

# Activating Mutations of the Stimulatory G Protein in the McCune-Albright Syndrome

The cause of the clinical symptomatology in McCune-Albright syndrome (MAS), including sexual precocity, multiple hyperfunctional endocrinopathies, polyostotic fibrous dysplasia, and café au lait spots, has been the subject of extensive speculation for many years. The capability of modern genetics to examine mutations of genes has now made it possible to specifically identify an abnormal mutation within exon 8 of the G protein  $\alpha$ -subunit ( $G\alpha$ ) that stimulates cyclic adenosine monophosphate (cAMP) formation. Four patients with severe MAS were studied by the authors and identified as having a mutation of the Arg<sup>201</sup> position in tissue. Two of the 4 had an His mutation and the other 2 a Cys mutation. The abundance of mutations in different tissues was variable. Not only was there evidence determined for mutations in testis, ovary, adrenal, pituitary and thyroid but also in the heart, lung, liver, kidney, thymus, and spleen. Two of the 4 patients died a sudden death, which may have been related to cardiac dysfunction. Unfortunately, the authors were unable to determine whether mutations were present in the polyostotic lesions or in the café au lait hyperpigmentation. Reasonable explanations are given why the mutant was not demonstrable in these 2 tissues as studied. In an editorial in the same issue, Dr. Michael Levine of Johns Hopkins reports finding the same defect in affected skin of 1 patient. Therefore, the defect remains to be identified only in bone, and this will probably be demonstrated in the near future.

The mutant abnormality produces a significant decrease in the guanosine triphosphatase (GTPase) activity of the  $\alpha$ -subunit of the G protein, with the end result of increased adenylyl cyclase activity.

The authors appropriately state that for each case only 1 specific mutation (R201C or R201H) is detected, which is consistent with a monoclonal abnormal cell population. This mutational event occurs prior to development of the trilaminar disc because of the widespread distribution and mutation of tissues derived from all 3 embryologic germ layers, and because of the variable abundance among tissues within a given patient. The absence of mutation in at least 1 tissue from each case is consistent with a somatic rather than germ line mutation. Intriguingly, the  $G\alpha$  mutations were present in virtually all affected

MAS endocrine tissues analyzed. The affected tissues within each organ had a greater proportion of the mutant population than did the unaffected tissues. The presence of activating Arg<sup>201</sup> mutations was first described in sporadic growth hormone-secreting pituitary adenomas, which have autonomous cAMP synthesis. Importantly, the authors clarify the association between Albright's hereditary osteodystrophy (AHO) and MAS. AHO is associated with  $G\alpha$  gene mutations, which lead to a deficiency in G protein. The mutations within MAS are different but of the same gene. Mutations in AHO impair the G protein signal transduction pathway while those found in MAS have the reverse effect, ie, the activation of the G protein pathway, an effect that probably underlies the clinical manifestations of the syndrome.

Weinstein LS, Shenker A, Gejman PV, et al. *N Engl J Med* 1991;325:1688-1695.

**Editor's comment:** *The findings reported in this article are exciting, thoroughly done, and now give us a much better understanding of MAS phenomena. The authors are to be congratulated for their fine work and for their contribution.*

*Clinicians now must be made aware that the symptomatology in severe cases of MAS may be much greater than previously understood. The presence of the mutant gene in multiple tissues can lead to diverse clinical pathophysiology. Incomplete presentations of MAS may represent cases in which there is an even more limited distribution of mutant cells. Liver, cardiac, and renal disease need to be considered in patients who present with MAS. Undoubtedly a much larger group of these patients than previously demonstrated produce excessive growth hormone, which may account for the fact that many patients with MAS do not have the short stature we usually expect in the typical patient with sexual precocity. Unexplained as yet is the significantly higher incidence of this syndrome in females than males.*

*Those interested in this report also will want to read the editorial by Dr. Michael Levine in the same issue of the New England Journal of Medicine, entitled "The McCune-Albright Syndrome: The Whys and Wherefores of Abnormal Signal Transduction."*

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