

Secondary Acute Lymphoblastic Leukemia in a Patient with Presumptive Weaver Syndrome

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- Weaver syndrome is a rare genetic disorder
- Characterized by developmental delay, overgrowth, and characteristic dysmorphic faces
- Mutations in the Enhancer of zeste homolog 2 (EZH2) gene
- Mutations 2230_2232dupATC, D664V, and E745K are thought to be pathogenic
- EZH2 is a histone methyltransferase which suppresses gene expression
- The mutations show overlap with mutations frequently identified in malignancies
- Less than fifty cases have been reported, two of which developed ALL

- 44-year-old female with PMH of developmental delay, seizure disorder, and high-risk childhood ALL who presented with fatigue and easy bruising and was found to have leukocytosis on her CBC (WBC = 96,000)
- Diagnosed with Philadelphia chromosome negative B-cell ALL
- Molecular evaluation revealed TET2, EZH2, and DNMT3A variants
- The EZH2 mutation was present in 48% of cells, suggestive of a germline variant
- Skin biopsy is planned to evaluate for a germline EZH2 mutation to establish a diagnosis of Weaver Syndrome
- Her B-cell ALL is in complete remission following induction chemoimmunotherapy
- An unrelated allogeneic hematopoietic stem cell transplant is planned for definitive therapy

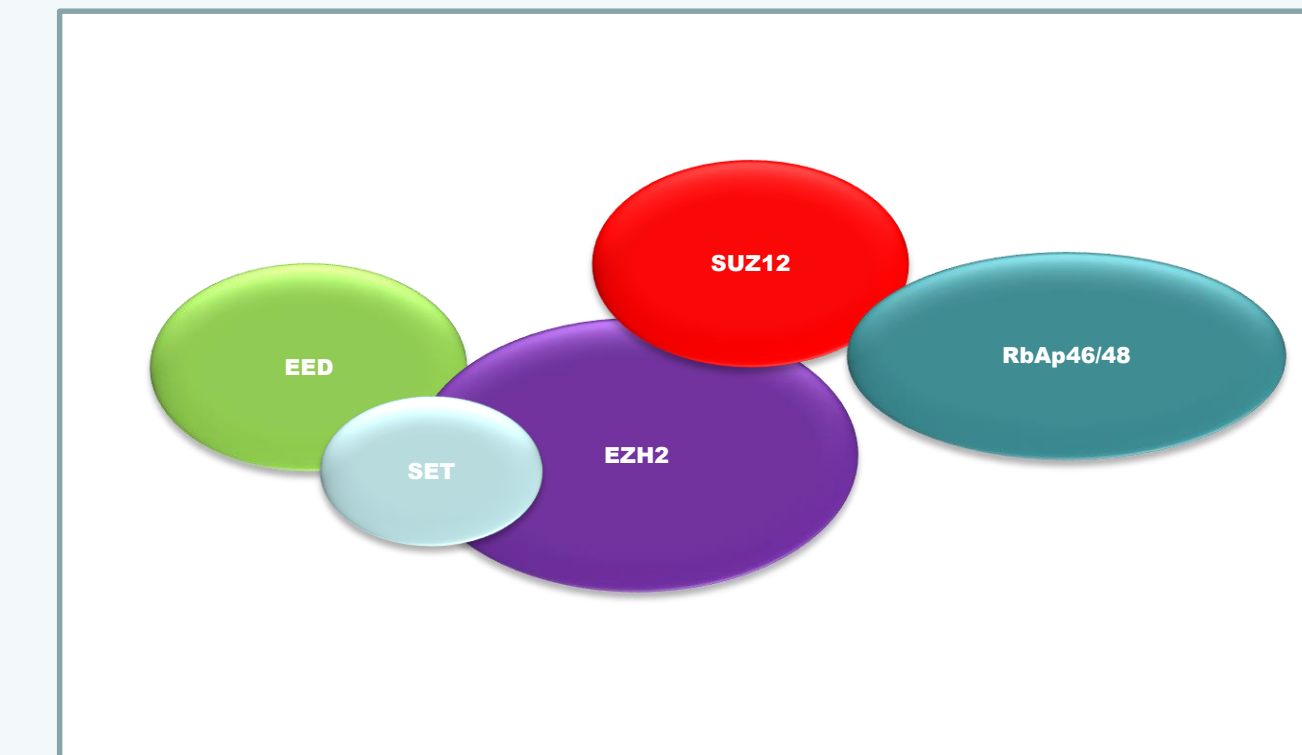


Figure 1: Components of the Polycomb repressive complex 2 (PRC2)

