Identification of a Novel Variant in the *MAD1L1* Gene in an Individual with Mosaic Variegated Aneuploidy Syndrome (MVAS)

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BACKGROUND

- Mosaic Variegated Aneuploidy Syndrome (MVAS) is a rare autosomal recessive disorder characterized by mosaic aneuploidy, chromosomal instability, developmental delays, congenital anomalies, and cancer predisposition.
- Variants in MVAS-related genes lead to defects in the spindle assembly checkpoint, a key mechanism that ensures chromosomes are correctly distributed to daughter cells during mitosis.
- Given the high cancer risk associated with MVAS, long-term follow-up, genetic counseling for family members, and ongoing surveillance are essential for patient care and risk assessment.
- The proband was a 6-year-old male with a prior history of right-sided Wilms tumor status post resection, chemotherapy, and bone marrow transplant who was evaluated at the genetic clinic due to global developmental delay, hyperpigmented macules, thrombocytopenia, and concerns for myelodysplastic disease. He was diagnosed with acute myeloid leukemia after genetic diagnosis.
- There was no significant family history that pertained to the patient's phenotype, though this patient's parents are reportedly consanguineous.
- **Objective: To identify and characterize a novel *MAD1L1* variant in a patient with MVAS.**

METHODS

- Genome Sequencing (GS) – Initial GS was performed to identify potential genetic variants (negative), followed by re-analysis after two years to investigate novel findings.
- Cytogenetic Analysis – Karyotyping of skin fibroblasts was conducted to assess chromosomal stability and detect mosaic aneuploidy, a hallmark of MVAS.
- In Silico Tools and Variant Classification – In silico tools (CADD, REVEL) were used to predict the pathogenicity of the identified variant, followed by ACMG criteria for classification.

Karyotype analysis of skin fibroblasts uncovered significant chromosomal instability, confirming mosaic aneuploidy as a key diagnostic feature.

SCIENCE ADVANCES | RESEARCH ARTICLE

CANCER

3 Biallelic germline mutations in *MAD1L1* induce a syndrome of aneuploidy with high tumor susceptibility

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1 Premature Birth (2017)

2 Baylor Genetics – Negative GS Rapid Trio Results (April 2022)

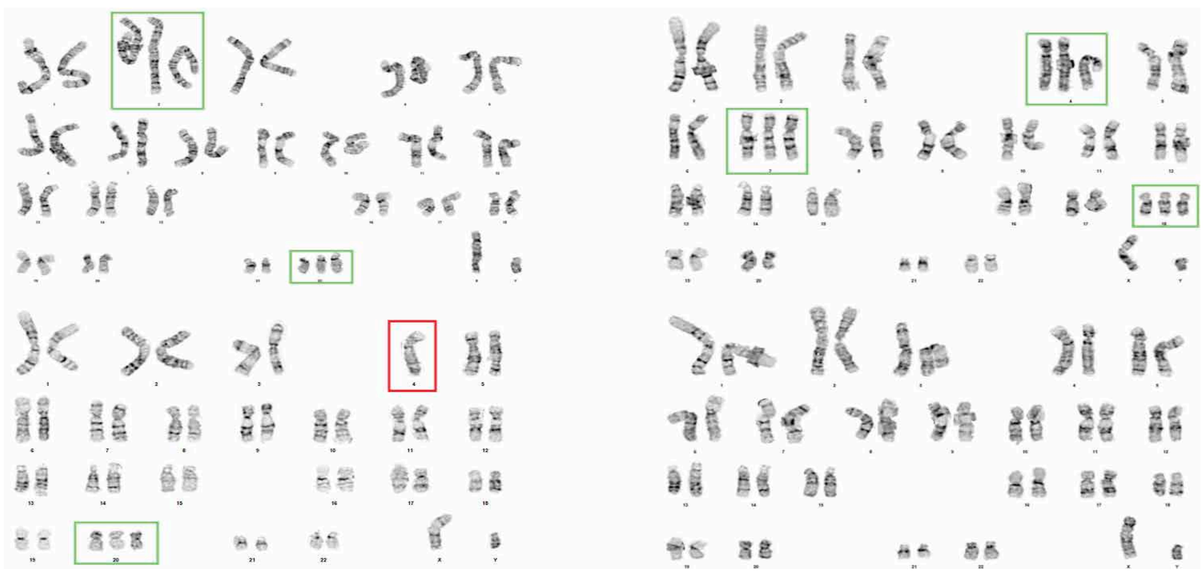
4 Baylor Genetics – Re-analysis GS Trio VUS in *MAD1L1* (November 2022)

5 Cytogenetic of MVAS (March 2024)

6 Baylor Genetics – Reclassify *MAD1L1* to LP (June 2024 – July 2024)

RESULTS

Karyotype analysis of skin fibroblasts uncovered significant chromosomal instability, confirming mosaic aneuploidy as a key diagnostic feature.



- GS re-analysis revealed a homozygous missense variant (c.1948C>T, p.Arg650Trp) in *MAD1L1*, previously unreported in ClinVar or gnomAD. Each parent is heterozygous for this variant.
- The novel variant is in the C-terminal region of the protein MAD1, which is critical for binding MAD2 to form the spindle assembly checkpoint. This was initially classified as a variant of uncertain significance (VUS).
- In silico predictions (CADD: 33.000, REVEL: 0.607), GS findings and cytogenetic evidence led to ACMG reclassification from VUS to likely pathogenic, making the molecular diagnosis of MVAS possible.

CONCLUSIONS

- The identification of the likely pathogenic ***MAD1L1*** c.1948C>T (p.Arg650Trp) variant is only the second documented case of *MAD1L1*-related MVAS. This reinforces the importance of continued genetic discoveries in rare diseases.
- This case demonstrates the value of periodic genetic re-analysis and cytogenetic testing in refining diagnoses, particularly for conditions with mosaic aneuploidy and complex clinical presentations.
- Given the risk of malignancy and other complications, long-term follow-up, guiding families of recurrence risk, and a multidisciplinary approach remain critical for optimizing patient care and improving clinical outcomes.

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