KMT2A Haploinsufficiency in a Patient with Multiple Congenital Anomalies, Recurrent Sinopulmonary Infections, and Relapsed Hodgkin Lymphoma

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Introduction

- Wiedemann-Steiner syndrome (WSS) is characterized by developmental delays, short stature, characteristic facial features, multisystem congenital anomalies, and hypertrichosis (especially hypertrichosis cubiti, or hairy elbows)[1].
- Approximately 250 cases have been reported, and at least 89 likely pathogenic monoallelic variants identified in its causative gene, KMT2A.
- Though autosomal dominant, over 55% of KMT2A mutations are de novo [1-3].
- Recent identification of novel KMT2A variants has illuminated significant heterogeneity in genotype–phenotype correlation with WSS and its increasing association with immunodeficiency [1-7]

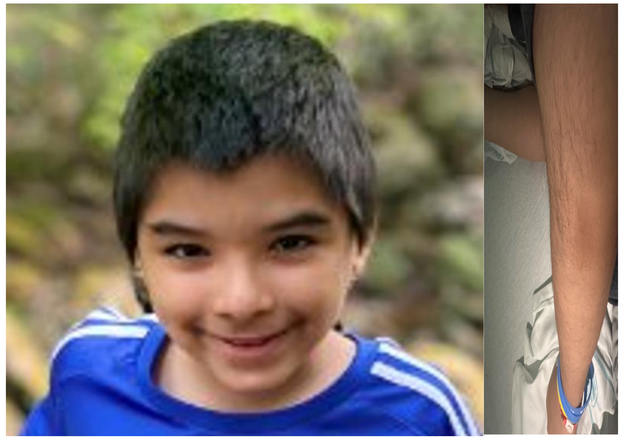

Figure 1. On the left, note characteristic facial features of WSS including downslanted and vertically narrow palpebral fissures, hypertelorism, a wide nasal bridge with a broad tip. On the right, demonstrates his hypertrichosis cubiti and appreciable on the left is facial hypertrichosis as evidenced by the thick eyebrows and long eyelashes [1].

Patient Presentation

- We present a 10-year-old male with developmental delays, congenital cardiac defects, horseshoe kidney with VUR and recurrent UTIs, pyloric stenosis, constipation, and poor dentition, diagnosed with Hodgkin lymphoma at age 8.
- He achieved remission after six cycles of therapy but relapsed within 18 months.
- During treatment, he was hospitalized multiple times for pneumonia. BAL on separate occasions revealed EBV and Haemophilus influenzae.
- Before lymphoma, he had recurrent skin and respiratory infections.
- At initial Hodgkin Lymphoma diagnosis, IgG and IgM were low-normal with elevated IgA. Results of Lymphocyte Subsets from that time are shown in Table 1.
- Subsequent immunologic evaluation was limited given the influence of immunochemotherapy.
- Respiratory infections persisted despite scheduled IVIG.
- Whole exome results are displayed in Table 2.
- Our patient received salvage immunotherapy, followed by high-dose chemotherapy with BEAM/rituximab and autologous HSCT [13].
- High-risk features of his lymphoma and immunodeficiency justify the plan for subsequent reduced intensity allogeneic HSCT [12, 14, 15].

At Initial Hodgkin Lymphoma Diagnosis	Absolute Count (mm^3)	Reference Range (mm^3)	Percentage (%) of Total Lymphocytes
Absolute Lymphocyte Count	684	1900-3700	n/a
CD3	248	1200-2600	36.2
CD4	148	650-1500	21.6
CD8	84	370-1100	12.3
CD19	246	270-860	35.9
CD16/56	176	100-480	25.7
4 months post initial Hodgkin Therapy	Absolute Count (mm^3)	Reference Range (mm^3)	Percentage (%) of Total Lymphocytes
Absolute Lymphocyte Count	2529	1900-3700	n/a
CD3	1032	1200-2600	41.3
CD4	352	650-1500	13.9
CD8	581	370-1100	23
CD19	518	270-860	21
CD16/56	855	100-480	34.7

Table 1. Lymphocyte subsets at initial diagnosis showed lymphopenia with proportionally decreased T and B cell subsets.Four months off therapy, CD4 lymphopenia persisted with normal CD8 and B cell numbers with an inverted CD4/CD8 ratio.

	KMT2A Novel Variant
Sequence Change	c.9487C>T
Amino Acid Change	p.Arg3283Ter
Classification	Interpreted as Pathogenic
Zygosity	Heterozygous
Mode of Inheritance	Autosomal Dominant
Inherited From	De Novo vs Germline Mosaicism
Type of Variant	Nonsense variant predicted to result in protein truncation or nonsense mediated decay in a gene for which loss of function is a known mechanism of disease
GnomAD Frequency	Not observed at significant frequency in a large population cohort
ClinVar	Not previously published as pathogenic or benign

Table 2. Whole exome found a likely pathogenic, de novo nonsense mutation in KMT2A that fit the WSS phenotype, including physical features and CVID-like phenotype [1-7].

Conclusion

- KMT2A encodes a lysine methyltransferase with an integral role in transcriptional regulation of hematopoiesis [8,9].
- This case is first to report a KMT2A-associated Hodgkin lymphoma and additionally novel, its consistency with WSS [8-12].
- ClinVar and GnoMad queries suggest his variant to be distinct in the clinical literature.
- This case emphasizes the need to improve understanding of the increased risk of lymphoma in CVID, its associated molecular pathways, and how these may impact treatment decisions.

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