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The Role of Mutations on Genes FGF23 & GNAS1 in McCune-Albright Syndrome

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Abstract

McCune-Albright syndrome (MAS) consists of at least two of the following three features: polyostotic fibrous dysplasia (PFD), café-au-lait skin pigmentation, and autonomous endocrine hyperfunction (e.g., gonadotropin-independent precocious puberty). Other endocrine syndromes may be present, including hyperthyroidism, acromegaly, and Cushing syndrome. Mazabraud syndrome, which can also exist in association with MAS, involves the occurrence of myxomas and usually PFD.

***Keywords:** McCune-Albright syndrome; Genetic disorder; FGF23; GNAS1 genes*

1. Overview of McCune-Albright Syndrome

McCune-Albright syndrome, also known as Albright syndrome, is a very rare and complex genetic disorder that classically affects bones, skin, and endocrine organs (FIG. 1). In patients with McCune-Albright syndrome, fibrous bone dysplasia and light brown patches occur in some areas of the skin and dysfunction in endocrine (metabolic processes) or developmental dysfunction in the gonads [1].

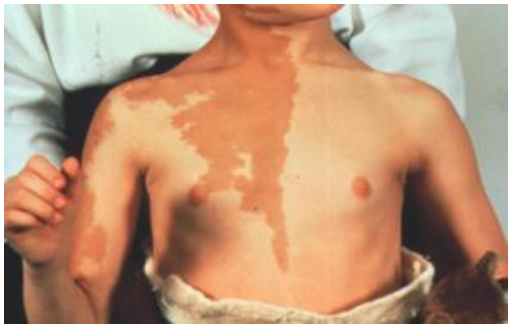

FIG. 1. **Image of a child with McCune-Albright syndrome with light brown spots on the skin.**

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2. Symptoms of McCune-Albright Syndrome

The McCune-Albright syndrome reveals a wide range of clinical manifestations and manifestations. Some children with McCune-Albright syndrome are characterized by overt abnormalities in the early infancy or increased hormone production by one or more endocrine glands. Some other children with McCune-Albright syndrome may also show no abnormalities in bone, skin or endocrine disorders (FIG. 2). Therefore, the severity of each person's symptoms may vary greatly. As mentioned, the parts of the body most commonly affected by McCune-Albright syndrome are: bone, skin, and the endocrine system [1,2].

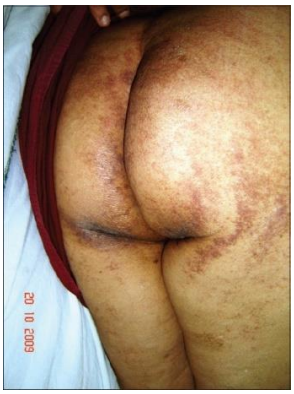


FIG. 2. **Aneurysm image of a person with McCune-Albright syndrome with brown spots on the skin of the anal area.**

3. Bone Malformations in McCune-Albright Syndrome

Polyostotic fibrosis dysplasia is a distinctive feature of patients with McCune-Albright syndrome. Dysplasia is a bone fibrosis-like scar that is replaced by abnormal connective tissue. Fibrous Dysplasia is a benign bone tumor and some see it as a growth defect rather than a real tumor. It begins at birth and is caused by a genetic defect in bone-forming cells, but usually remains asymptomatic until it is discovered at an early age, such as childhood, adolescence or even adulthood. It is not caused by a genetic defect in normal and healthy bones but in some areas of the body, it is weak and empty (FIG. 3). These weak bones that are scattered throughout the skeleton can cause bone pain or fractures, and sometimes the bones become deformed as a result. It accounts for approximately 7% of benign bone tumors. It can be seen in any bone but is more common in the thigh, leg, arm, hip, skull and ribs [1,3].

FIG. 3. **Image of the person with McCune-Albright syndrome, in a distinctive form, with the organs involved in the disorder.**

Fibrosis dysplasia is often seen in one bone but sometimes in multiple bones in the body. Occasionally, abnormalities of endocrine cell growth can occur in areas where several bones of the body show tumors together. This is called Albright syndrome. As one grows older, abnormal bone tissue grows and grows, causing parts of the bone to weaken. These weakened bones gradually become painful. Pain usually arises in the bones of the lower limbs because they have to bear the weight of the body and put pressure on them during weight bearing because they do not have the ability to tolerate this pressure. The pain worsens with physical activity and worsens with rest (FIG. 4). Gradually the pain intensifies [1,4].

