FGFR-Related Craniosynostosis Syndromes

Genetics

-Gene: FGFR1, FGFR2, FGFR3 (Basic fibroblast growth factor receptor 1, 2, and 3)

-AD

Clinical findings/Dysmorphic features

-Premature fusion of one or several sutures of the skull

-Comprises 8 syndromes: 1) Pfeiffer syndrome; 2) Apert syndrome; 3) Crouzon syndrome; 4) Beare-Stevenson syndrome; 5) FGFR2-related isolated coronal synostosis; 6) Jackson-Weiss syndrome; 7) Crouzon syndrome with acanthosis nigricans; 8) Muenke syndrome

-Muenke syndrome: unilateral coronal synostosis or megalencephaly without craniosynostosis

-FGFR2-related isolated coronal synostosis: uni- or bicoronal craniosynostosis only

-The other 6: bicoronal craniosynostosis or cloverleaf skull, distinctive facial features, variable hand and foot findings

1) Pfeiffer: DD/ID; extreme proptosis; cloverleaf skull; broad and medially deviated thumbs and great toes (towards each other); ankylosis of elbows; knees; brachydactyly

2) Apert: varying degrees of DD/ID (50%; related to timing of craniofacial surgery); turribrachycephaly (high, prominent forehead); midface hypoplasia; soft tissue and bony ("mitten glove") syndactyly of fingers and toes; fused cervical vertebrae (68%)

3) Crouzon: significant proptosis; external strabismus (one eye looks outwards); mandibular prognathism; normal ID and normal extremities; progressive hydrocephalus (30%)

4) Beare-Stevenson: ID; midface hypoplasia; abnormal ears; widespread cutis gyrata and AN; skin tags; bifid scrotum; normal extremities

5) FGFR2-related isolated coronal synostosis: ID normal; extremities normal

6) Jackson-Weiss: normal ID; mandibular prognathism; broad and medially deviated great toes; normal hands

7) Crouzon with acanthosis nigricans: 5% of individuals with Crouzon have AN (pigmentary changes in the skin fold regions)

8) Muenke: some with pathogenic variant have no clinically apparent abnormalities; normal to mild ID; uni- or bilateral coronal craniosynostosis, or only megalencephaly; midface hypoplasia; ocular hypertelorism; carpal-tarsal fusion diagnostic if present; brachydactyly; bilateral, symmetric, low- to mid-frequency SNHL

Etiology

-Prevalence all together: 1 in 2,100 to 1 in 3,000 at birth

Pathogenesis

-Two common Apert muts (98% of syndrome, FGFR2, p.Pro253Arg and p.Ser252Trp) are at same location as FGFR1 mut in Pfeiffer and the FGFR3 mut in Muenke: linker region between Ig-like loops II and III --> area critical in ligand binding; replacement of Pro for a bulkier Arg may alter the orientation of IgII and IgIII loops

-Both variants augment receptor binding affinity --> Gain-of-Function

Genetic testing/diagnosis

-Pfeiffer syndrome (5% FGFR1 - p.Pro252Arg; 95% FGFR2 – 80% in exon 8 and 10)

-Apert syndrome: targeted analysis of FGFR2 for p.Ser252Trp and p.Pro253Arg --> sequencing of FGFR2 --> partial-gene insertions/deletions

-Crouzon syndrome: FGFR2 – 80% in exon 8 and 10

-Crouzon syndrome with AN: usually caused by FGFR3 p.Ala391Glu

-Muenke syndrome: 100% p.Pro250Arg in FGFR3

-FGFR2-related isolated coronal synostosis: combination of uni- or bicoronal craniosynostosis and identification of FGFR2 pathogenic variant

Others

-Saethre-Chotzen Syndrome: TWIST1, big toes pointing away from each other