Cardio-facio-cutaneous Syndrome

Genetics

-BRAF (~75%), MAP2K1 (encodes MEK1) and MAP2K2 (encodes MEK2)(~25%), and KRAS (<2%)

-AD, mostly de novo

Clinical findings/Dysmorphic features

-Cardiac: pulmonic stenosis, septal defects, hypertrophic cardiomyopathy, arrhythmia

-Facial findings: high forehead, relative macrocephaly, bitemporal narrowing, hypoplasia of the supraorbital ridges, depressed nasal bridge with anteverted nares, highly arched palate, more coarse features and more dolichocephaly (long head) than Noonan syndrome

-Cutaneous abnormalities: xerosis (dry skin), hyperkeratosis, ichthyosis, eczema, ulerythema ophryogenes (rare cutaneous atrophic disorder

-Epicanthal folds and ptosis, ocular hypertelorism, telecanthus (increased distance between the medial canthi), down-slanting palpebral fissures,

Etiology

-Overall prevalence not known; in Japan 1: 810,000

Pathogenesis

-BRAF (serine/threonine protein kinase) is direct downstream effector of Ras --> proliferation, differentiation, motility, apoptosis, senescence

-BRAF has two known downstream effectors: MEK1 and MEK2

-BRAF pathogenic variants in CFC syndrome similar to somatic variants found in cancers

-Elevated kinase activity induce higher levels of MEK and ERK phosphorylation

Genetic testing/diagnosis

-Multigene panel for RASopathies/Noonan spectrum disorders that includes BRAF, MAP2K1, MAP2K2, KRAS

Others

-Most common BRAF pathogenic variant in cancer, p.Val600Glu, has not been identified in CFC syndrome, but a germline p.Val600Gly pathogenic variant has recently been reported in CFC