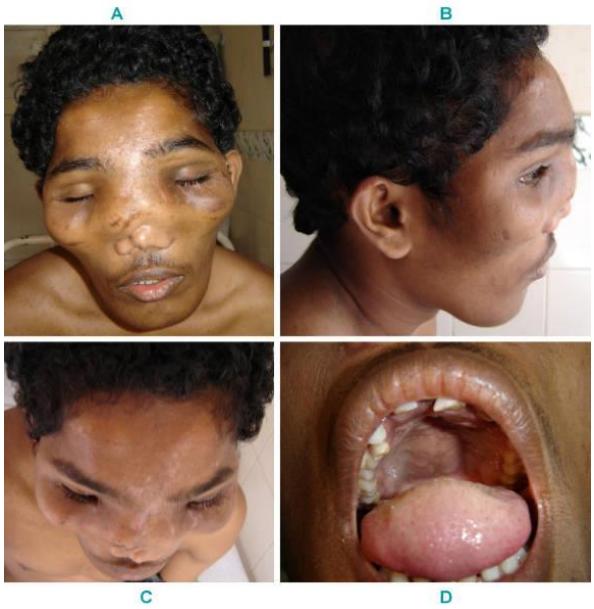


FIG. 4. **Images of a person with McCune-Albright syndrome with distinct malformations of the face and the appearance of teeth.**

Sometimes the bone becomes so weak that it can be fractured by mild trauma. Sometimes the bone becomes so weak that it can be mildly fractured by the daily stresses that enter the bone. These minor fractures cause pain, but the patient may be oblivious to the pain and not see an orthopedic doctor (FIG. 5). After some time, the fracture heals spontaneously and the pain subsides [1,5].

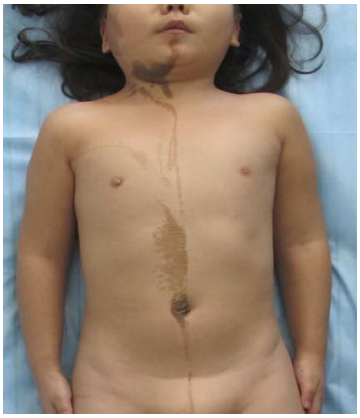


FIG. 5. **Image of a child with McCune-Albright syndrome with light brown spots on the skin and a presumed line that divides the body into two right and left hemispheres.**

When this happens repeatedly over several years, each time the bone is fractured and welded, the bone becomes slightly tilted. These tilts gradually increase so that after a few years the bone may completely deform. For example, it may be seen during a photograph of the patient's thigh that the thigh bone is completely arched [1,6].

If this deformity develops in the bones of the face and skull, there may be problems in hearing or vision, and in the organs this deformation of the bones may cause arthritis and wear on the joints [1,7].

Albright syndrome may cause premature puberty due to hormonal changes. This problem is most commonly seen in girls due to increased ovarian activity. Increased activity may also occur in the thyroid, adrenal, pituitary or parathyroid glands (FIG. 6). With the increase in activity in each of these glands, their specific symptoms develop [1,8].

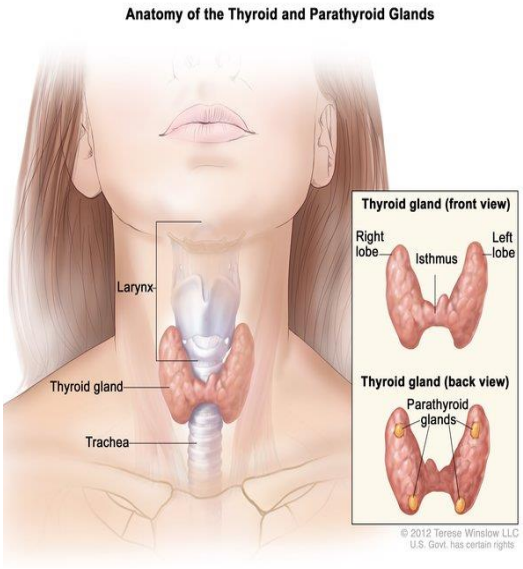


Fig. 6. **Schematic view of the thyroid gland anatomy in humans.**

These benign tumors can rarely become malignant and cancerous. When the pain in the masses worsens, the pain in the night wakes the patient up, or when the pain does not decrease with rest, the treating physician may suspect that malignancy has occurred. Malignant tumors occur about half a percent of the time, but the probability is 4 percent in Albright syndrome. The malignancy of these lesions is more likely to occur in fibrosarcoma tumors in areas with multiple bones. Spinal fibrosis dysplasia can cause abnormal spine curvature (scoliosis), which is often progressive. When long bones are affected by bone fibrosis dysplasia in McCune-Albright syndrome, it can lead to frequent fractures of the legs of patients with Albright Syndrome while walking [1,9].

