Paternal Constitutional Mosaicism Resulting in Inheritance of Weidemann-Steiner Syndrome: A Rare Case Report

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Introduction

Weidemann-Steiner syndrome (WSS) is a rare genetic condition characterized by hypertrichosis cubiti associated with short stature, distinctive facial features, and mild to severe developmental delay.

Reported cases are due to *de novo* mutations in the *KMT2A* gene, although a familial hypertrichosis cubiti was previously described.

We describe two siblings with inherited *KMT2A* mutations and the rare finding of paternal constitutional mosaicism.

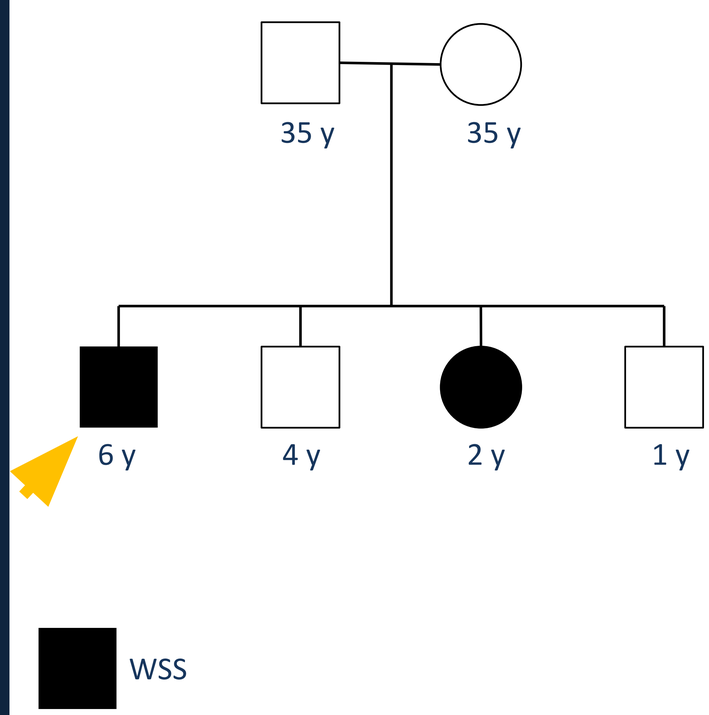
Case Presentation

The proband, a 6-year-old male, was born at term, the first child of non-consanguineous parents. He was evaluated for mild global delay with remarkable speech delay.

His family history was positive for his father with childhood mild speech delay, and his 2-year-old sister with mild global delay on a closer follow up.

Physical exam revealed a distinctive facial features detailed below.

Pedigree



Clinical Features

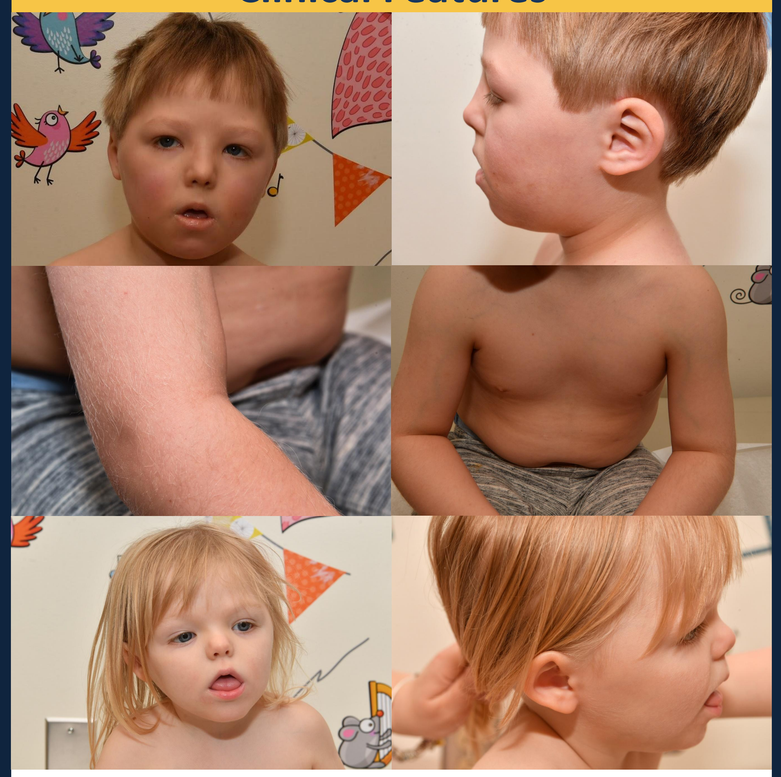


Figure 1. Clinical Features of Case Patients.
Thick eyebrows, wide nasal bridge, and down-slanting and vertically narrow palpebral fissures, flat face, short nose with thick alae, low-set ears, small mouth, hypertrichosis cubiti, and translucent skin.

Methods and Results

Whole Exome Sequencing (trio) was performed on the proband.

A pathogenic variant in the *KMT2A* gene (c.4706_4707ins10 (p.C1569X) was found on the proband which was reported *de novo* (parental testing was negative). The molecular diagnosis was consistent with his clinical phenotype confirming WSS.

Given the proband's diagnosis, targeted genetic testing was performed on the proband's sister, which revealed the same pathogenic variant in *KMT2A* as the proband.

The proband's other two siblings, where one also has mild speech delay, were also investigated, and targeted genetic testing was negative for the pathogenic variant in *KMT2A* on the proband. CMA results are pending for the sibling with mild speech delay.

Due to the father's history of mild speech delay, further testing was performed, which revealed a low-level mosaicism (4/96) for the *KMT2A* variant using next-generation sequencing.

	Proband 6 yo M	Sibling 2 yo F
KMT2A nucleotide alteration	c.4706_4707ins10 (p.C1569X)	c.4706_4707ins10 (p.C1569X)
Developmental delay	+	+
Hypertrichosis cubiti	+	-
Short stature	+	+
Flat face	+	+
Long philtrum	+	+
Low set ears	+	+
Epicanthal folds	+	+
Translucent skin	+	-

Discussion and Importance

Mutations in KMT2A should be considered in patients presenting with developmental delay, and the characteristic hairy elbows.

Understanding the molecular aspect of post-zygotic mutational event versus revertant mosaicism is important. Partial correction of a germ-line mutation (mutation rescued by somatic events) has been reported with the KMT2A gene mutation in blood disorders.

Constitutional mosaic studies in parents are important not only in WSS, but in unwell defined rare syndromes for accurate future reproductive risk estimates in cases where a variant is identified in a child.

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Acknowledgments

To the patients and their family