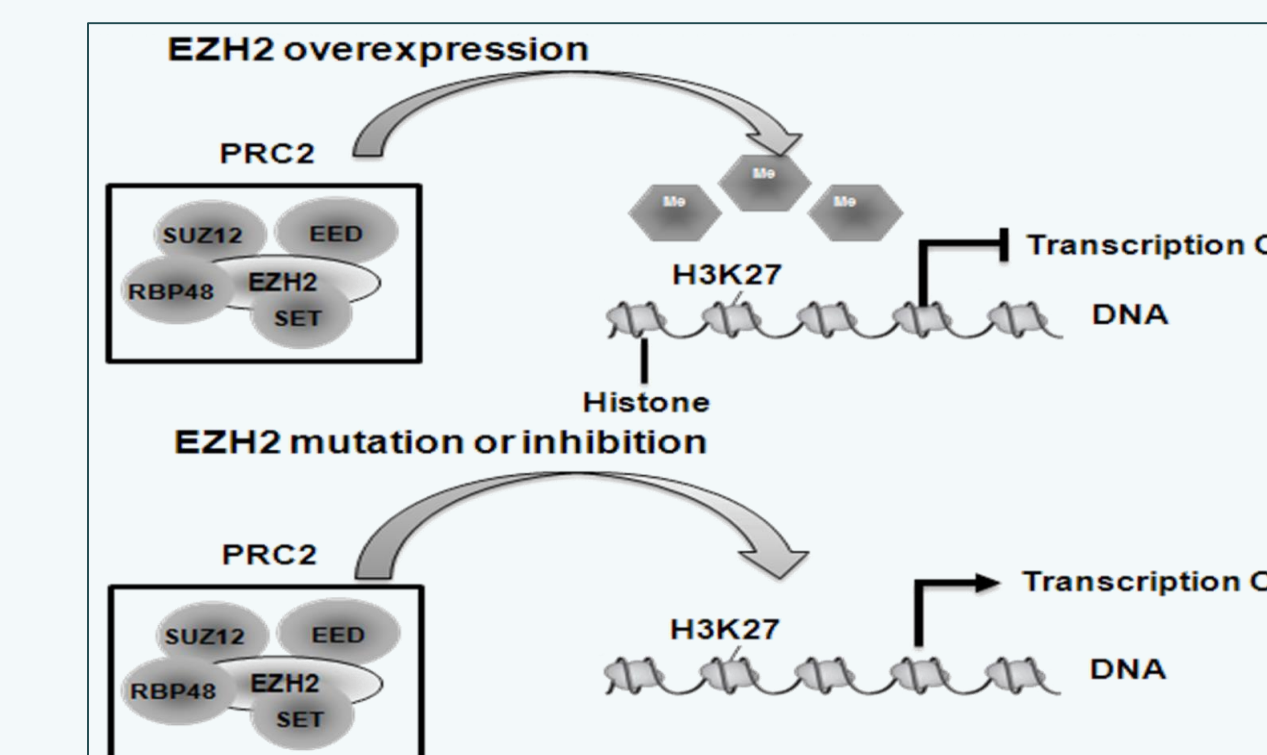


Figure 2: Mechanism of PRC2 dependent methylation in altering gene expression

Mechanisms of Action	Biological Functions
<ul style="list-style-type: none"> • PRC2- dependent H3K27 methylation • PRC2-dependent non-histone protein methylation • PRC2-independent gene modification 	<ul style="list-style-type: none"> • Cell cycle regulation • Promotion of autophagy and apoptosis • Promotion of DNA damage repair