Some people with polyostotic fibrosis dysplasia in Albright Syndrome may have complications such as: nasal congestion, defective tooth or deflected jaw, uneven jaw, facial asymmetry where one side of the face does not match the other, forehead Prominent abnormalities, experiencing raised eyes (proptosis) (FIG. 7) [1,10].

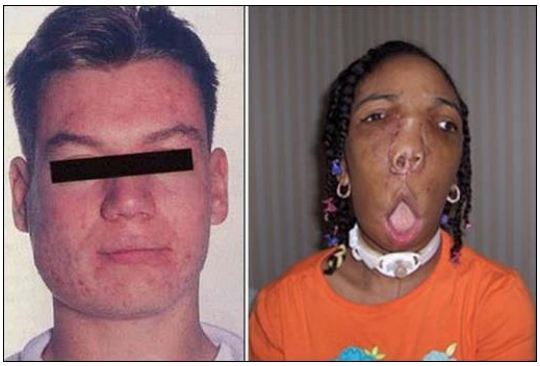


FIG. 7. **Other images of patients with McCune-Albright syndrome with unilateral facial asymmetry and malformed nose and raised eyes (proptosis).**

4. Skin disorders in McCune-Albright Syndrome

Some patients with McCune-Albright syndrome may show light brown patches in some areas of the skin. This may occur at birth or shortly after birth (neonatal period). There is also a hypothetical line in the middle of the body of patients with Albright syndrome, dividing the body into two right and left halves [1,11].

5. Endocrine Disorders in McCune-Albright Syndrome

The endocrine system controls the regulation of body growth, sexual development and some other metabolic functions. People with Albright Syndrome often experience an abnormal onset of early puberty (early gonadotropin maturation). In women with McCune-Albright syndrome, there may be vaginal bleeding or early development of breast tissue. Early development of breast tissue may occur in the first few months of life or in childhood between the ages of 6 and 7 years. Some women with Albright Syndrome may experience repeated attacks of vaginal bleeding. Early puberty, often associated with the development of benign ovarian cysts, can occur in girls with Albright syndrome. Early puberty in women with Albright Syndrome is more than 50% more common in men with this syndrome. In men with Albright Syndrome, the penis and one or both testes may be older than their physiological age (FIG. 8). The scrotum may also be thick and have excessive wrinkles [1,12].

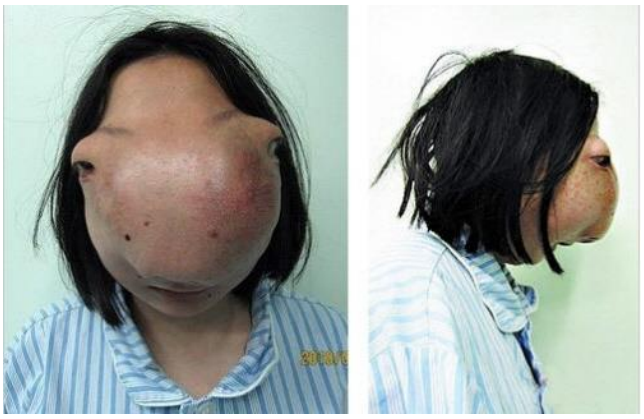


FIG. 8. **Image of a man with the rarest form of McCune-Albright syndrome with the strangest facial features.**

Also, men with Albright syndrome may experience excessive growth of penis hair, underarm hair, and body sweat. It is worth noting that children with Albright syndrome with early puberty often have tall stature [1,13].

Other disorders of the endocrine system in Albright's syndrome include the thyroid gland, pituitary gland and adrenal glands. The thyroid is a butterfly-shaped gland at the base of the neck that may be associated with enlarged thyroid (goiter) or hyperthyroidism (hyperthyroidism) in Albright syndrome. People with McCune-Albright syndrome, with thyroid disorder, may experience hyperthyroidism, which can include complications such as anxiety, fatigue, eye irritation, sweating, irregular heartbeat, unintentional weight loss, heat intolerance, and Have osteoporosis [1,14].

