A Case of Infantile Cushing's Syndrome from McCune Albright Syndrome: The Importance of Multi-Site Sampling for Genetic Testing

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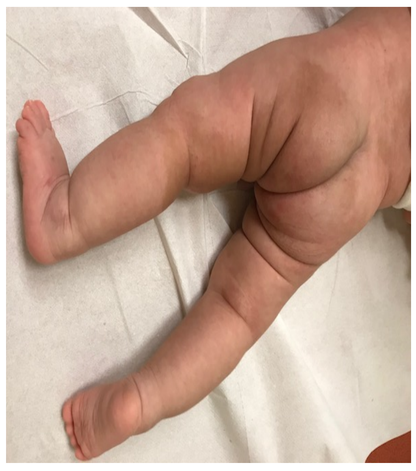
Case Description

We report a case of a 7-month old Vietnamese boy who presented with failure to thrive and a Cushingoid appearance from 1 month old. There was no history of exogenous steroid use. On examination, height and weight were <3rd centile. He was Cushingoid with motor development delay There were multiple large café-au-lait lesions over the posterior sacral region but no limb asymmetry to suggest fibrous dysplasia.

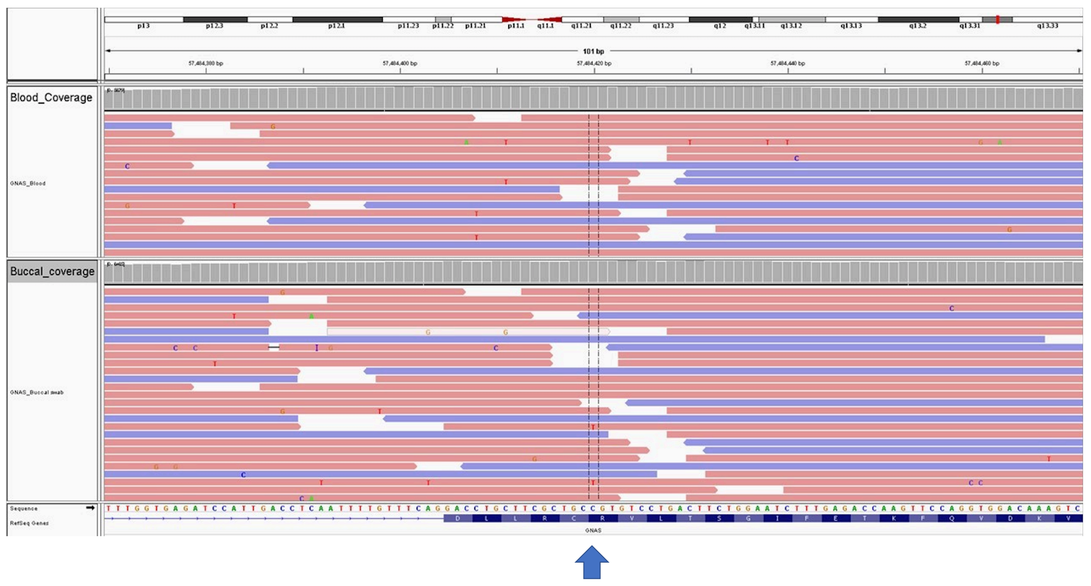


Endocrine investigations were consistent with adrenal Cushing's syndrome:

Investigation	Result	Normal Range
8am serum cortisol	852 (↑)	123.0 – 626.0 nmol/L
ACTH	2.1 (↓)	7.2 – 63.3 pg/mL
Testosterone	3.85 (↑)	0.42 - 0.72 nmol/L
DHEA-S	26 (↑)	0.00 – 1.2 umol/L
Overnight dexamethasone suppression test	Serum cortisol: 818.3 (↑) ACTH <0.22 (↓)	(Failure of cortisol suppression)
Low dose dexamethasone suppression test	Serum cortisol: 722.8 (↑) ACTH 0.22 (↓)	(Failure of cortisol suppression)
CT scan of the adrenals	No adrenal masses/ nodules	

We performed Sanger sequencing on DNA extracted from whole blood and buccal swab but no variants were identified in exons 7, 8 and 9 of the *GNAS1* gene for this patient. We proceeded to perform next generation sequencing (NGS) on these samples and were able to detect NM_000516.5(GNAS):c.601C>T (p.Arg201Cys) from buccal swab DNA at ~5%; the same SNP was not detected in whole blood DNA using NGS (figure on right). The mutation from the buccal swab DNA confirmed our suspicion of McCune Albright syndrome (MAS). Both parents were negative for the mutation.

Gene	Variant	Chr	Coordinate	Alt Variant Freq	Read Depth	Alt Read Depth
GNAS	C>C/T	20	57484420	5.17	5514	285



NGS results from blood and buccal DNA: SNP c.601C>T (p.Arg201Cys) detected at 5% frequency in buccal DNA but not in blood DNA

Patient management

Our patient was given a test dose of oral ketoconazole (4mg/kg/day) but developed hepatotoxicity after 1 week, making this unsuitable for therapy. Despite that, the patient improved clinically with good weight gain and linear growth, with decreasing cortisol levels to 478nmol/L within 3 months even without therapy. He was commenced on oral metyrapone 10mg/kg/day for further cortisol suppression. Within 1 week of treatment, his 8am serum cortisol had normalized. Metyrapone dose was weaned down step-wise until a low dose of 2mg/kg/dose, where serum cortisol remained normal throughout. He tolerated the metyrapone well with no side effects. At 2 years 2 months of age, he was successfully weaned off metyrapone and continues to have normal cortisol levels and good growth clinically.

1 year into treatment, the patient appears much less Cushingoid

Discussion

Infantile Cushing's syndrome (ICS) is a rare but early manifestation of MAS, and may precede the appearance of its skin and bone manifestation. ICS is unique among MAS-related endocrinopathies in its tendency to spontaneously resolve in some cases, due to foetal adrenal regression. In our case, the spontaneous improvement seen before treatment initiation and the ability to come off medications was likely explained by this phenomenon. Despite complete resolution of Cushing's syndrome, patients will require monitoring for neurocognitive development and development of fibrous dysplasia or other endocrinopathies associated with MAS.

Conclusion

This case reinforces the genetic pathogenesis of MAS, which is a mosaic disease arising from post-zygotic somatic mutations of the GNAS gene and may have low mutation abundance. We demonstrate how DNA sampling from multiple sites using NGS, particularly from affected tissues can be helpful in increasing the genetic diagnostic yield.

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