Table 1: Different mechanisms of action and biological functions of EZH2

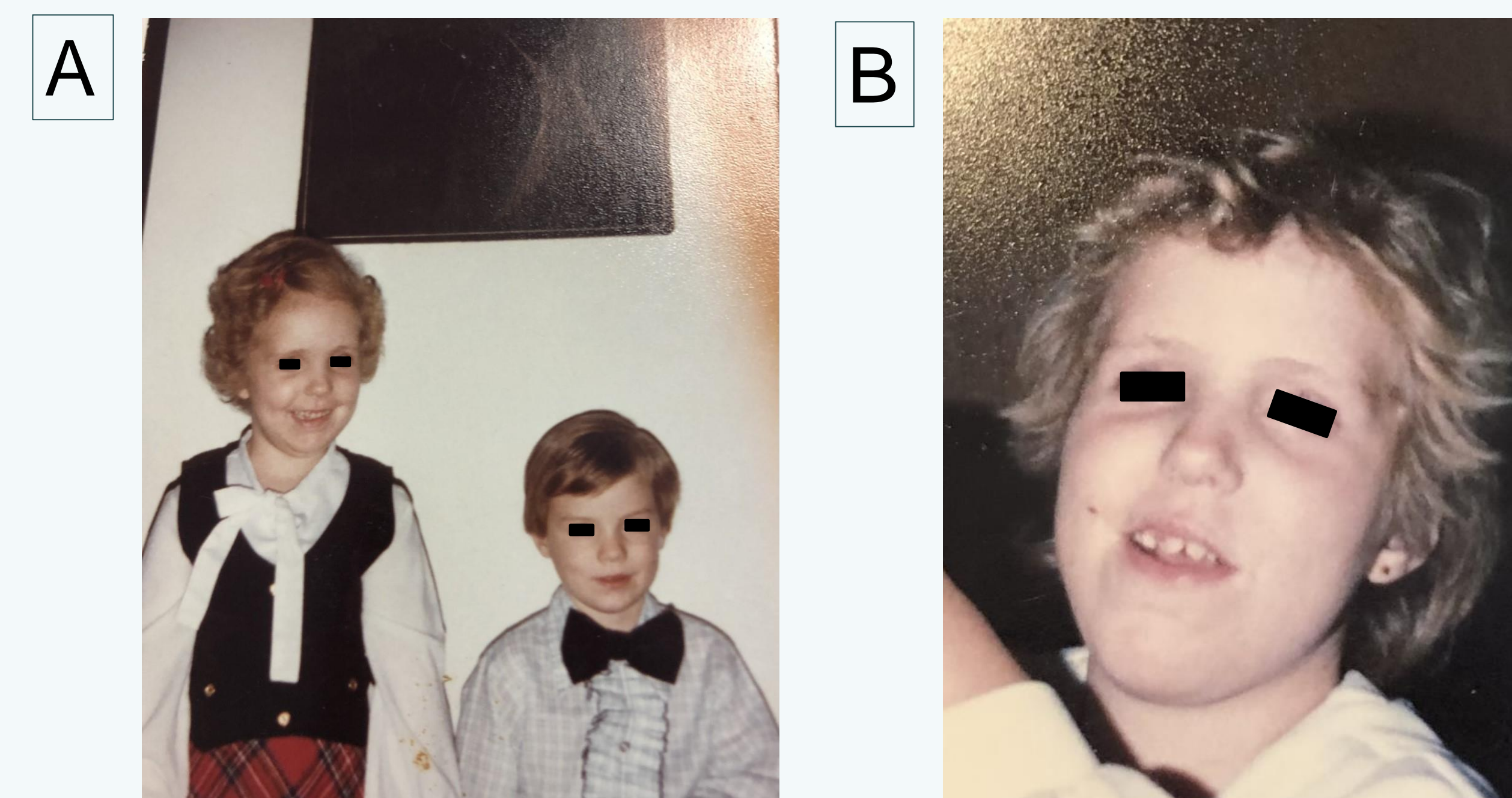


Figure 3: Childhood photos of case patient demonstrating signs of overgrowth and characteristic facies. A) Photograph of patient with an 18-month younger sibling. Patient's growth chart tracked in the 99th percentile through childhood. B) Photograph demonstrates epicanthal folds, down-slanting palpebral fissures, long philtrum, and low-set ears consistent with Weaver Syndrome.

Discussion

Weaver Syndrome is a rare overgrowth disorder, but case reports have indicated an increased malignancy risk, especially of solid tumors. In general, overgrowth disorders are known to be commonly associated with an increased malignancy risk in childhood. In our review of the contemporary literature, only two cases were identified of patients with Weaver Syndrome developing ALL, both in childhood. If a germline mutation is confirmed in this patient, this case raises many further questions. These questions include:

- 1) Is this patient's current ALL clone related to the childhood ALL clone?
- 2) Are patients with germline EZH2 mutations at risk for recurrent de novo ALL?
- 3) In this case, do the TET2 and/or DNMT3A mutations interact with a germline EZH2 mutation to contribute to the development of secondary ALL?

Somatic EZH2 mutations in leukemia are typically associated with poor overall survival outcomes and chemotherapy response. Further follow-up of this case is of great interest.

Selected References

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Acknowledgements

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