The pituitary gland is a small gland near the base of the skull that stores various hormones, including growth hormone, and releases them into the bloodstream to reach the body's required systems. Some patients with McCune-Albright syndrome experience excessive levels of growth hormone. Increased growth hormone can cause muscle mass growth, premature puberty in some cases, abnormally large head (macroscale) and vision problems. Some patients with McCune-Albright syndrome may experience acromegaly, especially in the skull. In medicine, the abnormal size of the lower parts of the body, such as the nose, jaw, and toes, is called acrobatics (FIG. 9). This syndrome occurs when the pituitary gland overproduces the growth hormone (hGH) epiphysis after the growth plate is closed [1,15].

FIG. 9. **Image of a girl with McCune-Albright syndrome Make sure your face and eyebrows are excessive and that you do not observe the normal distance between the eyes and the irregular shape of the nose.**

Several different abnormalities may cause the pituitary gland to develop, but it is usually caused by a growth hormone tumor derived from specific cells. These special cells are usually benign tumors called adenomas. Tuberculosis is more common in middle age. Tuberculosis is commonly associated with giants [1,16].

The adrenal glands are located above the kidneys near the back of the human body and produce various hormones including cortisol. Cortisol is a glucocorticoid, a class of steroid hormones that plays an important role in regulating glucose metabolism and modulating stress. People with Albright Syndrome may have elevated cortisol levels and experience disorders similar to Cushing 's syndrome (FIG. 10). In this case, patients with McCune-Albright syndrome may have

symptoms such as: obesity, round face, thin purple vein (striae) on the skin, increased fat around the neck, arms and slender legs [1,17].

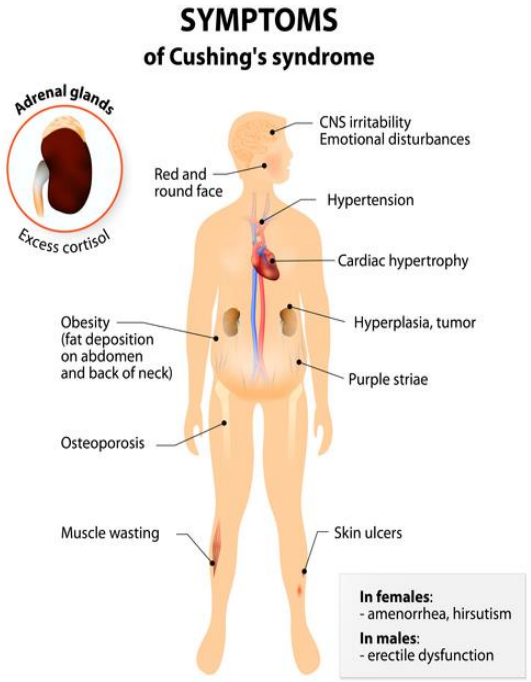
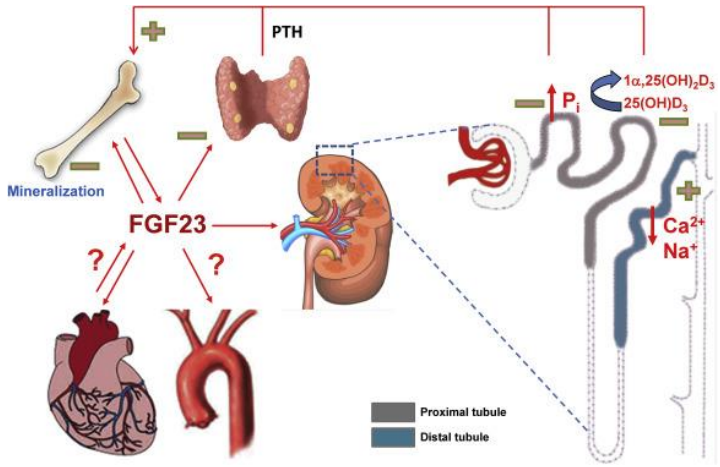


FIG. 10. **Schematic overview of the symptoms of Cushing's syndrome in humans.**

Some people with McCune-Albright syndrome may experience a decrease in the development of phosphate levels in the blood (hypophosphatemia), as the kidneys lose the ability to reabsorb phosphate. This occurs when fibrous dysplasia tissue produces a protein called fibroblast growth factor (FGF23). The FGF23 gene is located on the short arm of chromosome 12 at 12p13.32. The amount of FGF23 protein is correlated with the kidneys' inability to phosphate metabolize (renal phosphate loss). Thus, people with McCune-Albright syndrome with fibrotic dysplasia are more likely to develop hypophosphatemia (FIG. 11). Patients with McQueen-Albright syndrome with hypophosphatemia will experience complications such as severe bone loss or osteomalacia, fractures, and bone pain [1,17].



