Fibrous Dysplasia (McCune-Albright Syndrome)

Genetics

-GNAS (Guanine nucleotide-binding protein G(s), alpha subunit; 20q13.2)

-Early embryonic postzygotic somatic activating pathogenic variants

Clinical findings/Dysmorphic features

-Abnormal scar-like (fibrous) tissue in the bones (polyostotic fibrous dysplasia)

-Involvement of skin, skeleton, certain endocrine organs

-Polyostotic fibrous dysplasia --> high risk of fractures, deformity, functional impairment, pain

-Large irregular café au lait (“coast of Maine”)

-Cranial foramina thickening (may cause deafness and blindness)

-Gonadotropin-independent precocious puberty (early)

-Thyroid lesions with characteristic ultrasonographic features (+/- non-autoimmune hyperthyroidism)

Etiology

-1:100,000 to 1:1,000,000

Pathogenesis

-GNAS variants at residues p.Arg201 and p.Gln227 disrupt the activity of intrinsic GTPase, causing constitutive activity and inappropriately increased cAMP signaling

Genetic testing/diagnosis

-Targeted analysis of codons p.Arg201 and p.Gln227

-Somatic mosaicism for pathogenic missense variants at p.Arg201 has been identified in more than 95% of all published reports of FD/MAS

-Sample of affected tissue --> ~80% (yield) vs. ~20%-30% in peripheral blood lymphocytes

Others

-Not inherited (somatic mutations)

-Spectrum of FD/MAS: asymptomatic incidental findings to neonatal lethality