



## McCune-Albright Syndrome

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### Characteristics

McCune-Albright Syndrome (MAS) is a rare genetic disorder originally characterized as the triad of polyostotic fibrous dysplasia of bone, precocious puberty, and café-au-lait skin pigmentation (1-3). With time other associated endocrinopathies have been recognized, including hyperthyroidism, growth hormone excess, FGF23-mediated phosphate wasting, and hypercortisolism (4, 5).

MAS is caused by an activating mutation in the *GNAS* gene, which encodes the alpha subunit of the stimulatory G protein involved in G-protein signaling (6, 7). A missense mutation, typically Arg201Cys or Arg201His (NM\_001077488.3:c.604C>T, rs11554273), impairs the intrinsic GTPase activity of the G $\alpha$  protein, resulting in the constitutive activation of the G $\alpha$ -cAMP signaling pathway in the cells that contain the mutation.

The mutation arises early in embryogenesis and is distributed in a mosaic pattern. The clinical phenotype is therefore highly variable, depending upon the location and timing of the mutation during embryologic development. Skin manifestations are common and are usually present at or shortly after birth. The café-au-lait spots typically have irregular margins giving them a “coast of Maine” appearance, and usually show an association with the midline of the body.

In MAS, fibrous dysplasia of bone typically occurs at several sites (polyostotic), and commonly presents with fracture, deformity and/or bone pain (8). Radiographs show characteristic expansile lesions with a “ground glass” appearance. Craniofacial fibrous dysplasia can be severe in individuals who have pituitary disorders leading to hypersecretion of growth hormone. Treatment can be challenging and should begin as soon as possible.

In girls, precocious puberty is a common initial manifestation, with recurrent ovarian cysts leading to episodes of vaginal bleeding and breast development. Precocious puberty is less common in boys, presenting with penile enlargement, pubic and axillary hair, acne, body odor, and sexual behavior. However, in both girls and boys, there is a high frequency of gonadal pathology (ovarian abnormalities in girls, and testicular abnormalities in boys) (9).

### Diagnosis

The NIH Genetic Testing Registry, GTR, displays genetic tests that are currently available for the *GNAS* gene and the McCune-Albright Syndrome.

Currently, the diagnosis of McCune-Albright syndrome is made clinically in most cases. This is due to the mosaic nature of the disease whereby a negative genetic test result (e.g., in blood) does not exclude the presence of the mutation in other tissues. However, newer techniques such as digital PCR may improve the sensitivity of genetic testing in individuals who have clinical signs of McCune-Albright syndrome (10, 11).

## Management

Treatment is individualized based on each patient's clinical presentation. Letrozole (12) and/or tamoxifen (13) may be effective for treatment of precocious puberty in girls. Medications and/or surgery may be used for treatment of hyperthyroidism (14, 15), growth hormone excess (16, 17), and hypercortisolism (18). Management of fibrous dysplasia of bone is palliative, with surgery as needed for fracture and deformity (19, 20).

Bisphosphonates are effective for treatment of fibrous dysplasia-related pain, but have not been shown to have any long-term effect on the course of the disease (21, 22).

## Genetic Counseling

McCune-Albright syndrome is caused by a new (de novo) mutation that occurs after conception, at an early stage of development. Individuals with McCune-Albright syndrome have not been observed to pass the syndrome on to their children.

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## Version History

To view an earlier version (8 March 2012), please click [here](#).

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