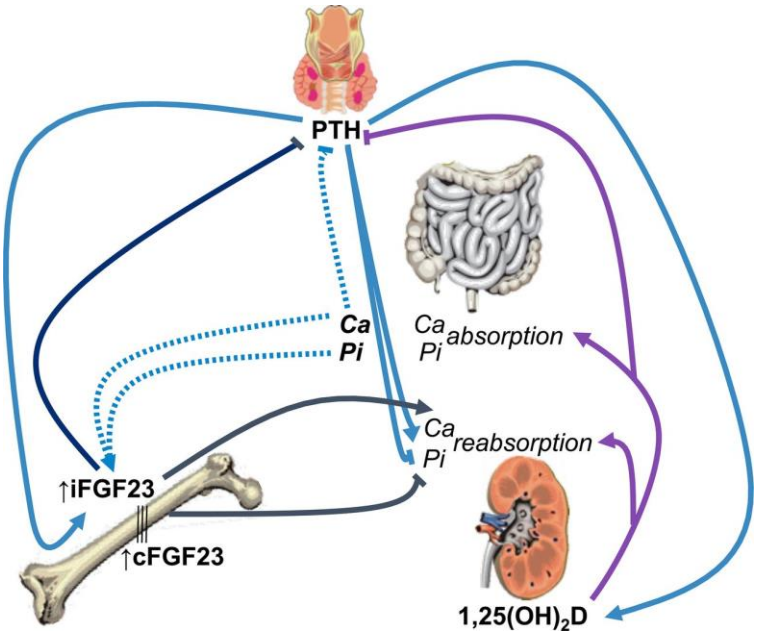


FIG. 11. **Schematic view of the mechanism of action of the FGF23 protein.**

6. Additional findings of McCune-Albright Syndrome

Less common symptoms that sometimes occur in McCune-Albright syndrome include: gastroesophageal reflux, gastric and intestinal polyps, pancreatitis, cardiac abnormalities such as tachycardia, high output heart failure, and aortic root dilatation. Be it. In less than 1% of patients with McCune-Albright syndrome who have developed fibrotic dysplasia, malignant transformation occurs to develop malignant tumors in the bone. People with McCune-Albright syndrome may also be at risk for breast cancer, or liver, biliary and pancreatic tumors. Some research suggests that this increased risk is greater in people who produce too much growth hormone (FIG. 12). Thyroid and testicular cancer have also been reported in very rare cases of McCune-Albright syndrome [1,17].

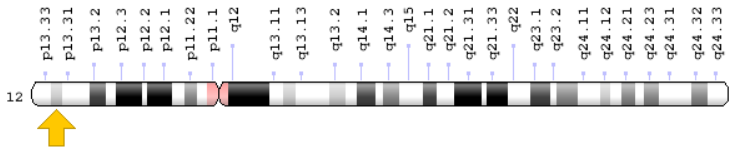


FIG. 12. **Schematic overview of chromosome 12 where the FGF23 gene is located in the short arm of chromosome 12p13.32.**

7. The Etiology of McCune-Albright Syndrome

McCune-Albright syndrome is caused by a gene mutation called GNAS1. The GNAS1 gene is located on the long arm of chromosome 20 at 20q13.32. The cause of the mutation is still unknown and, according to the researchers, the mutation in the

GNAS1 gene that causes McCune-Albright syndrome occurs randomly and a new mutation occurs at the time of fertilization in embryonic somatic cells and follows the mosaic pattern. Slow. The GNAS1 gene encodes a protein subunit called the G protein. In patients with McCune-Albright syndrome, the GNAS1 gene has a mutation that increases its expression and continuous G protein synthesis in body cells, especially in bone cells. Continued activation of the G protein, in turn, results in a molecular overproduction called cAMP or cyclic adenosine monophosphate that is involved in various biochemical processes in the body (FIG. 13). Therefore, the production of cyclic adenosine monophosphate (cAMP) is associated with the development of a variety of symptoms and clinical manifestations of McCune-Albright syndrome [1,18].

