol Genet* 2013;22:852–866.
5. Kramer JM, Kochinke K, Oortveld MA, et al. Epigenetic regulation of learning and memory by *Drosophila* EHMT/G9a. *PLoS Biol* 2011;9:e1000569.
6. Schaefer A, Sampath SC, Intrator A, et al. Control of cognition and adaptive behavior by the GLP/G9a epigenetic suppressor complex. *Neuron* 2009;64:678–691.
7. Liu J, Magri L, Zhang F, et al. Chromatin landscape defined by repressive histone methylation during oligodendrocyte differentiation. *J Neurosci* 2015;35:352–365.
8. Xiao B, Jing C, Wilson JR, et al. Structure and catalytic mechanism of the human histone methyltransferase SET7/9. *Nature* 2003;421:652–656.
9. Gallagher D, Voronova A, Zander MA, et al. Ankrd11 is a chromatin regulator involved in autism that is essential for neural development. *Dev Cell* 2015;32:31–42.
10. Kordeli E, Davis J, Trapp B, Bennett V. An isoform of ankyrin is localized at nodes of Ranvier in myelinated axons of central and peripheral nerves. *J Cell Biol* 1990;110:1341–1352.
11. Kleefstra T, van Zelst-Stams WA, Nillesen WM, et al. Further clinical and molecular delineation of the 9q subtelomeric deletion syndrome supports a major contribution of EHMT1 haploinsufficiency to the core phenotype. *J Med Genet* 2009;46:598–606.