

optimal dosing levels based on genetic subtype. On the other hand, we may discover that the degree of GH resistance in the *mut⁺* individuals is so great that cranking up the rhGH dose really cannot compensate effectively or may be associated with undesirable side effects. In this scenario (the second treatment strategy), treating with recombinant IGF-I and/or IGF-1/IGFBP-3 rather than rhGH, may be more appealing. These therapies have now become available and were recently approved by the FDA.

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References

1. Tiulpakov A, Rubtsov O, Dedov I, et al. J Clin Endocrinol Metab. 2005;90:542–547.
2. Kofoed EM, Hwa V, Little B, et al. N Engl J Med. 2003;349:1139–1147.
3. Woods KA, Camacho-Hubner C, Savage MO, Clark AJ. N Engl J Med. 1996;335:1363–1367.
4. Okubo Y, Siddle K, Firth H, et al. J Clin Endocrinol Metab. 2003;88:5981–5988.
5. Abuzzahab MJ, Schneider A, Goddard A, et al. N Engl J Med. 2003;349:2211–2222.
6. Schaefer F, Chen Y, Tsao T, Nouri P, Rabkin R. J Clin Invest. 2001;108:467–475.

Signal Transduction and Cardio-Facial Syndromes

The cardio-facio-cutaneous (CFC) syndrome (OMIM 115150) presents with heart malformations, skin defects, and characteristic facies. It overlaps phenotypically with Noonan syndrome (NS) and Costello syndrome (CS). Gain-of-function mutations have been identified in the protein tyrosine phosphatase SHP-2 (PTPN11) in about half of patients with NS. Recently, mutations of one of the RAS proteins known as HRAS were identified in several patients with CS. Interestingly, several CS mutations had been previously identified as somatic oncogenic mutations in tumors. SHP-2 and HRAS are components of a well-known signaling cascade through which many receptor tyrosine kinases transmit signals to the nucleus. Illustrated in the figure, this pathway, which is often referred to as the RAS-MAP kinase pathway, is often associated with proliferative and growth signals in developing tissues and in cancer.

Based on the suggestion that NS and CS might reflect activation of this pathway, a group headed by Aoki speculated that CFC syndrome might be due to mutations in genes encoding other proteins in this cascade. They first sequenced the entire coding regions of 3 RAS genes (*HRAS*, *KRAS*, and *NRAS*) in genomic DNA from 43 individuals with CFC syndrome. Two *de novo* *KRAS* mutations were detected.

Next, they screened for mutations in the 3 isoforms of RAF (*CRAF*, *BRAF*, and *ARAF*), which is immediately downstream of RAS in the signaling cascade. Eight *BRAF* mutations were identified in 16 patients, 6 of which mapped to the kinase domain, where mutations had previously been found in tumors.

The investigators proposed that the mutations they had identified enhance MAP kinase signal activity and tested this notion by expressing the mutant genes and their normal control counterparts in reporter cells that would allow downstream signal output to be measured. They observed a significant increase in signal output for 1 of the 2 *KRAS* mutations and in 4 of the 8 *BRAF* mutations, supporting their contention and the idea that increase MAP kinase signaling is common to all of the disorders in this group.

They reasoned further that if all of the disorders share a common increase in RAS-MAP kinase signaling activity, then there may be mutational overlap as well. Accordingly,

they screened for *BRAF* and *KRAS* mutations in *PTPN11*-negative NS patients and for *PTPN11* mutations in CFC patients negative for mutations in *BRAF* or *KRAS*. No additional mutations were detected, suggesting that the 3 disorders are distinct entities.

In an accompanying editorial,¹ it is noted that a recent publication identified *BRAF* mutations in 18 of 23 individuals with CFC. This study also found mutations in *MAP2K1* and *MAP2K2*, which are downstream effectors of *BRAF* in the RAS-MAP kinase signal pathway. The editorial also points out that molecules in which mutations have been found typically participate in other signaling pathways in addition to the primary linear RAS-MAP kinase pathway, which probably explains why each syndrome has unique features.

Niihori T, Aoki Y, Narumi Y, et al. Germline *KRAS* and *BRAF* mutations in cardio-facio-cutaneous syndrome. Nat Genet. 2006;38:294–296.

Editor's Comment: *MAP kinase signaling pathways are more complex than suggested in the figure, and there is extensive crosstalk between subpathways. Nevertheless, placing these syndromes into a group that results from enhanced RAS-MAP kinase signaling serves a useful purpose, especially as inhibitors of this pathway might potentially have therapeutic benefit for postnatal manifestations of these disorders, such as short stature.*

*In contrast to most cell types in which RAS-MAP kinase signaling is associated with cell proliferation and growth, such signals in growth plate chondrocytes, where they are generated downstream of *FGFR3*, inhibit both cell proliferation and growth. Thus, it is conceivable that achondroplasia, which is due to activating mutations of *FGFR3*, NS, CS, and CFC syndromes share a common pathogenetic mechanism that involves excessive output of the RAS-MAP kinase signaling cascade in growing bone.*

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Reference

1. Editorial. Nat Genet. 2006;38:267.