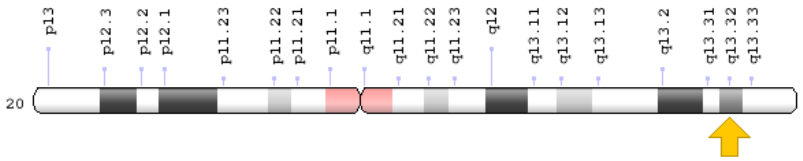


FIG. 13. **Schematic overview of chromosome 20 where the GNAS1 gene is located in the long arm of chromosome 20q13.32.**

8. Frequency of McCune-Albright Syndrome

McCune-Albright syndrome affects men and women in equal numbers. Early puberty is more common in women with McQueen-Albright syndrome. However, the prevalence of the disorder worldwide is estimated at about 1 in 100,000 or 1 in 10,000 live births (FIG. 14). Since most symptoms of Albright Syndrome are misdiagnosed or misdiagnosed, it is difficult to determine the true and exact frequency of this disorder globally [1,18].

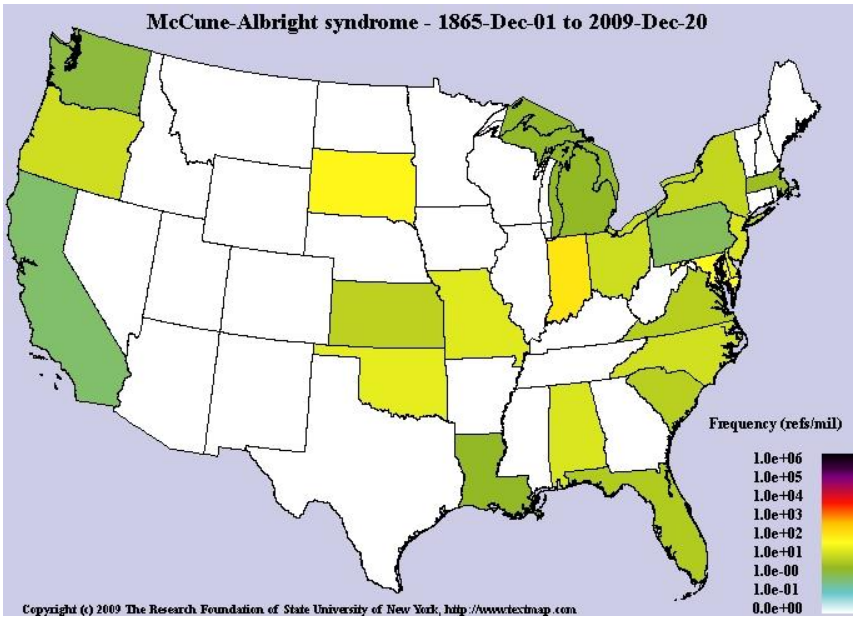


FIG. 14. **Schematic overview of the frequency map of McCune-Albright syndrome worldwide from 1865 to 2009.**

9. Diagnosis of McCune-Albright Syndrome

Diagnosis of McCune-Albright syndrome may be diagnosed at birth based on the detection of skin pigmentation (areas of the skin with light brown spots). However, in many cases, this disorder may be diagnosed as late as childhood or early adolescence or when bone changes occur. X-rays are used to diagnose skeletal disorders and blood tests to check hormone levels, computed tomography (CT), and MRI imaging are also used to diagnose McCune-Albright syndrome (FIG. 15). The most definitive method for the diagnosis of McCune-Albright syndrome is molecular genetic testing to determine whether there is a mutation or a second mutation in the GNAS1 gene [1,18].

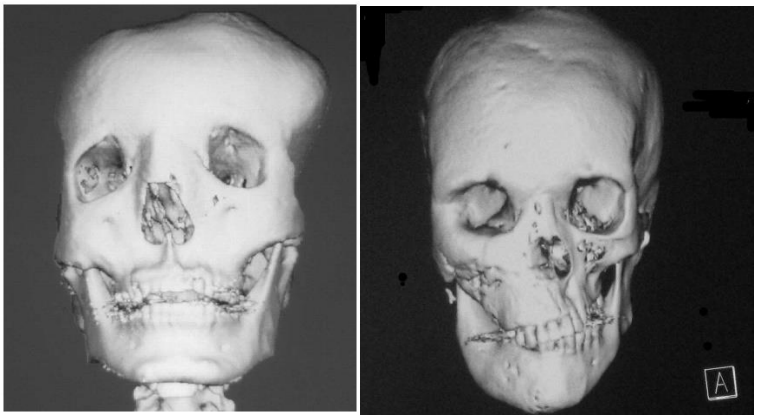
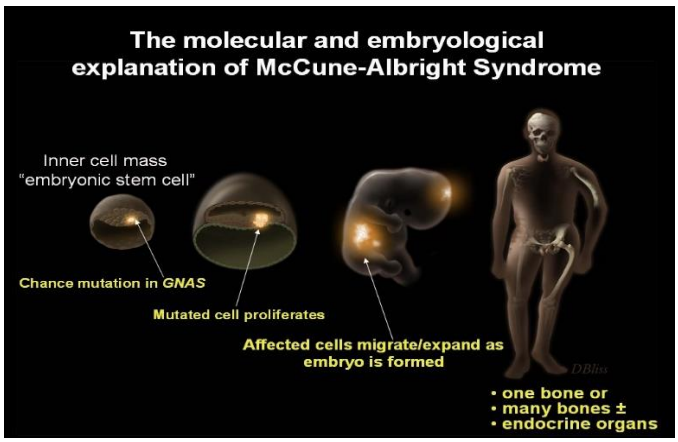


