Crouzon syndrome

Crouzon syndrome (CS) is an autosomal dominant disorder characterized by premature fusion of cranial sutures, midface and supraorbital ridge retrusion, exorbitism, and in some clinical scenarios strabismus, parrot-beaked nose, short upper lip and hypertelorbitism.

Etiology

Is a genetic disorder known as a branchial arch syndrome. Specifically, this syndrome affects the first branchial (or pharyngeal) arch, which is the precursor of the maxilla and mandible. Since the branchial arches are important developmental features in a growing embryo, disturbances in their development create lasting and widespread effects.

Crouzon-like craniosynostosis syndrome

Keupp et al. characterized a novel autosomal recessive Crouzon-like craniosynostosis syndrome in a 12-affected member family from Antakya, Turkey, the presenting features of which include: multiple suture synostosis, midface hypoplasia, variable degree of exophthalmos, relative prognathism, a beaked nose, and conductive hearing loss. Homozygosity mapping followed by targeted next-generation sequencing identified a c.479+6T>G mutation in the interleukin 11 receptor alpha gene (IL11RA) on chromosome 9p21. This donor splice-site mutation leads to a high percentage of aberrant IL11RA mRNA transcripts in an affected individual and altered mRNA splicing determined by in vitro exon trapping. An extended IL11RA mutation screen was performed in a cohort of 79 patients with an initial clinical diagnosis of Crouzon syndrome, pansynostosis, or unclassified syndromic craniosynostosis. We identified mutations segregating with the disease in five families: a German patient of Turkish origin and a Turkish family with three affected sibs all of whom were homozygous for the previously identified IL11RA c.479+6T>G mutation; a family with pansynostosis with compound heterozygous missense mutations, p.Pro200Thr and p.Arg237Pro; and two further Turkish families with Crouzon-like syndrome carrying the homozygous nonsense mutations p.Tyr232* and p.Arg292*. Using transient coexpression in HEK293T and COS7 cells, we demonstrated dramatically reduced IL11-mediated STAT3 phosphorylation for all mutations. Immunofluorescence analysis of mouse Il11ra demonstrated specific protein expression in cranial mesenchyme which was localized around the coronal suture tips and in the lambdoidal suture. In situ hybridization analysis of adult zebrafish also detected zfil11ra expression in the coronal suture between the overlapping frontal and parietal plates. This study demonstrates that mutations in the IL11RA gene cause an autosomal recessive Crouzon-like craniosynostosis [1].

1)
Keupp K, Li Y, Vargel I, Hoischen A, Richardson R, Neveling K, Alanay Y, Uz E, Elcioğlu N, Rachwalski M, Kamaci S, Tunçbilek G, Akin B, Grötzinger J, Konas E, Mavili E, Müller-Newen G, Collmann H, Roscioli T, Buckley MF, Yigit G, Gilissen C, Kress W, Veltman J, Hammerschmidt M, Akarsu NA, Wollnik B. Mutations in the interleukin receptor IL11RA cause autosomal recessive Crouzon-like craniosynostosis. Mol Genet Genomic Med. 2013 Nov;1(4):223-37. doi: 10.1002/mgg3.28. Epub 2013 Aug 19. PubMed PMID: 24498618.

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