Costello Syndrome

Genetics

-HRAS

-AD; p.Gly12Ser: 81.3%

-Complete penetrance

Clinical findings:

-Feeding issues, DD, ID, short stature, loose and soft skin; curly or sparse, fine hair

-Cardiac (hypertrophic cardiomyopathy, valvar pulmonary stenosis, arrhythmia)

-Facial findings: coarse facial features, full cheeks, full lips, large mouth, full nasal tip, epicanthal folds, wide nasal bridge, short full nose, deep, hoarse or whispery voice

-Papillomata (small wart-like growth on the skin) of the face and perianal region

Etiology

-Rare (300 individuals reported worldwide)

-Birth prevalence is estimated at 1:300,000 in the UK

Pathogenesis

-Pathogenic missense variants result in constitutive activation of the abnormal protein product --> increased signaling through Ras-MAPK and PI3K-AKT pathways

Genetic testing/diagnosis

-Sequence analysis of HRAS (only gene currently known) --> pathogenic missense variants in 80%-90% of individuals with the clinical diagnosis

-Targeted analysis for pathogenic variants: > 95% affect amino acid p.Gly12 or p.Gly13

Others

-No other phenotype is known to be associated with germline mutation of HRAS

-Approx. 15% lifetime risk for malignant tumors (rhabdomyosarcoma and neuroblastoma, transitional cell carcinoma of the bladder)