FIG. 15. **Radiological image of the face and skull of a person with McCune-Albright syndrome.**

10. McCune-Albright Syndrome Therapies

The treatment of McCune-Albright syndrome is characterized by symptoms that appear in each individual. The treatment may be coordinated by a team of specialists including: pediatrician, orthopedic surgeon, endocrinologist, dermatologist, molecular genetic or medical geneticist and other health care professionals. Bone fibrous dysplasia may be treated with medications such as pamidronite or alendronate. Surgery can also be effective in improving the status of skeletal disorders in patients with McCune-Albright syndrome (FIG. 16 & 17). Unfortunately, this syndrome, like many genetic syndromes, has no cure. Genetic counseling can also be important for parents who have a family history of genetic disorders, as well as for all parents who want a healthy, natural child [1,18].



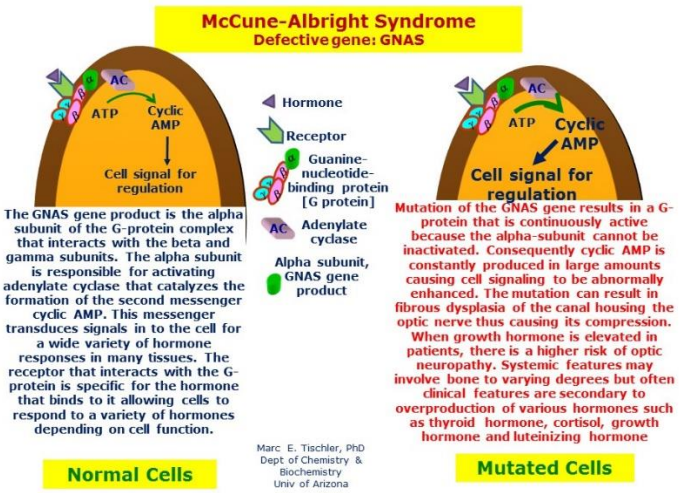


FIG. 16. **Schematic overview of the molecular and embryological mechanisms of McCune-Albright syndrome.**

