

# Parental gonadal mosaicism for a BRAF mutation in Cardiofaciocutaneous syndrome

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## Case Report

Two brothers presented for paediatric management of failure to thrive and developmental delay. The parents are healthy, unrelated with one unaffected daughter.

The first boy was born at term with a normal birth weight (50<sup>th</sup> centile). There was polyhydramnios, intrauterine growth restriction and right sided hydronephrosis noted on antenatal scans. The neonatal period was complicated by failure to thrive and gastro-oesophageal reflux disease. A phenotype suggestive of Noonan syndrome with short stature, pulmonary stenosis, global developmental delay, and sensorineural hearing loss became apparent. Fifteen months later his brother was born at term with a normal birth weight (50<sup>th</sup> centile). Echocardiogram showed concentric left ventricular hypertrophy. He required nasogastric and subsequently percutaneous endoscopic gastrostomy (PEG) feeding. He has a similar phenotype to his brother. They have both presented with recurrent hypoglycaemia during gastroenteritis which has improved beyond early childhood. The older boy underwent glucagon stimulation testing which was borderline for growth hormone deficiency with a peak growth hormone of 7.8 ug/l (normal > 7.0ug/l). Both brothers have delayed neurodevelopment.

## Genetic Investigations

High resolution microarray analysis was normal. Mutation analysis of the PTPN11, MAP2K1 and MAP2K2 genes, testing for Noonan syndrome was normal. Mutation analysis of the BRAF gene showed heterozygosity for a pathogenic mutation in BRAF c.770A>G (p.Gln257Arg) in both brothers.

The specific mutation has been described in other patients with Cardiofaciocutaneous syndrome (CFCS). This gave a diagnosis of CFCS in both brothers.

Parents were tested and neither healthy parent had the BRAF mutation in their blood DNA.

The likely explanation for these findings is that one or other parent has mosaicism for the BRAF mutation at least in their gonadal tissue.

There could be up to a 50% chance of the parents having another child affected by CFCS.



Figure 1: Photos of the two brothers showing frontal bossing, down slanting palpebral fissures and hypertelorism. Parental consent obtained.

## Cardiofaciocutaneous syndrome (CFCS)

- A rare autosomal dominant (AD) condition characterized by cardiac abnormalities, a distinctive craniofacial appearance and short stature.
- Endocrine manifestations include growth hormone (GH) deficiency and precocious puberty.
- Part of a group of related conditions including Noonan, LEOPARD and Costello syndromes, all of which are caused by mutations in gene encoding proteins in the RAS/MAPKinase pathway.
- The four CFCS associated genes are BRAF, MAP2K1 and MAP2K2, and KRAS. Most individuals represent new sporadic mutations.

## Discussion

CFCS was first described in 1986 by Reynolds et al<sup>1</sup>. Eight patients with a previously undefined multiple congenital anomalies and intellectual disability syndrome were designated the Cardio-Facio-Cutaneous (CFC) syndrome which includes congenital heart defects, characteristic facial appearance, ectodermal abnormalities, and growth failure. Since the initial case report about 60 cases have been described allowing for further detailing of the clinical phenotype. There is significant phenotypic overlap with Noonan and Costello syndrome. Sparse hair and eyebrows, follicular hyperkeratosis and palmoplantar hyperkeratosis are typically used to characterise CFCS. There is also genetic overlap with Noonan’s Syndrome, both KRAS and MAP2K2 mutations have been found in patients with a Noonan’s phenotype with no PTPN11 mutation.<sup>3-6</sup> Mutations in BRAF are the most common and have been found in 35-78% of patients with CFC phenotype.<sup>2,6,7</sup> The majority of described mutations are spontaneous. There are two descriptions of AD inheritance of a heterozygous mutation of MAPK gene<sup>8,9</sup> but this is the first described case of parental gonadal mosaicism in CFCS.<sup>1</sup>

## Conclusion

To our knowledge this is the first reported family with cardiofaciocutaneous syndrome due to parental gonadal mosaicism for a pathogenic BRAF mutation.

## References

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