Bilateral pheochromocytomas, hemihyperplasia, and subtle somatic mosaicism: the importance of detecting low-level uniparental disomy (2013)

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Background

It can be difficult to molecularly diagnose and classify tumor risk in patients presenting with isolated hemihyperplasia/hemihypertrophy (now known as isolated lateralized overgrowth) and Beckwith-Wiedemann syndrome (BWS). One of the molecular causes of BWS is uniparental isodisomy of chromosome 11p15 (pUPD11). Patients can have mosaic changes (some cells with genetic changes and some normal cells) and some patients may have low-level mosaicism in their blood, or a very low number of cells with a genetic change. Current molecular testing for these changes, such as methylation analysis, may not be sensitive enough to detect these changes.

Purpose

This study demonstrated that single-nucleotide polymorphism (SNP) array analysis is a sensitive test for detecting mosaicism in patients with Beckwith-Wiedemann syndrome (BWS) due to uniparental isodisomy (UPD). SNP array looks at whether there is one copy of chromosome 11p15 from the mother and one from the father. In BWS and isolated hemihyperplasia due to pUPD11, there are two copies from the father.

Findings

At four months of age, a girl presented to genetics clinic with isolated lateralized overgrowth. She was suspected to have BWS but methylation testing and a SNP array in a blood sample were normal. Tumor screening was initiated and at 18 months of age, pheochromocytomas (a rare hormone-secreting tumor) were found in both of her adrenal glands (bilateral tumors). Genetic testing by SNP array analysis was performed on the tumor which showed pUPD11. A skin biopsy sample from the larger limb also demonstrated low-level mosaicism (5% of cells affected) for pUPD11.

Four other patients with lateralized overgrowth were diagnosed with pUPD11 by SNP array analysis. In three patients, blood testing by SNP array detected low-level mosaicism, which was not seen in the methylation testing. In one additional patient, the blood testing was normal and a skin biopsy sample was positive for pUPD11.

Conclusion

These patients demonstrate that BWS is a mosaic disorder. SNP array analysis can help detect low-level mosaicism for pUPD11 and testing multiple tissues can help detect pUPD11 when blood testing is normal.

Key Points

- SNP array analysis is a sensitive tool to detect low-level mosaic pUPD11.
- Testing multiple tissues can help identify pUPD11 in patients with negative blood testing.
- This added sensitivity is important for identifying patients at higher risk for malignancy.

Reference

Kalish JM et al. Bilateral pheochromocytomas, hemihyperplasia, and subtle somatic mosaicism: the importance of detecting low-level uniparental disomy. *Am J Med Genet A*. 2013;161A(5): 993-1001. PubMed PMID: 23532898