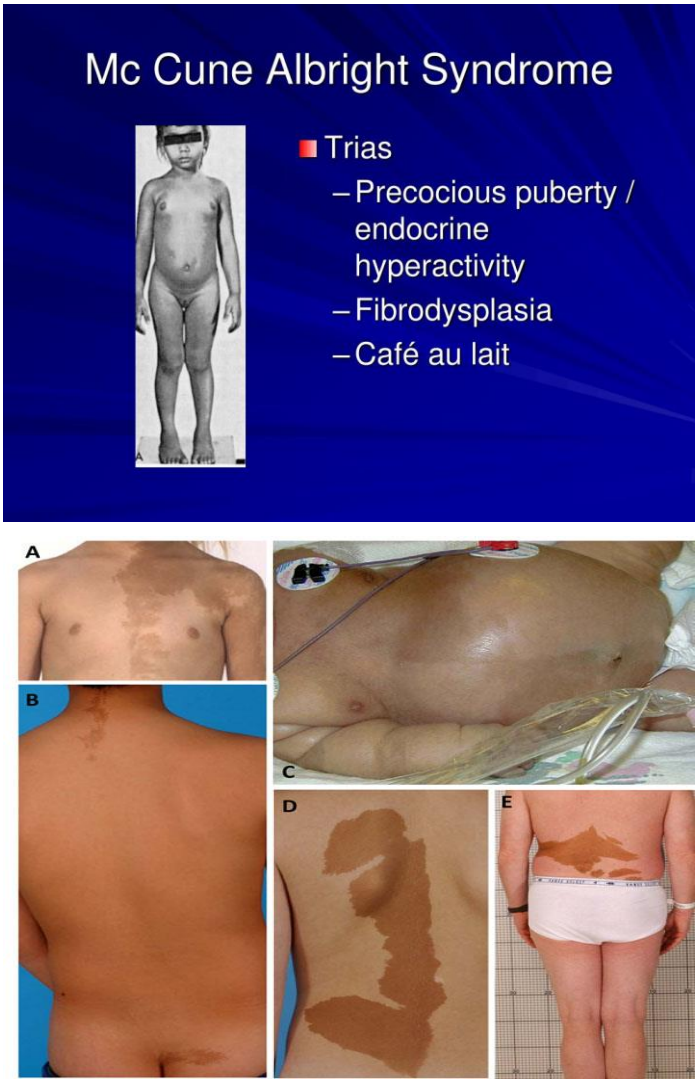


FIG. 17. **Images of a girl with McCune-Albright syndrome with premature puberty and premature enlargement of breasts and light brown spots in different areas of skin.**

11. History of McCune-Albright Syndrome

McCune-Albright syndrome was first described in 1937 by James Donovan McCune and Fuller Albright (FIG. 18) [1,18].

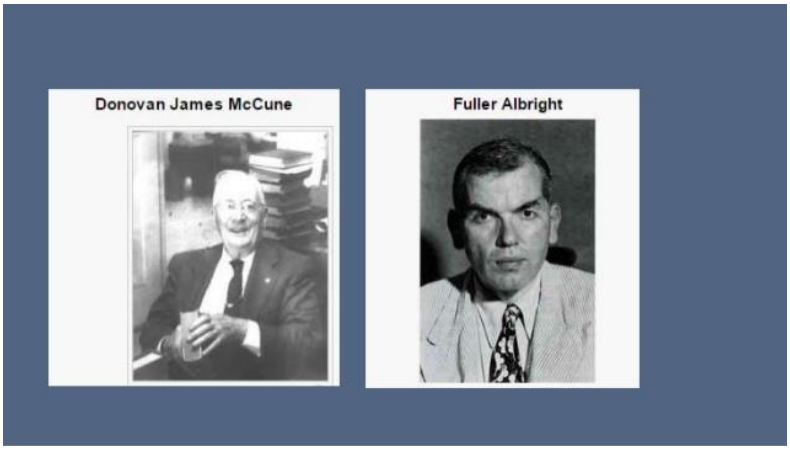


FIG. 18. **Images of the discoverers of McCune-Albright syndrome.**

12. Discussion and Conclusion

McCune-Albright syndrome (MAS) is a rare, heterogenous, clinical condition caused by a rare genetic mutation. The disorder is more common in females and is characterized by a triad of cutaneous, bone and endocrine abnormalities. We describe a girl patient with MAS having precocious puberty and multiple cafe-au-lait macules and deforming polyostotic fibrous dysplasia of bone.

Clinical presentation and X-ray finding were strongly diagnostic for MAS, Patients with McCune-Albright syndrome reach the adult age with a significant burden of the disease that continuously reduces their quality of life. Skeletal deformities, fractures, hyperthyroidism, and hyperestrogenism are just few of the many challenges in the management of these patients. These disorders with close observation and early detection can be controlled. The disorder is the result of post-zygotic somatic mutation in the gene GNAS 1 on chromosome 20q13-13.2 9, coding for the alpha subunit of stimulatory G protein (Gsa). G proteins couple cell surface receptors to intracellular proteins to activate or inactivate signaling cascades. The stimulatory G protein is normally activated when a hormone or other ligand binds to the cell surface receptor. The activated Gsa subunit subsequently dissociates from the receptor, binds to adenylyl cyclase and stimulates an increase in the intracellular cyclic adenosine monophosphate (cAMP) levels. The Gsa subunit is then inactivated, which re-associates with the receptor and is again available for hormone-mediated reactivation [1,18].

The clinical expression depends on the number of mutated cells and affected organs. Thus, the presentation can be heterogenous, involving various endocrine and non-endocrine organs. The precocious puberty can also be an early manifestation of McCune-Albright syndrome and the etiologic diagnosis of early sexual precocity is based on careful history and physical examination. Children with precocious puberty should be evaluated for endocrinopathies and hormonal studies may be necessary in such cases [1,18].

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